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Volume 25, June 2015

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*Robert L. Mauck, George R. Dodge
It is with immense pride that we introduce the 25th edition of the University of Pennsylvania Orthopaedic Journal (UPOJ). The UPOJ was first published in 1985 under the leadership of Dr. Carl T. Brighton, and it has been a fixture of the department for many years. With this 25th edition, we celebrate the 30th anniversary of the nation’s first fully resident-run journal of orthopaedic surgery.

We dedicate this momentous volume to two wonderful people, who have been the faces of the program for several decades: Dr. John L. Esterhai and Barbara Weinraub. Dr. Esterhai’s relentless dedication to his patients, his students and the values of Penn Orthopaedics has been profoundly inspirational to generations of trainees and peers over the last 39 years. Dr. Esterhai semi-retired in April but his sincere mentorship, his seminal research work and his exemplary clinical care will be remembered at Penn Orthopaedics as shining illustrations of a consummate physician. Barbara Weinraub, who has worked for the department for 5 decades (including as the residency coordinator since 1991) retired from her full time responsibilities in January. Her passion for our program, and her tireless dedication to the residents, will be fondly remembered by all those who had the privilege to interact with her in the course of their training.

The UPOJ is continuing this year with its well-received “extended abstract” format, which has allowed for increased representation of both clinical and basic science research. We have had the honor of reviewing articles from nearly all clinical divisions and primary investigators of the Department of Orthopaedic Surgery at the University of Pennsylvania.

Furthermore, we are thrilled to put forth the very exciting developments taking place in our Department and Health System through their respective sections. The accelerated consolidation of the Musculoskeletal and Rheumatology service line, the grand opening of our state of the art Penn Medicine University City site, and the move of the Level 1 Trauma Center from the Hospital of the University of Pennsylvania to Penn Presbyterian Medical Center have defined a pivotal year for our Health System. We also highlight a number of exciting and important events that have occurred in the Health System and the department this year, including symposia on Excellence in Orthopaedics and throwing disorders; regional courses for arthroplasty, hand surgery and Orthopaedic education; and a Visiting Professor lectureship that included several internationally recognized leaders and experts in Orthopaedics.

Following the tremendous work by previous editors, the UPOJ will once again be made available online. We want to thank Daniel Steinberg for his phenomenal efforts to continuously improve on the fantastic groundwork developed last year.

The UPOJ has been financially independent from the Department of Orthopaedic Surgery since 1997 thanks to the generous financial support from our advertisers. We wish to sincerely thank our sponsors, on behalf of our department, for supporting the educational and research missions of Penn Orthopaedics.

The publication of the UPOJ would not be feasible without the prodigious support and guidance of our chairman, Dr. L. Scott Levin; our Program Director, Dr. Craig L. Israelite; and our faculty advisers, Drs. Samir Mehta and Jaimo Ahn. Our section editors were instrumental in reviewing the superb clinical articles that we received this year. We extend our deep and heartfelt gratitude to Drs. Jason B. Anari (Pediatric Orthopaedics), Keith P. Connolly (Arthroplasty), Joshua A. Gordon (Hand and Microvascular Surgery), Daniel P. Lim (Trauma), Philip A. Saville (Spine Surgery), Russell N. Stitzlein (Epidemiology), Michael T. Talerico (Sports Medicine) and Zachary R. Zimmer (Shoulder and Elbow Surgery) for their hard work and dedication.

On behalf of our fellow authors, editors, and mentors, we proudly present the 25th edition of the UPOJ. It is our sincere hope that this volume highlights the culture of academic challenge, collaborative discovery, scientific exploration and clinical leadership that makes Penn Orthopaedics such an exceptional program.

Sincerely,
Alexander L. Neuwirth, MD and Tyler R. Morris, MD
Editors-in-Chief
The University of Pennsylvania Orthopaedic Journal
Volume 25
Letter from the Chairman
L. Scott Levin, MD, FACS

As I approach the completion of my first term as Chairman of Orthopaedic Surgery at the University of Pennsylvania School of medicine, I pause to reflect on our team’s accomplishments and the challenges and opportunities that remain ahead. Penn’s medical school’s 250 year history is being celebrated next month. Our department’s heritage is approximately half as old as the medical school founded by Benjamin Rush and Ben Franklin. Often, I take visitors through the historic areas of Pennsylvania hospital-the library, the great court, and operating theater-illuminated by the magnificent skylight that was the guiding light for the surgery our forefathers attempted before the days of electricity, antibiotics, X-rays, managed care, bundled payments, and maintenance of competency. Our team proudly operates at Pennsylvania Hospital as well as Presbyterian medical center and Hospital of the University of Pennsylvania. With an eye on our past but also with forward thinking, care delivery includes patient risk stratification to decrease morbidity and mortality, MP3 Pain protocols that have enhanced the patient experience following joint replacement, and a hip preservation program that includes the use of vascularized fibular grafts as an alternative to joint replacement in young patients with avascular necrosis. What would the Department’s first chair Deforest Willard say about our progress?

This past year has marked several milestones that are unique in the history of the department. With pride, we are now ranked #3 in NIH research funding. My vision statement in 2009 (following the suggestion of Jim Collins in Good to Great, that such evolution requires a BHAG- a “Big Hairy Audacious Goal”) was to become a “top five in five” Orthopaedic Department. Translated- I wanted us to be ranked in the top five Orthopaedic programs in the United States. We have reached the number three ranking based on outstanding scientific productivity by our research faculty, led by Lou Soslowsky. Special recognition goes to Robert L. Mauck, Ph.D., who won this year’s young investigator Kappa Delta award for his work with Jason Burdick and Dawn Elliot from the School of Engineering titled “Engineering Dense Connective Tissues: Mechanical, Material, and Mechanobiologic Considerations”.

Our grant portfolio includes funding from the NIH, DOD, OREF, Hans Jorg Wyss Foundation, Biedermann family and Industry. Our educational programs, which include a robust residency and increasing fellowship positions in multiple divisions, are nationally recognized, currently ranking 1-4th out of 89 programs. Our clinical ranking in US News and world report has been as high as 13 in the country-currently ranked in the top 20. While multiple factors account for this ranking we are striving to improve our patient care, quality and safety and we have done a great job at this. For example, several years ago our mortality index was unacceptable. Rather than accept poor performance, we pulled together with our medical partners, hospital administrators and faculty and chartered a course that dramatically improved our results over the last two years. The point of the discussion centered on rankings: that our work to improve across all missions is never done. Maintaining the status quo, thinking that we will never be the “best” or not shooting for #1 in all missions is a grave mistake. Penn Orthopaedics is a team that always strives to do better- and we have. Within the health system Penn Orthopaedics took the lead on same day access for patient appointments. For example-if a patient calls at 9 am- we will see the patient that day for evaluation and treatment. Many said this could not be done. Impossible…they said. As it turns out, our same day access has been a huge success, and is now being marketed by other providers in our region. We set the trend; others now follow.

This program served as the primer for our Musculoskeletal and Rheumatology Service Line that began with the opening of our new Musculoskeletal Center in September 2014. Our service line includes PM and R, Rheumatology, MSK imaging, Pain management, Physical Therapy and Orthopaedics. We have changed musculoskeletal care delivery at Penn and strive to get the patient to the right provider at the right time. We now manage care as disease teams, rather than practitioners who perform an operation or prescribe infusion therapy. Our new building is a state of the art think-tank and diagnostic center, capable of diagnosis, testing, treatment, and rehabilitation under one roof. Complimentary to patient care is the Human Performance Center which creates a unique research opportunity for patients to measure their outcomes after intervention. Gait analysis, EMG, real time motion analysis and kinematic studies are all possible in this state of the art laboratory located in the center of the clinic. In addition to the HPC, we will have a new biomechanics lab in our building sponsored by the Biedermann family. The lab will allow residents and faculty to explore news ways to treat MSK conditions by enhancing design of trauma implants and joint prostheses. Efficient use of time and immediate translation of ideas generated while delivering patient care, can be actualized in a research space adjacent to our operating rooms and clinics. This integration of the missions of clinical care, resident and fellow education, and research, all under one roof, will pay huge dividends for our future. We have modelled the Penn MSK Center after the Perelman center for Advanced Medicine that has successfully integrated all three missions of academic medicine in one location.

As a tribute to our new methods of delivering Musculoskeletal care and in celebration of Penn Orthopaedic’s new home, we held a symposium entitled: “Excellence in Orthopaedics.” Key American Orthopaedic thought leaders were invited to
give their perspectives on excellence. The attendees included Richard Gelberman (Washington University), Parker T. Vail (UCSF), William Cooney (Mayo clinic), Gerry Williams (The Rothman Institute), Joe Ianotti (Cleveland Clinic) Michael Gagnon (Duke), Louis Soslowsky (Penn) and Bruce Browner (University of Connecticut). Each speaker provided insight into what it takes to be “excellent” and shared successes (and some of the failures) in their journey to greatness. Common themes included personal humility, communication of objectives, the value of research, faculty recruitment and retention, and global perspective on the burden of musculoskeletal disease. Dean Larry Jameson and UPHS Health system CEO Ralph Muller provided their overview of Penn’s leadership position in American healthcare.

In addition to our downtown locations, the health system has purchased Chester County Hospital, and is close to establishing a relationship with Lancaster General Hospital. These strategic alliances broaden the reach of Penn Medicine, and allow our teams to expand and meet the needs of patients in these regions. Further expansion of clinical facilities in Cherry Hill and in Valley Forge provide flexibility for our patients and sites for our service line to expand beyond center city.

Our educational programs have grown significantly over the past 6 years. Under the direction of Craig Israelite, Samir Mehta and Jaimo Ahn we continue to attract and match exemplary medical students into our residency program. Two of our six residents continue to spend a year in the research laboratory, and their accomplishments include OREF grant funding, selection for AOA surgeon scientist workshops, and representation of our lab at the Orthopaedic Research Society. This academic year we reorganized the didactic portion of the resident experience. Historically, the department convened for a grand rounds format on Thursday mornings from 6:30-8:30 am. Resident attendance, although required, was limited in some instances by their urgent commitments in the OR, ER, wards or by duty hour restrictions. The program directors, faculty and I felt that this was wrong. As a result of significant planning and rescheduling, our didactic program has evolved into a four hour Thursday block from 6:30—10:30 am. These sessions include faculty and resident lectures, anatomic dissection, Quality Improvement conference, and time with our robust visiting professor program. All residents attend this protected time—no exceptions! This builds teamwork and demonstrates the faculty’s commitment to education. The residents have universally embraced this new educational opportunity.

Over the past six years, I have worked hand in hand to develop mutually beneficial programs between CHOP and Penn Orthopaedics. These include Sports Medicine, Hand Surgery, Extremity Trauma care, Hip preservation and combined research efforts between the laboratory of Mauricio Pacifici and the McKay lab. My outstanding partner in these initiatives, John Dormans, has recently announced that he will be taking on a new challenge at Texas Children’s hospital as Orthopaedic Surgeon in Chief. Jack Flynn has been named as John’s successor. The momentum will not be lost on our collective efforts. Jack and I are hard at work to assure a smooth transition and deliver on the plans that John and I outlined for excellence in joint programs. John Dormans will never be forgotten as an exemplary leader at CHOP for 23 years. I personally want to thank him for his support the last six years.

A key indicator of departmental success is the need to hire additional physicians and support personnel. At the time of publication of this article we hope to have added another hand surgeon, foot surgeon, spine surgeon for our Philadelphia sites and joint surgeon for Chester county hospital. John Manna and Christopher Lyons have joined our clinical enterprise at Chester County as of April 7, 2015 and will anchor our clinical expansion at that site. Their vast experience and talent will jump start another phase of MSK delivery for Penn Medicine.

In January of this year, the Department underwent a review (both by an internal committee and an external review panel) which occurs in all Departments every six years at the request of the Dean. I welcomed this process and was interested in an objective assessment of my leadership and the progress of our team across all missions. The internal review was led by Lee Fleisher MD (Chairman of the Department of Anesthesia) and the external review committee was led by Richard Gelberman and included Louis Bigliani and Parker T Vail. Our rigorous preparation included a report of our clinical growth, faculty expansion, research portfolio and educational experience. Multiple interviews were conducted throughout the school of medicine and health system with faculty, administrators, residents, students and deans from other Schools at the University of Pennsylvania. To summarize, I will be reappointed for another six year term. More importantly, and the main objective of any departmental review, is to clarify where we can improve, to point out areas of relative deficiency, and also to recognize where we have strength that can help us grow further. I am profoundly grateful to all who participated, but particularly to the outstanding Orthopaedic leaders who served on the external review panel. Based on the review and feedback, a strategic plan has taken shape that will take Penn Orthopaedics to the next level of achievement. The journey of going from “good to great” will continue. I want to recognize all of the clinical and research faculty, residents, fellows and support staff who are now on “the bus”. We seem to be driving in the right direction and will be fueled to go farther in the coming years. Your support and encouragement are vital to our success. I am counting on you to offer suggestions on how we can continue to improve. It is an honor and privilege to lead such an outstanding team.
Letter from the Program Director
Craig L. Israelite, MD

Individually and collectively as a department, we are driven to make a demonstrable difference in the education of orthopedic residents at the University of Pennsylvania. The education of residents and fellows has been and continues to be one of the greatest strengths of the Department of Orthopedic Surgery. As a testament to our national position we receive approximately eight hundred applicants annually for our eight highly coveted and competitive positions. The commitment to resident education continues to be emphasized at the highest levels, which begins with our department chair Dr. L. Scott Levin, MD, vice chairs, division chiefs and faculty. It is truly a team effort and has led to the continued academic success of the department.

Currently there are forty-two residents within the department. There are eight new residents which matriculate each year, of which two residents spend an entire year doing full time research between their post graduate two and three years. With the continued growth of the department both in faculty recruitment and volume, it is our intention to successfully be approved for an additional resident per year. Institutional approval has already been granted for these additional residents in order to support our departmental mission.

All general and subspecialty sections of orthopedic surgery are expertly covered by our distinguished faculty. Residents rotate primarily through the University of Pennsylvania Health System (UPHS) hospitals of HUP, Pennsylvania Hospital and Penn-Presbyterian Hospital. PGY2 and 4 residents spend 3 months at the Children's Hospital of Pennsylvania (CHOP) ranked at the top of all pediatric programs. Additionally our residents support the orthopedic missions at the Philadelphia Veterans Hospital as well as a community rotation at Bayhealth Hospital (Dover, DE). This newly acquired community rotation now allows our residents access to evaluate community health practices, while at the same time allows for a new referral base involving complex patients to our own health system. Lastly, our residents have participated and will be encouraged to pursue global outreach programs.

While our affiliations are large and diverse, our department continues to strive for a balanced and well-structured core curriculum. The curriculum is now run on two year cycles and covers all areas of our specialty. Grand rounds are required and take place every Thursday morning with four continuous hours of protected educational time. Additionally, each subspecialty delivers at least one academic didactic session each week. These morning conferences are comprised of faculty within the division, fellows, residents and students (Penn and visiting). These lectures are reviewed, critiqued and discussed with each division chief in order to maintain updated goals and objectives for each section.

In addition to our core academic mission and educational activities, this robust program is further enhanced by numerous additional activities. The visiting professor lecture series occurs each month and are sponsored and named sessions. The series is comprised of the most renowned national and international faculty. In addition to visiting faculty, our residents are encouraged and supported to attend numerous off-site courses to enhance their learning each year.

While obviously it is our main mission to educate each of our residents, the evaluation of our residents has become even more critical. The department provides a strong mentorship program which pairs faculty to incoming trainees. Furthermore, all active faculty are required to evaluate each resident regarding knowledge and professionalism. Newly developed milestones documentation evaluations are now electronically based. Evaluations are submitted to the Clinical Competency Committee (CCC) which is comprised of the chairman, program director and assistants and a faculty member of each division. Careful and meaningful evaluations are then documented with respect to each resident's academic and professional growth and recommendations are made regarding their advancement in our program. This newly developed CCC has been invaluable with respect to real time evaluation of residents necessary for promotion or remedial work.

Another highlight of the departments' evaluation process involves the monthly meeting of our own Graduate Medical Education Committee (GMEC). This highly functioning and motivated group consists of the chairman, program directors, faculty as well as two members of each resident class who are elected by their peers. The program can therefore constantly review current situations and respond with ease to any needed changes. Many of our new programs have been initiated by resident suggestions during these meetings.

In addition to striving for continued academic and clinical excellence, new CLER initiatives are being developed. As one of the few orthopedic programs nationally to have a vice chair for compliance officer, Dr. Levin has appointed Dr. Hume to join with the program directors in order to provide safety measures for the residents' delivery of patient care. Numerous projects have been completed and new ones are beginning.

The cost of supporting our growing mission of education continues to increase. The human cost, measured in hours, has largely been covered by the spirit and volunteerism of department members. Faculty is omnipresent with regard to mentorship, educational development and research. Countless non-clinical hours are devoted to GMEC, CCC and research. Intra-mural and extra-mural funding has been raised in order to support the entire curriculum. One unique and noteworthy development has been the use of iPads which have been provided to each resident. The ability to locate
Lastly, I would be remiss if I did not thank those who have gone above and beyond their normal duties of providing commitment to our program. While we have one of the greatest department faculties, some truly are contributing above and beyond. Dr. Scott Levin continues to put the educational quality of our residents at the forefront of all missions. He continues not only to be an exemplary leader of the faculty, but knows, meets and provides exceptional guidance to all of the residents. There are no words which can say how much Barbara Weinraub has meant to the continued success of our program. While “officially” retiring in December, it is a testament of her commitment and undeniable qualities that she continues to work and mentor our newly hired Program Coordinator Shanna Kurek. Shanna obviously has big shoes to fill but has already shown exceptional skill. Drs. Mehta and Ahn continue to not only be exemplary role models and educators, but are invaluable to the continued success of our residency. Our academic chiefs this year were Christos Photopoulos, John (Gabe) Horneff, and Ryan Taylor, who kept the ship running smoothly. This was an incredible year of transition as we moved the trauma division to PMC as well as the opening of our brand new outpatient offices. They never complained and have honed their leadership skills that will serve not only them but the orthopedic community at large for many years to come. Truly they are the heart and soul which drives each resident to reach their highest level of competency. I am indebted to all of these exceptional individuals that I am privileged to work with in addition to what I consider the best faculty and staff in the nation.
Dedication to Dr. John L. Esterhai

Alexander L. Neuwirth, MD & Tyler R. Morris, MD

It is with great pride that we dedicate the 25th Volume of the University of Pennsylvania Orthopaedic Journal to Dr. John L. Esterhai, who has provided outstanding clinical care and academic excellence to the Department of Orthopaedic Surgery at the University of Pennsylvania over the last 39 years.

Dr. Esterhai was born in Philadelphia on October 23rd, 1946 and raised in Roxborough. His great grandfather was a haberdasher in Manayunk. When just four years old, he had a ruptured appendix, prompting his fascination with medicine and caring for others. His primary care physician, a World War Two veteran and family friend, made frequent house calls and served as one of his first medical role models.

After graduating from Central High School in 1964, he attended Gettysburg College. His interest in Orthopaedics started with a left knee total medial meniscectomy - long before arthroscopy - when one of the marks of an excellent surgeon was being able to remove the entire meniscus with a Smiley knife. Air Force ROTC helped to defray the costs of his junior and senior years in college and senior year at Temple University School of Medicine. He and Carol married in 1969. He finished his General Surgery PGY-1 year at Temple in 1973.

In 1973, during the war in Vietnam, the Air Force needed flight surgeons more than orthopedists. During training in Aerospace Medicine at Brooks Air Force Base in San Antonio there was perfect weather and abundant time for Dr. Esterhai to obtain a private pilot license. From 1973 to 1976 he and Carol were stationed at Kadena Air Force Base in Okinawa, Japan. During this time, he served as a Flight Surgeon with the 44th Tactical Fighter Squadron, caring for fighter pilots, aircrews, and their families.

In 1976, Dr. Esterhai returned to Philadelphia to pursue Orthopaedic training at the University of Pennsylvania with Chairmen Drs. Edgar Ralston and Carl Brighton. During his research year his projects involved electrical stimulation of osteogenesis.

Drs. Esterhai and Cuckler shared the role of administrative chief resident and received the Deforest Willard Award for their outstanding service. After graduation in 1980, he was selected to remain on staff at Penn to help with Dr. Brighton’s large patient volume because of the latter’s international reputation for fracture nonunion care.

As an attending, Dr. Esterhai focused his energy on the care of patients who were unable to adequately care for themselves, a philosophy that has driven his entire career. He sought to establish relationships with patients, interested in the long term care of their problems. This coupled with his earlier personal experience with prolonged treatment after the ruptured appendix led to his interest in the care of patients with musculoskeletal infections and nonunions. There were no peripherally inserted central catheters or sophisticated soft tissue transfers. Patients frequently spent more than six weeks in the hospital, receiving intravenous antibiotics, extended wound care, and hyperbaric oxygen treatment. It was in the care of these patients that he also established a close relationship with the members of the Department of Infectious Disease.

As a young attending he joined a group of Infectious Disease physicians and orthopaedic surgeons in founding the Musculoskeletal Infection Society (MSIS) in 1989 in an effort to collaboratively advance knowledge in the field of musculoskeletal infection and its treatment. The MSIS has been instrumental in improving the quality of care for people with musculoskeletal infections. As one of its founding members, Dr. Esterhai’s focus on research and clinical care in the areas of osteomyelitis, antibiotic therapies, and the use of hyperbaric oxygen have resulted in his world-renowned expertise in the area. He has served as MSIS President twice, in 1997 and 2008.

Dr. Esterhai has had a deep commitment to veterans of the American military. Through his personal experience in the Air Force and his robust practice at the Philadelphia Veterans Affairs Medical Center (PVAMC) he has devoted considerable time and resources in their clinical care. As Chief of the Orthopaedic service at PVAMC since 2001, he interacts daily with administration, staff, and faculty involved in the treatment of US Military Veterans with musculoskeletal needs.

As a researcher, Dr. Esterhai’s primary interest has been in the field of musculoskeletal infection, particularly in the setting of traumatic injuries. He has produced two hundred twenty-five textbook chapters, original papers, and abstracts, been an editor for one research textbook, and presented nationally and internationally. He helped develop a platform for the research program at the PVAMC run by Drs. Mauck and Dodge.
Dr. Esterhai was privileged to work in Haiti with the surgical team from the University of Maryland after the 2010 earthquake. He and his family have worked with Orthopaedics Overseas in St. Lucia and faith-based Medical Ministry International in Jamaica and the Dominican Republic. He is on the Board of Directors of Orthopaedics Overseas, and he is a lifetime member of the Christian Medical and Dental Association. He would be among the first to remind that to whom much is given, much will be required, while affirming that none of this would be possible without the dedicated care supplied by the men and women of the University of Pennsylvania Health System.

Dr. Esterhai is described by his peers as a consummate physician, one loved by his patients, students, and staff. At the University of Pennsylvania, he is regularly mentioned by residents and attendings as an inspiration and as a role model to emulate. His patients are known to travel from around the country to see him, and many have been under his care for decades as they respect his opinion above all others. Dr. Esterhai exemplifies the traditional role of the physician who places patient needs above his own, and beyond his medical and surgical expertise, serves as a confident leader in his community. In the operating room, he ceaselessly engages the residents, sharing his surgical experience and encouraging physicians to always give the best care possible. Residents and colleagues regularly mention his calm yet commanding approach in the operating room, while maintaining his trademark humility, politeness, and kindness.

Outside of the field, Dr. Esterhai is recognized as a devoted and loving family man. Carol and he celebrated their 46th wedding anniversary. They have two grown children and six grand-children under the age of eleven. He frequently references their daughter and son and their families as a blessing in their lives. Carol and he share the joy at having them all within an hour of their home.

It is impossible to capture the breadth of Dr. Esterhai’s accomplishments, and the depth of his impact, within the confines of this journal. His glowing personality, his compassion, and his selfless focus on the well-being of those around him have served to inspire thirty-six years of graduating Orthopaedic Surgeons who have trained under his phenomenal mentorship. His contributions to musculoskeletal knowledge cannot be overstated, as his vision has resulted in changes to the very practice of Orthopaedic Surgery. Dr. Esterhai continues to see patients, teach, and conduct innovative research at Penn Orthopaedics, further solidifying his profound impact on his field and securing his legacy. Most importantly, he will be forever remembered by all who have had the honor and privilege to work with him as a dear friend and good man.
Thank you. Carol and I appreciate this honor. The dedication of this volume should never be about, or to, the two of us. This journal is about all of us together and our effort to learn, educate, and help the patients entrusted to our care now and into the future.

Some of Carol’s ancestors and mine have been here since before the Revolution. One, David Jones (1736-1820), was a chaplain with MadAnthony Wayne, one of Washington’s generals.

Growing up in Philadelphia after World War Two we were raised by men and women considered part of the “Greatest Generation”. Many of the men we knew had been away for as much as four years, fighting in one theater or another. Although the Lord didn’t call me to be a pastor, He did call me to be a physician using a ruptured appendix. Providential the way such an experience could define a vocation; what a blessing to have a firm goal from such a young age!

I can still remember my interview with Dr. Steinberg in 1975 in the days before the Resident Match. Carol and I were stationed on Okinawa, Japan. I had flown home to CONUS (Continental United States) on a KC-135 Air Force refueling tanker to interview. Frances Hickman (read Barb Weinraub 1975) was as gracious and affirming as Barb has been for each of us over the past three decades.

Then as now the research year was the best year of the residency. Six of the eight of us had the privilege of working with Drs. Black, Ralston, and Friedenberg in the lab even before it was McKay. To this day, though distracted, being able to work with Annamarie Horan, Rob Mauck, and their associates is energizing and the best part of many of my days.

Dr. Ralston, the first Penn chairman I knew, turned the reins of the department over to Dr. Bright on 1977 with this comment from Chronicles at the Resident’s dinner: “As long as he sought the Lord, God made him to prosper.” He did.

We still have the benefit of learning from some of the men who were my core mentors during residency: Drs. Carl Bright on, Malcolm Ecker, Bruce Heppenstall, Paul Lotke, and Marvin Steinberg. Unfortunately most reading this never knew John Greg, Jim Nixon, Ed Ralston, or Rudi Schmidt. Their legacy and memory lives on in Dr. Gentchos. All were excellent surgeons.

Dr. Lackman became chairman in 2000. We were at the Christmas party. The man who had been Chief of Orthopaedics at the Philadelphia Veterans Administration Medical Center had left the health system. Dr. Lackman asked me to take that role. My reasoned response that the veterans from Korea and Vietnam needed a sub-specialty educated total joint arthroplasty expert did not prevail. My sense of Penn’s mission and the importance of providing care for our veterans are described elsewhere in this volume. Leading means going first and being on point every day.

Dr. Heppenstall was the Chief of Orthopaedics at the Hospital of the University of Pennsylvania. Drs. DeLong and Born returned to Penn from Cooper University Hospital in Camden, New Jersey in 1996-7 and led the trauma service until November 2003. I had the opportunity to try to fill their shoes until February 2008 when first Dr. Mehta, then Drs. Ahn and Donegan returned. Those four years were very busy. Drs. Heppenstall, Keenan, Lackman, and Okereke were wonderful covering the operating room at HUP on those days I was at the VA. I asked my subspecialty partners to care for patients with complex elbow and shoulder injuries that I knew they could repair better than I. Patients with complex acetabular fractures were sent to subspecialty trauma orthopaedists at Hahnemann and Temple. Dr. Mehta has eloquently emphasized the team concept so vital to trauma care. The trauma division has been uniquely blessed by his leadership and the members of the team he has assembled, especially Adele Hamilton, our gifted in-patient nurse practitioner. After decades of Level I trauma care at HUP he has successfully led the transition of the orthopedic trauma service to Penn Medicine University City at 3737 Market, Penn Presbyterian Medical Center, and, under Dr. Donegan, Pennsylvania Hospital. Everyone involved has made that remarkable journey as seamless for our patients as possible.

Within the health system Level 1 care would be impossible without the best and the brightest: indefatigable residents and students who deliver personal, tender, hands-on attention through the full spectrum of care from the trauma bay to pre-op, intra-op, and post-op floor care and follow-up office visits. In so many ways it is the quality of our residents - mentally, technically, and humanistically - that determines the quality of each patient’s experience. The level of individual responsibility transcends that required in many other departments in the health system with full utilization of the skill sets available at all post graduate year levels.

Optimal patient care in the 21st century will continue to be a team effort, and that team must have the patient at the center. One of my professional goals has been to be a physician and a surgeon. Once physicians and especially surgeons were MDentities. Because patients have felt that we had a special position in their lives, they wanted us to be better than mere human beings. Yet, as our technical skills have improved, our professional reputations have suffered. We must encourage each other to try to be present in the moment. Patients understand that we are busy, but it only takes a few moments to really look into a patient’s eyes to pass back and forth the humanity that we share. We must acknowledge uncertainty and practice empathy. There are things that you and I don’t know. If we are unable to admit that to our patients they will feel manipulated by the covert understanding that we do.
know everything when it turns out otherwise. The reason so many families ask what we would do if the patient was our family member is because they want to know that we can stand in their shoes.

It is always a great honor when young people with whom you have worked choose to continue the relationship after their education. Carol and I could not be more thankful and proud of the superb orthopaedic surgeons who have elected to return to work at the University of Pennsylvania after being residents here. Each has chosen an unparalleled opportunity but at a personal cost of delivering care to patients regardless of their ability to pay.

The Department is on a wonderful trajectory: Dr. Levin’s dynamic leadership- likely without equal in the health system; nationally and internationally recognized basic and clinical research faculty with the highest levels of funding across disciplines; attractive new venues for care; academic partnership with the Children’s Hospital of Philadelphia (the premier children’s hospital in the nation); research and clinical faculty within the department and across the health system dedicated to teaching and mentoring; and the nation’s most capable resident physicians already delivering exceptional, personal care and preparing to advance the state of the art at twenty-first century speed into the future. None of this would be possible without the commitment at all levels by our excellent professional, administrative, and nursing members who make every encounter as productive and beneficial for our patients as they can be. Such care for trauma patients also generates tremendous paperwork. No one plans for “emergency trauma surgery.” Not one patient expected to be disabled. Each patient has forms for carriers, visiting nurses, primary care givers, employers, therapists, disability underwriters, medical assistance applications, or utilities. Most have attorneys. Over the years organizing, completing, and then following through with that aspect of care would be impossible were it not for the tireless work and meticulous attention to every detail by Lori Hardy, Kathy Pusicz, and Jeff Mack.

It is natural to be thankful in an environment with so many exceptional blessings and resources. I cannot express my gratitude for the opportunity to work with more than three hundred brilliant, indefatigable young men and women, each of whom wants to provide the best care possible for others. Every resident has made my patients’ experiences what they have been. Each of us must remember every morning that to whom much is given, much will be required. Consider these rhetorical questions: “For who is greater, the one who is at the table or the one who serves? Is it not the one who is at the table?” The man who asked the questions then completed his thought: “But I am among you as one who serves.” We speak in academic medicine of a lowly, three legged milk stool of research, education, and patient care. Even a child knows that a three legged stool is not going to be sufficient if one wants to reach as high as possible. When that is the goal one needs transcendent vision with top priorities of God, Country, and Family.

If the Lord wills it, my very best friend and I plan to leave day to day work with you next year for short term medical missions overseas again, not-for-profit boards, hands on service locally, and nurturing young families. Long into the future, I will commit to continue to pray for you.
It is our honor and privilege to dedicate this section of our journal to Barbara Weinraub, who has been the face of Penn Orthopaedics since 1991 serving the Department with profound dedication as the residency coordinator. “Barb” (as the residents and faculty affectionately call her) is a Philadelphia native, who has chosen to stay in the area her entire life. Barb admits to loving the Jersey Shore, and she particularly likes to spend the little free time that she has in Sea Isle. Ms. Weinraub can best be defined as a loving mother and grandmother. The mother of two and grandmother of five, she has also nurtured over 250 residents since she began to work at Penn. This is best illustrated by her great stories of the current leaders of our department as she remembers them as medical students and residents, applying and training in a different era of medical education. Barb has been an integral part of several transitions in the program: from the move from PAH to PPMC, to the most recent shift with the grand opening of the John J. Pryor Trauma Center, she has been a unique actor in the evolution of the residency. We wanted to give her reflections on her time in the program to be expressed in her own words in an interview format.

Barb, what has been your favorite part about working at Penn Orthopaedics?

The residents! I absolutely love spending time with the residents. I love working with all of you for five or six years at a time and watching you grow and change and learn, and I know how hard you work. I know some people call me the “Den Mother,” and I just love it.

How has your job changed since you started?

Well I started initially as a receptionist and switchboard operator in 1978. I had been a cocktail waitress at Tudor House, when my friend Louanne Henderson told me to apply for the job. My son was starting kindergarten, so I wanted a more stable job. In 1980, an office coordinator job opened, and I took it on Dr. Brighton’s recommendation. I trained under, and worked for, Francis Hickman for many years. She is deceased now, but she was my best friend and a wonderful mentor. She taught me everything I know. Then in 1991 I interviewed for the residency coordinator job and did that, along with being the faculty coordinator for all the paperwork and credentialing for the faculty. It’s definitely a lot more work now, and there are so many people to keep track of, but I’ve always loved it!

What has been your least favorite part about the job?

Well, there’s so much paperwork these days! Whether it’s duty hours or operative logs, getting everyone’s credentials in on time, submitting requests to the ACGME, running the OITE or inputting the monthly schedules, there’s always more to catch up on. Also, sometimes the faculty have disagreements about things and I get caught in the middle. I try and keep things calm but sometimes they just drive me crazy!

Do you have any regrets about your time at Penn Orthopaedics?

I have no regrets at all about my time at Penn. I am sad about all the people we’ve lost. Leo Leung passed away as a resident about to become chief, and that was very upsetting. We’ve lost other prior residents that went on to do other things but died as young men and women, and it really breaks your heart.

What sets Penn Orthopaedics apart from other residencies?

Well we have many attendings, who were residents here and chose to come back; that just shows you what type of place this is. People love working here; I spend a lot of time
with Ryan, Christos and Gabe as the chief residents, and of course they get frustrated by the chief resident job, but they’re always so nice to me and I think it’s the people that make this place so special.

What do you wish was different about Penn Orthopaedics?
I wish the residents had better schedules! I see how hard you all work and how much call and how many hours you have to put in, and I feel so badly for you. I know it’s part of your training, but I wish there was a way to make your hours better.

What do you think about the growth of the faculty in the recent past?
Well, it’s great for the residents. And I love them because so many of them were former residents, and some of my favorite residents! I remember all my residents, but some of the special ones came back to teach and work here at Penn, and I just love them: doctors like Samir [Mehta], Jaimo [Ahn], [Charles] Nelson, Brian Sennett, [John] Kelly. And there have been ones that always have a special place in my heart, like Randy Culp who is at the Philadelphia Hand Center.

What are your thoughts on the transition in leadership during your tenure here?
Well, I came to the department in 1978, right as Dr. Brighton was taking over for Dr. Ralston. He was a wonderful chair, and we’ve had so many wonderful doctors come through the department, in a lot of different roles. Obviously I worked closely with Dr. Lackman for many years, and I thought Dr. Sennett was such a good interim chief!

When Dr. Levin came here in 2009, he asked me to be his executive assistant and still do all the residency coordinator duties. I didn’t think I could do it, but he and Dr. Sennett insisted and I’ve been doing it ever since. I love Dr. Levin; he is so good to me and always makes me feel important to the program. His wife Helga has been incredibly helpful too. His schedule drives me crazy sometimes, but I love him to death.

What are you going to do now that you’re retiring?
Well I’ve got a big trip planned to Cancun in August with my family that I’m really excited for. I love to play games and babysit my grandkids, and I’m looking forward to spending more time with my husband and kids. We are trying to plan a cruise or two in the future with them.

Can we convince you to stay?
No way! I was making $700 a night as a cocktail waitress back in 1968; even if you offered me that much, I’m not staying!

Any final words to the residents?
I’m proud of you.

Since Barb joined Penn…

“Millenial generation” began… and all 42 current residents were born!
Over 275 residents have graduated from Penn Ortho
Hollywood has made over 18,000 movies
Invention of the internet, CD-ROM, and iPod
Smallpox eradicated, first human embryonic stem cells isolated, and first mammal cloned

Voyager 1 has traveled over 12 Billion miles
Worldwide population increased from 4.5 to 7.3 billion
Collapse of the Soviet Union, end of Apartheid, and demotion of Pluto as a planet
47 new countries were formed
8 US Presidents inaugurated
8 Constitutional Amendments passed
Subtrochanteric Femur Fractures: Optimal Incision Location for Clamp-assistant Intramedullary Nailing

Summary
Subtrochanteric femur fractures are technically challenging fracture patterns to treat. Securing and maintaining closed anatomic reduction is often impossible given the strong deforming forces. Open reduction through a small lateral incision allows for more control over the proximal fragment to facilitate reduction maneuvers. When put in the appropriate anatomic location a single lateral incision can be used for proximal fragment control and reduction as well as the site for placement of the cephalomedullary component of an intramedullary nail (IMN). We describe a technique for ideal placement of this incision to minimize incision size and number, limit soft tissue disruption, and facilitate open reduction.

Introduction
Subtrochanteric femur fractures are complex fracture patterns of the proximal femoral shaft associated with high complication rates and often require difficult reduction maneuvers to restore anatomic alignment. These fractures normally are treated with antegrade reamed intramedullary fixation with fixation into the femoral head. Other options exist, like fixed-angled plates, but are less frequently used due to the success of intramedullary fixation. Reconstruction intramedullary nails are the preferred design because the cephalomedullary component increases device to bone contact points in the proximal fracture fragment. Biomechanical studies revealed implant designs with more control in the proximal fragment, like reconstruction nails, allowed for less motion at the fracture site and improved stabilization in comminuted fracture patterns.

Previous reports document the rates of malunion and non-union of subtrochanteric femur fractures. As less than anatomic reductions are not accepted in these fracture patterns more surgeons are progressing to open reduction. Beingessner et al. recently published a retrospective cohort of patients with subtrochanteric femur fractures and more than half, 56%, required open reduction. In their series 55/56 patients who had open reduction, 98%, went onto union and maintained adequate alignment in both the sagittal and coronal planes. These results indicate open reduction as a safe method for treating patients with these injuries. Once the decision has been made to perform open reduction, determining where to place the incision can be complex. Goals include maintaining control of the proximal fragment with enough purchase to overcome the strong deforming forces. It is also important to consider that if a cephalomedullary component will be used, incisions should not be in locations that result in an area of avascular tissue. If one could predict where the cephalomedullary component would need to enter the skin, then a single incision could be used for both proximal fragment control and the head-neck fixation component. The technique described has proven to be provide a reliable method for identifying the ideal location for this incision and is currently used in practice.

Procedure
The patient with a subtrochanteric femur fracture is positioned either supine on a radiolucent (Jackson) table with the injured extremity draped freely and elevated compared to the contralateral side using a radiolucent bump or supine on a fracture table with the fractured limb placed in boot traction. Intravenous prophylactic antibiotics are given and the extremity is prepped and draped in the usual sterile fashion. An attempted closed reduction is performed by manipulating the limb with the use of traction and strategically placed bumps. If the fracture reduces easily, then a standard closed nailing is performed. If it is evident that the proximal fragment will not easily reduce, then the closed nailing is converted to a limited open nailing.

Location of the incision is determined by the following technique. The insertion jig with an aiming arm for the cephalomedullary fixation is assembled on the back table (Figure 1). Once assembled, the jig is placed on the anterior aspect of the prepped limb (Figure 1). Using fluoroscopic guidance, the jig is positioned such that the jig is superimposed with the nail entry point (Figure 2). The proximal and distal boarders of an incision needed for placement of cephalomedullary fixation is marked with a surgical pen with the jig overlying the extremity (Figure 2). The markings are used as a guide to make an incision about 3 cm long just posterior...
to the mid-lateral axis of the femur (Figure 2). This incision can be extended proximally and distally as necessary for open reduction and proximal fragment control. Superficial dissection involves incising the iliotibial band. The vastus lateralis is raised off the intramuscular septum while being mindful of perforating vessels. Deep dissection allows access to the femur for the placement of reduction tools.

Access to the femur at this level allows for control of proximal fragment in the face of deforming forces causing flexion, abduction, and external rotation (Figure 2). The cephalomedullary component can be passed through the same incision (Figure 3). With this technique, open reduction and internal fixation with a cephalopmedullary device can be performed on complex subtrochanteric femur fractures through three small incisions (Figure 3).

**Discussion**

We started using this technique for all subtrochanteric femur fractures that cannot be treated with closed reduction
By placing an incision in the correct location one can transform a complex femur fracture to a simpler pattern and therefore less stressful procedure. As these fracture patterns continue to increase in numbers as the population ages, it becomes all the more important for adult orthopaedic surgeons taking trauma call to know the techniques available to facilitate optimal treatment of complex fracture patterns.

Methods at our institutions. Patients of various BMI’s, both high and low, are amenable to this method. This technique is easily reproducible, takes minimal operative time, and decreases the likelihood of necrosing skin by minimizing the need for multiple incisions. The method described is an expansion on the previously described technique by Afsari et al. in JBJS 2010, where they first detail the use of reduction clamps and cerclage wires for open reduction methods in complex subtrochanteric femur fractures. By placing an incision in the correct location one can transform a complex femur fracture to a simpler pattern and therefore less stressful procedure. As these fracture patterns continue to increase in numbers as the population ages, it becomes all the more important for adult orthopaedic surgeons taking trauma call to know the techniques available to facilitate optimal treatment of complex fracture patterns.

Figure 2. (A) Jig superimposed on anterior aspect of prepped limb for determining incision placement; (B) Location of incision for cephalomedullary fixation & open reduction marked out; (C) 3cm incision marked of just posterior to the mid-lateral axis of the femur; (D) Single incision being used for open reduction.
References


Figure 3. Fracture reduction held with intramedullary fixation being placed on AP (A) and lateral (B) radiographs; Final AP (C) and lateral (D) radiographs after cephalomedullary fixation.
The Failed Pilon: Factors Associated with Delayed Amputation, Arthroplasty, or Arthrodesis after Open Reduction and Internal Fixation

Introduction

Tibial pilon fractures are high-energy axial injuries with metaphyseal comminution, multiple articular fragments, and significant soft tissue injury. Ruedi and Allgower in 1969 reported a successful series of pilon fractures treated with open reduction and internal fixation (ORIF), describing 4 principles that remain keystones to modern surgical treatment: restitution of the correct length of the fibula, reconstruction of the articular surface of the tibia, cancellous autograft, and medial support by a buttress plate. Early studies evaluating immediate ORIF of pilon fractures yielded very high wound complications, which led to the development of current two-stage treatment protocols—early external fixation followed by soft tissue rest, then delayed definitive ORIF. Despite a reduction in the soft tissue complications with modern protocols, pilon fractures continue to have high reported rates of post-traumatic arthritis, stiffness, persistent pain, and poor functional outcomes. The purpose of this study was to assess failure of pilon fractures treated with ORIF, comparing demographic and injury factors associated with delayed amputation, arthroplasty, or arthrodesis.

Materials and Methods

Study design was a case control with 1:1 matching for controls, by date of surgery. Inclusion criteria included: age > 18, OTA type 43B or 43C tibial plafond fractures treated with ORIF at a single institution. For the cases, “failure” was defined as amputation, arthrodesis, or arthroplasty performed at greater than 3 months post-ORIF. For controls, a minimum of 3 months of follow-up was needed. Demographic variables were collected, which included: age, gender, race, BMI, marital status, diabetes, vascular disease, smoking, alcohol, worker’s compensation. Injury variables were collected, which included: open vs. closed injury, OTA type, vascular injury, radiographic severity score, radiographic alignment, bone loss, impaction, anterior plafond impaction, fibula fracture location. Operative variables were collected, which included: single vs. two stage treatment of the pilon component, and need for flap coverage. Complications of minor infection (requiring oral antibiotics) or major infection (requiring operative debridement or intravenous antibiotics) were recorded. Univariate analysis was performed for each variable, with odds ratios reported, and significance at p > 0.05. Results were entered into stepwise logistic regression for variables with p > 0.1.

Results

Between January 2000 and May 2014, 1560 43B or 43C injuries were treated with ORIF. 37 met the inclusion criteria for failure (21 fusion, 9 amputation, 7 arthroplasty) and 37 controls were matched. The average length to follow-up was 764 days (cases) and 452 days (controls). Factors associated with failure were: OTA type (C-type OR 5.6, p = 0.01), two-stage management (OR 5.44, p = 0.02), minor infection (OR 7.9, p = 0.01), major infection (OR 12.6, p > 0.01), radiographic overall severity (p > 0.001), radiographic articular severity (p > 0.001), and anterior plafond impaction (p = 0.001). Stepwise logistic regression demonstrated major infection (p = 0.03), overall radiographic severity (p = 0.01), and anterior impaction (p = 0.006) to be most predictive of pilon failure.

Discussion

Multiple injury factors, including anterior impaction, overall radiographic severity and major infection were associated with failure of ORIF of tibial pilon fractures, which required delayed amputation, arthrodesis, or arthroplasty. Early recognition of the injury factors and early intervention, perhaps at the time of injury with a salvage procedure, may improve the reportedly high rates of poor outcomes following these injuries.
References

Operative Technique: A Modification of the “Push-Pull Screw” Distraction Technique for Obtaining Fibular Length

Introduction
Attaining fibular length during fixation of a comminuted distal fibula fracture is important to restoring ankle joint integrity and normal biomechanics. Restoring length of a comminuted fracture pattern utilizing a bridge plate construct can prove challenging, and in this manuscript we describe a modification of the “push-pull screw” distraction technique. Specifically, we distract using a laminar spreader with tongs placed between a “push-pull screw” and a threaded drill guide secured in a locking compression plate hole. This technique produces a force vector that both distracts across the fracture site to achieve length and pushes the plate onto its bony footprint. This method utilizes instruments commonly found on compression plating sets, and we have had good clinical and radiographic outcomes. We received IRB approval at our institution to review patients who underwent fixation using this technique.

Background
The goal of surgical fixation of ankle fractures is to restore the integrity of the joint and near-physiologic biomechanics. An asymmetry of the articulation between the talus and the tibia and fibula suggest ankle instability. A cadaveric study by Ramsey found that 1 mm of tibiotalar displacement may decrease ankle joint contact area by 42%.1 Restoring anatomic fibular length after lateral malleolus fracture is a well described radiographic parameter for assessing adequacy of a reduction. On an anterior-posterior radiograph disruption of the “ball sign” and on the Mortise view an abnormal talocrural angle are suggestive of fibular shortening.2 Attaining fibular length during open reduction and internal fixation can present a technical challenge, particularly when the fracture is comminuted. In this paper we describe a modification of a distraction technique using a “push-pull screw”3 and a lamina spreader for attaining length when bridge plating comminuted lateral malleolus fractures.

Preoperative Evaluation and Indications
This operative technique is useful in the setting of a comminuted and shortened distal fibula fracture amenable to bridge plate fixation. Preoperative evaluation is the same as for any ankle fracture, and includes a thorough physical examination with particular attention to the integrity of the soft tissue envelope and a standard series of ankle radiographs.

Procedure
The patient is positioned supine on a radiolucent table with a small bump under the ipsilateral hip to prevent external rotation of the extremity. A non-sterile tourniquet is placed on the proximal thigh, although we do not routinely inflate it during the procedure. The operative extremity is elevated on a radiolucent foam ramp to facilitate intraoperative fluoroscopy. The contralateral extremity is well padded and secured. The fluoroscopy unit is placed on the contralateral side of the table, and the fluoroscopy monitor is positioned at the foot of the bed. The injured extremity is then prepped and draped in the usual sterile fashion.

We prefer a direct lateral approach to the distal fibula in the absence of a posterior malleolus fracture in need of fixation. A 10 to 15 cm skin incision is made over the posterior aspect of the fibula centered over the fracture. The deeper tissue is incised in line with the skin taking care to protect the superficial peroneal nerve proximally and the sural nerve and peroneal tendons posteriorly. Careful placement of small Homan retractors facilitates exposure for deeper dissection. The fracture site is identified and exposed for evaluation of comminution severity. If the fracture is comminuted enough to preclude fixation with an absolute stability construct all efforts are made to preserve the periosteal soft tissue around the fracture site with the intention of placing an extraperiosteal plate. The dissection along the fibula is extended to accommodate a bridge plate of sufficient...
OPERATIVE TECHNIQUE: A MODIFICATION OF THE “PUSH-PULL SCREW” DISTRACTION TECHNIQUE FOR OBTAINING FIBULAR LENGTH

transitioned to a cam walker boot two weeks after surgery but remains non-weight bearing. The patient is re-evaluated six weeks after surgery and if there is evidence of fracture healing they are advanced to weight bearing as tolerated and prescribed formal physical therapy.

Postoperative Protocol

Immediately following surgical fixation the patient is immobilized in a short leg splint and instructed to be non-weight bearing on the operative extremity. If the patient has any risk factors for venous thromboembolism we prescribe a course of aspirin as prophylaxis. Patients return to the office two weeks after surgery for wound examination and suture removal. Our postoperative weight bearing protocol varies based upon the pattern of the ankle fracture (e.g., isolated fibula fracture versus a trimalleolar pattern). For example, in the case of a bimalleolar fracture pattern the patient is
in the setting of comminution utilizing a “push-pull screw”, threaded drill guide, and a lamina spreader with a bridge plate construct. Unique to our technique is the placement on the lamina spreader tongs between the “push-pull screw” and the threaded drill guide in the LCP (Figure 2). The tong located in the axilla formed by the threaded drill guide and the surface of the plate creates a downward force pushing the plate onto the bone in addition to the distraction force. This is an improvement over our prior experience of placing the tongs between the “push-pull screw” and the proximal end of the plate, which would create a troublesome lifting force that pushes the plate away from the bone while attempting to achieve distraction. We have had clinical success using our described technique in properly selected patients. A patient’s injury, intraoperative, and postoperative radiographs are included as an example (Figures 2 and 3). The technique is low risk and can be accomplished using instruments commonly found on commercially available fracture plating systems.

References

Discussion
Restoring fibular length during ankle fracture fixation is important to restoring joint stability and biomechanics. This paper describes a technique to achieve fibular length
Circumferential Negative Pressure Wound Therapy for Lower Extremity Fractures: A New Technique

Introduction

Soft tissue edema resulting from trauma is a major obstacle in expeditious and successful care of lower extremity fractures. Techniques that can alleviate or mitigate post-injury and postoperative edema are of great use in the care of lower extremity fractures. Since the development of negative pressure wound therapy (NPWT), the nature of traumatic wound management has significantly changed. We propose that circumferential NPWT can help decrease time to definitive fixation and prevent the number of postoperative wound complications in lower extremity fractures.

Previous methods used to accelerate resolution of edema incorporate passive techniques that can lead to a prolonged and unpredictable course, ultimately delaying definitive treatment. Early reports on intermittent pulsed compression devices have not yielded significant improvements compared to more conventional techniques. While early fracture care is preferred, premature intervention can lead to compromised soft tissue envelopes. Staged protocols have been shown to be beneficial in the management of these injuries, however, only passive techniques have been employed to deal with both post-injury and postoperative edema.

NPWT has been shown to be beneficial in the management of soft tissue injuries after significant trauma. It has been successfully utilized over operative incisions in the acute postoperative period of operatively treated fractures. In this article, we describe a new technique, which actively employs circumferential NPWT applied to the zone of injury or postoperative extremity, to help reduce both the time to definitive fixation and postoperative wound complications.

Materials and methods

This technique consists of using circumferential NPWT over the entirety of the distal tibia, ankle, and foot to prevent excessive postoperative edema as well as accelerate its resolution. The application requires basic NWPT dressings including an open pore sponge, semi occlusive dressing (petroleum gauze), airtight adhesive dressings (such as iodophor impregnated adhesives), and a negative pressure source. All of these are readily available at most hospitals and are simple to apply and operate. Additionally, they can be maintained under splints, around external fixators, and over both open and closed wounds.

For preoperative application, the zone of injury is dressed with non-adherent petroleum laden gauze. The entirety of the skin is covered so that none of the sponge directly contacts the skin. The sponge is then applied in a circumferential fashion around the distal extremity taking great care so that no area of skin is directly exposed to the sponge. A larger sponge can be cut so that it folds around the ankle, hindfoot, and forefoot in one continuous sleeve or multiple sponges can be combined within one semi-occlusive dressing. When placing one large sponge around the entire distal extremity, slits should be cut two thirds of the way down the long axis of the sponge, each one third of the total width of the sponge. This can then be placed on the anterior aspect of the leg with the slits at the level of the ankle and the distal third of the sponge on the plantar aspect of the foot. A corresponding sponge can then be placed on the anterior aspect of the distal leg with a fold at the ankle and distal third of the sponge on the dorsal aspect of the foot. The NPWT system is then set to 125mm Hg continuous therapy in conjunction with strict elevation and non-weight bearing precautions.

Postoperatively, the entirety of the surgical site should be covered. Our practice is to keep the dressings in place for at least 5 days.

Results

Between August of 2012 and September of 2014 this technique was utilized successfully in four patients during the acute postoperative period. Of those four, three were fractures of the talus that underwent open reduction and internal fixation through dual medial and lateral approaches and one was a trimalleolar ankle fracture treated acutely with open reduction and internal fixation.

None of the four patients had serious wound complications that necessitated reoperation and none required an extended course of antibiotic therapy. One incision had mild drainage after discontinuation of circumferential NPWT that resolved with superficial wound care. No patient had any wound complication related to
rates of complications still remain high. Vallier et al. reported a wound complication and infection rate of nearly 9% (3.3% superficial wound, 3.3% wound dehiscence, 5% deep infection).11

In operatively treated calcaneal fractures, Folk et al. found an overall wound complication of 25%.12 Howard et al. performed a RCT comparing nonoperative versus operative management of displaced intraarticular calcaneal fractures and found that 16% had superficial wound slough with 4.4% going on to deep infection early and 0.4% going on to deep infection late.13

Conclusion

Circumferential NPWT for pre and postoperative edema control is a simple, noninvasive method to accelerate edema resolution preoperatively and mitigate high rates of wound complications in lower extremity fractures.

References

An Economic Evaluation of Posterior Spinal Fusion for Adolescent Idiopathic Scoliosis (AIS)

Introduction:
Rising healthcare costs in the United States have led to increased scrutiny of elective procedures in healthy adults and children.\(^1\) With annual health care expenditures estimated to be more than 100 billion dollars,\(^2\) spinal disorders get particular scrutiny because they are so expensive to treat. Some have suggested that the natural history of AIS is not terribly negative, with only minimal impact on functional activities compared to the general population.\(^3\) Thus, the overall value of spinal fusion procedures in healthy adolescents is unclear, and could be perceived as cost-inefficient.

To the best of our knowledge, there are no published studies that examine cost-benefit tradeoff of the surgical management of AIS while accounting for uncertainty in costs and gains. This study seeks to evaluate whether surgical intervention for AIS is cost-effective for patients who elect to undergo a spinal fusion procedure.

Material and Methods

Cost Determination
Costs are defined as the sum of direct costs associated with the post-operative hospitalization plus the professional fees for the surgeon and anesthesiologist. Indirect and opportunity costs were not included. To derive the mean and interquartile (IQR) range for hospitalization costs, itemized cost values reported in a recent cost-analysis by Kamerlink et al\(^4\) were used. Differences in cost related to severity of curvature are accounted based on Lenke-type curve prevalence in the general population.\(^5\) Physician fees were estimated from the CMS 2012 physician fee schedule for CPT codes 22802 (posterior arthrodesis for spinal deformity), 22843 (posterior segmental instrumentation), and 00670 (anesthesia for extensive spinal procedure). Billing for anesthesia services was based on an average procedure time of 338 minutes.\(^6\)

Health Related Quality of Life (HRQL)
A literature search was conducted on the PubMed database using the key words, “adolescent idiopathic scoliosis quality of life”, “adolescent idiopathic scoliosis HRQL”, and “adolescent idiopathic scoliosis effectiveness”. The search identified fourteen studies examining postoperative changes in HRQL attributed to surgery.\(^7\)\(^-\)\(^20\) These studies measured quality of life in AIS patients using the SRS24, SRS22 or SF36 survey instruments. The scoring used by different instruments was normalized to a scale of 0-1, with 0 representing death and 1 representing perfect health.

Average Cost per QALY ratio
The ratio was calculated by dividing total costs by QALY gains accumulated over the lifespan. This was considered to be the base case. We used the standard discount rate of 3% per annum.\(^21\) Two-way sensitivity analysis is then built upon to base case to allow the cost and QALY gain inputs to take on a range of values spanning the IQR for each variable. This was done to stress test the model to determine cost per QALY ratio in less favorable conditions.

Monte Carlo Analysis
Next, we introduced new variables, including additional costs and the impact on QALY gains resulting from surgical site infection (SSI) or death into the model. Compared to literature, chance of successful surgery and the chance of developing an infection are deliberately estimated to be somewhat lower and higher, respectively.\(^22\)\(^,\)\(^23\)

Namely, probability of complication-free surgery is 90% +/− 10%. Of those who sustained a complication, an estimated that 90% +/− 3% is accounted for by infection. Each infection is estimated to add $10,000 in costs with a standard deviation of $2,000.\(^24\) We also attribute to infected cases a hypothetical range of 30% +/− 10% loss in QALY.

This model was simulated 1000 times, representing 1000 hypothetical patients, with each case visualized as a dot in Figure 2.

All analyses above were performed using TreeAge Pro 2012 (TreeAge Software, Williamstown, Massachusetts) and summarized in a decision tree in Figure 1. Data inputs for the model are summarized in Table 1.
Table 1. Cost Analysis Model Inputs

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<td>Total Cost</td>
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Utility (Quality of life)

- Preoperative: 0.764 (8, 16-20)
- Postoperative: 0.843 (0.82, 0.864, 7-20)

Discount Rate

- 3% (21)

Patient Characteristics

- Life Expectancy (yrs): 78.1 (WHO)
- Age at initial operation: 14.3 (8, 16-20)

Results

In the base case analysis, having a spinal fusion for AIS yields an overall gain of 2.22 QALYs and cost of $35,786, which yields a cost per QALY ratio of $16,114 per QALY. When subjected to two-way sensitivity analysis by varying both costs and QALY over the IQR, the range of average CER was $10,167 to $40,133.

Using Monte Carlo simulations in Figure 2 to model the hypothetical impact of infection or death, decision to undergo surgery is below the threshold of $50,000 per QALY greater than 99% of the time.

Discussion

As demonstrated by our base case estimates, the ratio of $16,114 per QALY is below the traditional $50,000 WTP threshold, and when compared against other surgical interventions in orthopaedics, the surgery for AIS ranks favorably.

Given potential uncertainty in cost and HRQL, we stressed the model using two methods. First, we employed two-way sensitivity analysis to account for variation in both cost and HRQL; and second, we used Monte Carlo analysis to simulate the impact of a hypothetical complication. From the model,
even an operation with higher cost due to complication and lower QALY gains due to infection could achieve a ratio less than the benchmark of $50,000.

There are a few limitations to this study. First, costs attributed to surgery were based on a single-center study by Kamerlink et al. In their study, success rate was high with few readmissions, and cost variability was mainly attributed to differences in Lenke curve types. We recognize that these costs may vary by location, complication rates, and other downstream costs.

Second, physician fees may depend on geography, hospital contracts with payers and hospital payment procedures. This study attempted to use standardized national CMS data to broadly reflect a nationally representative cost, but may not be representative for a specific patient living in a specific locale.

Third, all data used are derived from retrospective observational studies. Lack of high quality data on cost and outcomes continues to be a challenge. Fortunately, SRS questionnaires are validated and accepted instruments for measuring quality-of-life in AIS patients. While data from these studies were not summarized using traditional meta-analysis methods, we feel that they provide an accurate estimate of the population level QALY gains.

**Conclusion**

Despite these limitations, this study is the first to use standard cost-analysis methodologies to provide a general estimate of the cost per QALY ratio of surgery in AIS. Our data demonstrates that the surgical management of AIS is cost-effective by traditional healthcare standards. As more comprehensive data on downstream costs, family burden, and complication rates become available, these models can serve as a framework for ongoing value analyses of AIS operations.

**References**


Spinal Deformity Surgery in a Limited-Resource Environment: Trinidad, West Indies

Introduction

Access to care is a major obstacle to the worldwide treatment of spinal deformity. While surgical correction is often considered a resource-intensive intervention, we aim to report the perioperative safety of a series of procedures performed in a limited-resource environment.

Materials and Methods

We performed a retrospective review of a non-consecutive series of posterior spinal fusions (PSF) from 2006 to 2013 in Trinidad, West Indies. All procedures took place in operative suites that include C-arm fluoroscopy, cell-saver, and total-intravenous anesthesia capability. No intensive care unit (ICU) was available on site. Additional donations included instrumentation and intraoperative neuromonitoring services. Primary outcome measures were surgical time, estimated blood loss (EBL), and complication rates at a minimum of three months postoperatively. We hypothesized that our series would demonstrate perioperative safety comparable to reports in the literature.

Results

A total of 56 procedures were performed, including 45 primary PSF, 8 revision PSF, and 3 growing constructs, all via posterior-only approaches. Of the 45 primary PSF, there was a minimum three month follow-up data for 37, with a median follow-up of 12 (range 3-36) months, including 11 males and 26 females at a median age of 16.4 (9.5-46.9) years. Diagnoses included idiopathic (n = 28), congenital (n = 5), and neuromuscular (n = 4) scoliosis. Median surgical time was 5.0 (2.8-8.8) hours and EBL was 1,300 (261-2,517) mL. Complications included two unplanned transfers for ICU care, two infections (one superficial, one deep), one pneumothorax, one instrumentation failure, and one dural tear. All intraoperative neuromonitoring events reversed with appropriate measures, and there were no neurologic complications or mortalities. Median major curve Cobb angle preoperatively was 80 (50-120) degrees, and at last follow-up 30 (0-70) degrees, with a median correction of 61 (30-100) percent.

Discussion

Spinal deformity represents a substantial worldwide burden of disease with similar impacts on health-related quality of life across a wide range of cultures and locations. Surgical correction of spinal deformity is a complex and resource-intensive intervention with the potential for severe complications, and there is limited agreement on standards of care for surgical treatment. Even within developed nations, significant variability exists with regard to rates and types of interventions performed.

Few reports exist of clinical outcomes following non-tuberculous spinal deformity correction using modern spinal instrumentation techniques from sites within the developing world. Unnikrishnan et al reported retrospectively on a series of 235 patients undergoing surgical correction of adolescent idiopathic scoliosis. Of this series, 123 patients underwent all-posterior correction and fusion with pedicle screw or hybrid constructs. Mean percent major curve coronal plane corrections varied from 58 to 84% depending on fixation strategy, with improved corrections seen in the all-pedicle screw group. A total of eight complications (3.4%) were reported, including one mortality due to vascular injury during anterior surgery, three neurologic deficits (two full recoveries, one partial recovery), three infections, and one pseudoarthrosis. Nemani et al also reported on a series of 29 patients that underwent spinal deformity correction following the use of preoperative halo-gravity traction, 21 of whom had deformities not secondary to spinal tuberculosis. They observed a mean preoperative major curve correction of 31% with halo gravity traction, with a mean final 56% correction postoperatively. Greater corrections were achieved in patients with pure scoliosis as opposed to kyphosis, and only one three column osteotomy was required in the non-tuberculosis group. There were no neurologic complications with traction, and only one transient neurologic complication postoperatively following a two-level vertebrectomy. In addition to facilitating surgical correction, the authors postulate that traction may have other potential benefits in terms of preoperative optimization of pulmonary...
Figure 1. Preoperative clinical photographs and posterior-anterior radiograph of a 13 year old female with severe idiopathic kyphoscoliosis treated in 2014 at the Princess Elizabeth Centre, Port of Spain, Trinidad, West Indies. The preoperative major curve Cobb angle measures approximately 160 degrees.

Figure 2. Postoperative clinical photographs and chest radiograph of the same patient following two weeks of halo-femoral traction and subsequent T3-L4 instrumented posterior spinal fusion with multiple Ponte osteotomies and bilateral costectomies. The postoperative major curve Cobb angle measures approximately 70 degrees.
function, nutritional status, and even mental health. This technique may be especially useful in ameliorating the challenges specific to performing spinal deformity correction in the developing world. These series and our results are largely consistent with reports from similar procedures performed in developed nations.6,7

Conclusion

The complication rates and corrections in our series compare favorably to those reported from the developing world as well as institutions with greater resource availability. By achieving these results with relatively small donations of time and equipment, the authors hope to encourage the ongoing expansion of spinal deformity outreach work to other underserved areas.

Acknowledgements

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References

Avoiding Pedicle Subtraction Osteotomies with Hyperlordotic Anterior Cages. A Case Report

Introduction

JP is a 54-year-old male, who presented with a chief complaint of inability to stand up straight, and increasing low back pain, since being struck by a car 10 years ago. He had tried several courses of epidural injections and physical therapy without any improvement. His medical history is significant for hepatitis C and hypertension. The patient described the pain as a constant dull ache. 95% of his pain was lumbago, and 5% was radicular pain. Patient denied any radiation of pain beneath the knees. Pre operative examination revealed a severe sagittal imbalance with the plumb line falling 45 cm in front of his femoral heads. There was a fixed loss of lumbar lordosis, with no associated hip flexion contracture. Patient had a stopped forward gait, with significant flexion of the knees. His lower extremity neurological exam was normal. No examination findings consistent with myelopathy or radiculopathy were elicited.

Radiographic examination revealed a severe sagittal deformity. Lumbar Cobb angle was 10 degrees of kyphosis and a positive sagittal balance of 51cm. His pelvis was severely retroverted. Patient had a pelvic incidence of 64 degrees, a sacral slope of 24, and 40 degrees pelvic tilt. Deformity was fixed with no correction on supine extension films.

Procedure

Patient was taken to the operating room for staged anterior correction of deformity and posterior instrumentation and fusion. Anterior releases were carried out at L3/4, L4/5 and L5/S1. 20, 20 and 30 degree hyperlordotic cages were placed at L3/4, L4/5, and L5/S1 respectively. Anterior instrumentation was placed prevent kick out of the cages between the two stages. Screws were only placed through the inferior holes on the cages, to allow further correction during posterior component of procedure. To enhance fusion, the cages were packed with calcium phosphate soaked in autogolous marrow aspirate.

On the second post operative day, posterior instrumentation from T3-Pelvis was conducted with Smith-Peterson osteotomies at L1/2, L2/3, L3/4, and L4/5. Fusion was obtained with local decortication and BMP application.

Overall blood loss was 2000ml for anterior surgery and for 2000ml posterior surgery. Post-operatively the patient had normal neurological function. Radiographs post operatively revealed a positive sagital balance of 2cm, and a lumbar Cobb angle of 65 degrees lordosis.

Discussion

Sagittal balance is assessed by drawing a vertical plumb line from middle of C7 vertebrae and assessing where it lies in relation the posterior superior corner of the S1 vertebral body. Neutral alignment is defined as the C7 plumb line intersecting the L5/S1 disc space. Positive sagittal balance is defined as the plumb line is anterior to S1 vertebrae. This occurs in conditions that lead to a loss of lumbar lordosis (such as degeneration)

Positive sagittal balance has been shown to be the radiographic parameter most closely linked with adverse health stats outcomes and severity of symptoms increases in a linear fashion with increasing positive sagittal balance.1,2

It has been shown that restoring sagittal balance to within 5cm of neutral is associated with improved pain relief following adult spinal deformity surgery.3

Failure to correct sagittal balance is associated with an increased risk of junctional kyphosis and pseudoarthrosis of posterior fusion.5

Correction of sagittal plane deformities can be achieved with posterior based osteotomies, and or anterior and posterior fusion. Depending on the degree of correction desired at individual levels 2 main options are available to the operative surgeon.

The Smith-Peterson Osteotomy (SPO) is a resection of the posterior elements of the spinal column, by closing the wedge posteriorly the disc space opens anteriorly. This requires a compliant disc space. At each level a SPO can correct 10° of sagittal balance.4 In this case this would have required more than 8 SPO with the risk of not enough correction as the anterior column was fixed, and the disc space may not
have opened up during correction. SPO’s have also been associated with a loss of reduction over time.

The Pedicle subtraction Osteotomy (PSO) is a V shaped resection of the posterior elements and vertebral body. A PSO can correct 30° per level.5,6 Given the greater correction obtained with a PSO, several authors have suggested utilizing PSO’s for corrections greater than 10cm of sagittal imbalance.4,5 However in this case to achieve enough correction this would have required doing two PSO’s, typically one at L2 and the other one at L4. PSO’s are associated with 8% rate of neurological compromise per level,6 and significantly higher blood loss when compared to a 3 level SPO (1.4 vs 2.6L).5

In this case the use of hyperlordotic anterior cages provided sufficient correction and stability, obviating the need for PSO’s, and theoretically avoiding their increased complication rate. In total 75 degrees of sagittal plane correction was obtained with a combination of anterior cages and SPO’s. It was felt that the majority of the correction was obtained with the initial anterior surgery and hyperlordotic cage insertion. The SPO’s were carried out to ensure the relative hyper extension of the lumbar spine didn’t impinge upon neural structures, and to allow fine tuning of the correction at the level and above the anterior fusion.

In summary we present the use of anterior hyperlordotic cages as an alternative to PSO’s in severe sagittal imbalance where the deformity is rigid but not fixed.

References
Operative Repair of an Adolescent Knee Dislocation: A Case Report

Introduction

A knee dislocation involves a multi-ligamentous injury (MLI) that result in disruption of the tibiofemoral articulation. These are an uncommon orthopedic injury with prevalence between < 0.02% and 0.2% of orthopedic injuries. In adults, these injuries can occur in high energy trauma, such as a motor vehicle collision, or through low energy mechanisms, typically related to sports injuries. Low velocity injuries have been reported to be more common, representing up to 75% of MLI knees. Knee dislocations during sports occur with excessive varus or valgus force on a hyper-extended knee. The increased size and strength of athletes in today’s contact sports may lead to higher collision forces that are capable of causing a MLI. In reviewing current literature, there are no examples of MLIs specific to adolescent patients. Musculoskeletal injuries in the immature musculoskeletal system require a different set of considerations than injuries in adult individuals. In this case report, we describe a sports related MLI knee in an adolescent athlete with open physes. Written authorization for this case report was provided by the patient’s family prior to its submission.

Case Information

A 13+0 year-old male football player was tackled in a game, resulting in a lateral femorotibial dislocation (Figure 1). He was reduced and transferred to our facility. Upon arrival, he had a normal neurovascular status, confirmed by ultrasound, but the knee was unstable. He was Tanner III with open growth plates. Magnetic resonance imaging (MRI) study demonstrated complete tear of anterior cruciate ligament (ACL), medial collateral ligament (MCL), and avulsion of the posterior cruciate ligament (PCL) off of the medial femoral condyle, a Schenck Classification KD-IIIM (Figure 2). Fifteen days post-injury, the patient underwent arthroscopic PCL suture repair over a bone bridge and excision of the ACL remnant. The patient’s distal femoral growth plate was open, so intra-operative fluoroscopy was utilized to ensure the physis was not breached during tunneling. Two weeks post-operatively, the patient began a standard PCL physical therapy protocol. At 2 months, repeat MRI demonstrated healing of the MCL and repaired PCL. Four months post-injury, he returned to the operating room for trans-epiphyseal ACL reconstruction with autologous hamstring graft, sparing the femoral physis but traversing the tibial side.

The patient was started on a standard ACL reconstruction physical therapy protocol post-operative day one. He was cleared for moderate sports training, with no cutting, three months after surgery. He began sport-specific training five months post-operatively and returned to all activities, including competitive football, ten months post-injury. Over the following year he excelled as a three sport athlete. Final follow up at 26 months post-injury demonstrated full athletic function, no growth restriction, pain, mal-alignment, ongoing instability, arthrofibrosis or hardware irritation/prominence.

Prior Reports and Relevant Literature

Knee dislocations are uncommon, and are even rarer in the presence of open physes. Existing studies of MLI demonstrate high variability in study sample size, injury severity, concomitant injuries, and treatment techniques. Furthermore, the lack of subjective outcome
instruments designed for these injuries makes outcomes comparison difficult. Prior literature rarely includes skeletally immature patients. A meta-analysis of 31 patients from 2000 - 2010 showed an average age of operatively treated patients to be 30.5 (range 22-35.1) years, and was similar to a previous aggregate of studies published before 2000.6,7 Bui et al examined 20 patients with knee dislocations over a 6 year period.3 Of these, three were 15-16 years of age, however, there was no comment on their physeal status. Two of these patients sustained their injury during sports, with one undergoing surgical repair. No outcome data was given. Two epidemiological studies included 255 children with traumatic knee injury and hemarthrosis examined by MRI or arthroscopy and demonstrated zero patients with knee dislocation.8,9 This report provides a treatment modality for a rare injury that led to complete return of function.

Discussion

Although the treatment approach of isolated ligamentous injuries is accepted, these principles cannot be extrapolated to MLIs. Unfortunately, no prospective study exists comparing surgical with non-surgical management. Non-operative management with prolonged immobilization has been associated with loss of motion, residual instability, and poor knee function.10-12 The goal of surgery is to improve stability, retain motion, and achieve knee function that allows the patient to perform daily activities. However, the timing, graft selection, and surgical technique of MLI reconstruction remains debatable.13-15 Delaying surgery 10-14 days allows for resolution of acute inflammation and soft tissue swelling, and has been shown to reduce the risk of post-operative arthrofibrosis secondary to improved ROM and quadriceps strength.16 In a large systematic review, staged treatment of KDIII or IV was found to yield the highest percentage of excellent and good subjective outcomes and the least number of ROM deficits.15 Repair of the PCL should occur first because PCL deficient knees result in posterior sagging that puts the knee in a state of misalignment, which is detrimental to healing of ligaments and the joint capsule. Open physeal plates complicated operative management of adolescent patients with MLI. In the initial repair of the PCL, the distal femoral physis was spared in order to avoid causing a growth disturbance to the affected leg. The repeat MRI obtained after just prior to the ACL reconstruction demonstrated interval closure of the proximal tibial physis so the tibial physis was not spared and a standard tibial tunnel was created (Figure 3). Post-surgical stiffness and loss of knee motion remain the primary post-operative concern. Rehabilitation protocols emphasize early protection with immobilization and gradual return to activities, but the clinician must balance these against the risks of loss of stability and failure of the reconstructed ligaments.

Conclusions

Given the low incidence of adolescent MLI, high-level evidence on which to base treatment decisions will be difficult. In this case report we have shown successful reconstruction of a knee MLI in a physeal immature patient. While further studies are needed to confirm the beneficence of our treatment plan, we believe this treatment approach can produce a positive outcome.
References

Non-Arthroplastic Treatment of Glenohumeral Osteoarthritis

Introduction
Osteoarthritis of the glenohumeral joint is a common cause of pain and dysfunction. For active individuals, it can have a dramatic impact on quality of life due to limitations in range of motion and pain resulting in significant restriction of activities. A variety of treatment options exist for glenohumeral arthritis ranging from non-operative modalities to total shoulder arthroplasty. However, the diagnosis of early osteoarthritis is difficult to make based on radiographs alone, as articular cartilage loss can be underappreciated in the absence of joint space narrowing. The decision to recommend arthroplasty becomes increasingly challenging when caring for younger patients. Outcomes of shoulder arthroplasty in patients younger than 60 years old are less predictable, and therefore may not be the best option for that particular population. It is also possible that total joint arthroplasty may be contraindicated in young patients due to functional limitations that the procedure presents postoperatively. Not to mention the belief that younger patients’ propensity to place greater stress on the prosthesis may result in premature prosthetic loosening, destruction of bone stock, and therefore enhanced complexity of revision surgery.

The purpose of this review is to evaluate the effectiveness of alternative methods for the treatment of glenohumeral arthritis using non-arthroplastic techniques.

Materials and methods
A literature search was performed using the National Center for Biotechnology Information, National Library of Medicine Databases and Google Scholar. Inclusion and exclusion criteria are listed in table 1.

Inclusion criteria were determined based on type of procedure, follow up for patients involved, and reporting of pre-op and post-op pain levels. Non-arthroplastic procedures also include palliative treatments, injections, and biologics such as platelet enriched plasma. Exclusion criteria were determined based on type of treatment, location of treatment, and whether or not treatment was performed on human patients.

Results
The literature revealed many alternatives to arthroplasty which can be considered for younger patients (less than 60 years of age) who are diagnosed with mild-moderate glenohumeral arthritis. Table 2 displays the efficacy of the non-arthroplasty procedures that were reviewed. Failure was based on whether or not the patient progressed to full arthroplasty or saw no decrease in pain.

Discussion
Eustace et al studied the effect of corticosteroid injection (triamcinolone) patients with chronic shoulder pain. When injections were accurately placed, patients reported greater pain relief compared to the patients with inaccurate injection. However, the benefit of corticosteroid injection did not reach clinical significance.

Nizlan et al investigated arthroscopic suprascapular neurectomy. He utilized a shaver and a radiofrequency device to decompress the nerve within the spino-glenoid notch. 75% of the patients reported good-excellent results post-operatively. The authors confirmed the effectiveness of suprascapular neurectomy as a viable procedure in selected patients.

Table 1.

<table>
<thead>
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<th>Criteria</th>
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<tr>
<td></td>
<td>non-Arthroplasty procedure</td>
<td>total shoulder arthroplasty</td>
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<tr>
<td></td>
<td>follow up</td>
<td>animal studies</td>
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<td></td>
<td>pre-op and post-op pain levels reported</td>
<td>Procedure not performed on glenohumeral joint</td>
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Cameron et al, McCarty et al, and Richards et al present data on the outcomes of arthroscopic debridement with or without capsular release. These studies support the role of arthroscopic debridement in the treatment of patients with moderate degenerative changes. However, less favorable results were seen in those patients with severe arthritic changes. Specifically, patients with early grade IV osteoarthritis with lesions less than 2 cm in diameter reported significant pain relief and gain of function. Additionally, it was concluded that patients with unipolar lesions had significantly greater outcomes than patients with bipolar lesions. It is therefore safe to conclude that arthroscopic debridement with capsular release can delay more significant procedures while improving pain and range of motion.

Millet et al examined outcomes of the comprehensive arthroscopic management procedure (CAM). The CAM procedure involves glenohumeral chondroplasty, humeral osteoplasty, osteophyte resection, capsular release, subacromial decompression, axillary nerve neurolysis, biceps tenodesis, and removal of loose bodies. Significant pain relief was observed in 80% of patients. The authors successfully showed that the CAM procedure improved pain, function, and provided a joint sparing alternative to arthroplasty.

Savoie et al investigated arthroscopic resurfacing of the glenoid using a Restore biologic patch combined with capsular release. 65% of patients reported satisfaction at final follow up with only 22% going on to arthroplasty. They concluded that biologic resurfacing provided significant improvement for young patients diagnosed with severe glenohumeral arthritis.

Muh et al studied patients upon which he performed open resurfacing of the glenoid and capsular release. He utilized Graftjacket in seven patients and achilles tendon allograft in nine patients. 44% of patients required conversion to total shoulder. Because of the high failure rate, Muh et al felt that their hypothesis, that biologic resurfacing would be a durable solution for early shoulder arthritis, was inconclusive.

Strauss et al reported on 45 patients that underwent open biologic resurfacing using a lateral meniscus allograft combined with prosthetic humeral head resurfacing or replacement. 51% of patients went on to conversion to total shoulder arthroplasty, or had an ASES score of less than 50 points on a post-op survey. Strauss et al described their results as having an unacceptable failure rate and proposed that biological resurfacing may have little to no role in the treatment of glenohumeral arthritis.

After reviewing the relevant literature, it would appear that some common patterns have emerged with regard to particular procedures. Arthroscopic debridement is most successful when performed in young patients (≤ 60), on lesions less than 2 cm in diameter, and with patients presenting with unipolar lesions of the glenohumeral joint. Although outcomes have shown good results, patients who fail arthroscopic debridement accept poor outcomes or go onto arthroplasty.

Patients who underwent biologic resurfacing have received mixed results. However, Savoie et al demonstrated positive outcomes in their cohort of patients receiving arthroscopic biologic resurfacing. Muh and Strauss both reported negative outcomes for their procedures using biologic resurfacing with and without utilization of prosthetic humeral head resurfacing. It is worth noting that each of the authors used different materials for grafting during their respective procedures and that the severity of arthritis may be variable from group to group. Therefore, it is possible that more research needs to be conducted on the material used in resurfacing procedures and their respective indications in order to conclude in regards to possible outcomes.

**Conclusion**

Determining the proper treatment plan for patients with glenohumeral arthritis depends on a multitude of factors including the patient’s age and desired activity level, severity of arthritis, and extent of dysfunction. A variety of non-arthroplastic treatment options exist for the younger cohort and/or those presenting with only mild-moderate glenohumeral osteoarthritis. Patients undergoing non-

<table>
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<th># of Patients</th>
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<tr>
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<tr>
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<td>34</td>
<td>Minimal</td>
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Table 2.
arthroplastic treatments have demonstrated improved function, decreased pain, and improved quality of life. As research advances, new methods of treating glenohumeral osteoarthritis may emerge. Biologics such as platelet-enriched plasma are showing promise in pain reduction and may one day play a role in the treatment of osteoarthritis.13

References
Post-Traumatic Patellofemoral Joint Ankylosis

Introduction
Post-traumatic knee stiffness following peri-articular fractures is not a rare occurrence. Limitations in range of motion can be attributed to flexion contracture, extension contracture, or a combination of both. The etiology of the contracture must be considered prior to treatment. Intra-articular scar tissue and/or bony impingement can contribute to contracture, but extra-articular muscular adhesion to bone, or adhesion between soft tissue layers must be considered as well. In this case report, we found arthrofibrosis of the patellofemoral joint to be the unexpected and, to our knowledge, previously un-reported etiology of post-traumatic knee stiffness.

Case Information
A 56 year-old female sustained a tibial plateau fracture due to a motor vehicle collision in May 2013 and was initially cared for at an outside facility. She presented to our trauma clinic for continued care. Her fracture had been definitively treated in an external fixator, which was removed in July 2013. Upon presentation, her complaints included an inability to actively straighten the leg, and the inability to adequately flex the knee. She was ambulatory with a walker. Upon physical exam, her external fixation sites were well healed without any signs concerning for infection. She had an extensor lag of 40 degrees, which was passively correctable to 0 degrees. Her active flexion was limited to approximately 80 degrees, this was not passively improved. She did not demonstrate any signs of ligamentous laxity. Radiographs (Figure 1A & B) revealed a proximal tibial mal-union demonstrating a 20-degree procurvatum deformity. An MRI was also obtained for review, which confirmed continuity of the extensor mechanism, without major abnormality. A metabolic and infection work-up was unremarkable, aside from Vitamin D deficiency, for which supplementation was initiated.

The patient underwent corrective osteotomy in April 2014. Post-operative radiographs (Figure 1C & D) demonstrate corrected alignment. Of note, intra-operatively, it was noted that the tibial tubercle had healed in a position that had effectively shortened the patellar tendon. The appropriate limb length, alignment, rotation, and tubercle position were achieved upon conclusion of the corrective procedure. Her post-operative course was complicated by difficulty obtaining full range of motion. At four months post-operatively, range of motion from 0 degrees to 60 degrees was attainable passively. There was a firm block to further flexion. Additionally, a 40-degree extensor lag was re-demonstrated. Radiographs at this time point (Figure 2A & B) demonstrate maintenance of correction, healing of the osteotomy, and a normal appearing patellar tendon length.

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Figure 1. (A & B) Pre-operative radiographs demonstrating the proximal tibial malunion.
The patient underwent surgical arthroscopy of the knee for lysis of adhesions and manipulation under anesthesia in September 2014. Intra-operatively extensive adhesion and scar tissue formation was encountered in the supra-patellar pouch, as well as in the medial and lateral gutters, enveloping the tibio-femoral joint. After extensive debridement, the patellofemoral joint was visualized (Figure 3A). It was noted that a calcified scar tissue had developed within the patellofemoral articulation. This was osteotomized with a cobb elevator (Figure 3B). Accessory posteromedial and posterolateral portals were utilized to provide the complete debridement of the adhesions circumferentially (Figures 3C & D). After the debridement, the knee was manipulated. Range of motion for 0 degrees to 115 degrees was obtained.

With aggressive post-operative physical therapy, the patient was able to maintain a range of motion of 0 to 80 degrees, with only a 5 degree extensor lag. She is now able to ambulate with a single cane. She will be undergoing a second arthroscopic lysis of adhesions and manipulation in an attempt to further improve her flexion.

**Figure 2.** (A & B) Follow up AP and lateral radiographs demonstrating healing of the osteotomy with maintenance of correction.

**Figure 3.** (A) Obliteration of the patellofemoral joint. Removal of soft tissue. (B) Osteotomy of ankylosis of patellofemoral joint with cobb elevator. (C) Mobilization of patella. (D) Completed debridement of patellofemoral articulation.
Prior Reports & Relevant Literature
To our knowledge, arthrofibrosis of the patellofemoral joint has not been discussed in the literature as an etiology contributing to post-traumatic contracture. However, there are reports reviewing the myriad of other factors to consider, and recommendations for a systematic approach to caring for these patients.

Hulet et al., Jouffroy et al., and Alici et al. have reported upon the treatment of post-traumatic flexion contracture. Excellent results are reported for arthroscopic anterior arthrolysis, with average post-operative flexion of 117 degrees, compared with 66 degrees pre-operatively. Additionally, for contractures with quadriceps adhesion involvement, similarly promising results have been reported for arthroscopic quadriceps release, with average post-operative flexion of 120 degrees, compared with 60 degrees pre-operatively.

Mariani et al. and Lobenhoffer et al. have reported on the treatment of post-traumatic extension contracture. Excellent results are reported for arthroscopic posterior arthrolysis, with average post-operative extension to 3 degrees, compared with only extension to 26 degrees. Open posterior release has been shown to have similar results, with average improvement in extension to 2 degrees from 17 degrees pre-operatively.

Acquired patella baja can develop if scar tissue causes contracture of the infrapatellar fat pad. This can severely restrict knee motion. Lengthening of the patellar tendon, allograft reconstruction and proximalization of the tibial tubercle have all been described methods for addressing this pathology.

Discussion
Post-traumatic knee stiffness is a common condition, and can pose many challenges with regards to treatment because of the many factors that can contribute to the clinical presentation. Successful treatment is dependent on thoughtful and thorough consideration of the etiologies contributing to the loss of motion, and the execution of a treatment strategy that addresses each of those pathologies. Additionally, meticulous post-operative care is essential to minimize pain and swelling, thereby allowing for the necessary aggressive physical therapy.

Conclusions
This patient presented with flexion contracture and extensor lag of the knee following traumatic proximal tibial mal-union, despite corrective osteotomy and restoration of appropriate patellar tendon length. The unexpected etiology of patellofemoral anklylosis was discovered during arthroscopic treatment. We have demonstrated that osteotomy of the patellofemoral fusion, in addition to anterior and posterior arthroscopic arthrolysis, significantly improved knee flexion and nearly eliminated extensor lag.

References
Diagnostic Utility of Wrist MRI in The Pediatric Population

Introduction
Pediatric patients often present with hand and wrist pain. The source of approximately 70% of wrist pain in this population can be determined by history alone.1 Although plain radiographs can identify the majority of fractures and dislocations, they provide limited information on soft tissue pathology.2 MRI scans have the advantage of showing both osseous and soft tissue structures. However MRI scans have a limited role as screening tool due to their high cost and limited availability.

The appropriate use of MRI imaging for evaluation of the painful wrist remains a topic of controversy. While MRI has greater sensitivity than plain radiography when evaluating for occult or incomplete fractures,3,4 it also often yields positive findings in clinically asymptomatic patients.5,6 Complicating this issue further, the majority of pediatric hand and wrist injuries heal spontaneously without complications or interventions,7,8 making justification of expensive diagnostic tests difficult. Despite this, the American College of Radiology still recommends an MRI for all patients with chronic wrist pain following negative X-rays.9

To the best of our knowledge, no studies have explored the clinical utility of MRI in the workup of pediatric patients presenting with acute or chronic wrist pain. Here, we aim to describe an evidenced-based outcome analysis of MRI utility in a cohort of pediatric patients.

Methods
Institutional Review Board approval was obtained. Electronic medical records were retrospectively reviewed for all consecutive patients who obtained a wrist MRI at our institution. A scoring system from 0 to 3 was developed and applied to each MRI report in order to evaluate and quantify its clinical impact on future treatment, with 0 indicating a normal result, 1 minimal clinical impact or incidental finding (e.g. bone edema), 2 moderate clinical finding and 3 indicating a result with high/definitive clinical significance. Final variables associated with number of patients were analyzed by the Chi-square test based on the expectation of equality between the genders. All other variables were analyzed through confidence intervals.

Results
A total of 313 records were reviewed from all patients who obtained a wrist MRI at our institution between 2007 and 2012. In that MRI is very sensitive, and incidental findings are often observed, we developed the clinical scoring system described above. As described in Table 1, analysis showed that boys were statistically more likely than girls to have an MRI with a higher clinical impact (p < 0.05).

A specific indication for obtaining the study was noted in 171 studies (55%), with the primary indications being to assess for occult bony/ligamentous injury in those presenting with pain, characterize a mass/cyst, evaluate for suspected osteomyelitis and evaluate for arthropathy. Those studies that listed a specific reason for ordering the MRI had an average score of 1.62, while those without an indication had an average clinical score of 1.11 (p < 0.05).

Looking at these indications further, we found that MRI was most useful in delineation of a mass, evaluating for arthropathy and evaluating osteomyelitis. Conversely, MRI was least useful in diagnosing generalized wrist pain. (Table 2) Further evaluation of the patients presenting with pain revealed neither the time frame of the pain (acute vs. chronic) nor the mechanism of injury (pain of traumatic origin vs. that of generalized/non-specific origin) had any

<table>
<thead>
<tr>
<th>Table 1. Summary of Normal MRIs and Average Clinical Score by Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>
Pediatric patient for wrist MRI. Based on our results, we feel that wrist MRI is not an ideal screening tool in children, and should only be used to exclude or confirm a specific diagnosis, as it provides limited useful clinical information for the evaluation of generalized wrist pain.

Disclosures
There was no outside funding for this study.

References
Introduction

The purpose of this article is to serve as an educational tool for orthopedic residents who will complete a rotation at the Children’s Hospital of Philadelphia. With the goal of patient safety in mind, it is important that residents feel comfortable and confident when entering the OR. This article will review helpful preparation tips for performing a knee arthroscopy, the most commonly performed orthopedic procedure,1 and a closed reduction with percutaneous pinning fixation (CRPP) for supracondylar humeral fractures, the most common pediatric elbow injury.2

Arthroscopy

Preparation

The patient is placed in the supine position, and the contralateral leg is secured to the OR table using tape. A cloth towel is placed on the genitalia for protection. Next, the hair on the operative extremity is removed. Cotton cast padding is then applied circumferentially in two layers, making sure not to form any wrinkles. A pneumatic tourniquet is applied over the cotton cast padding and snugly secured. Drapes are placed at the edge of the cuff to prevent prep solution from pooling under the drapes and damaging the patient’s skin or become labile to a fire hazard.

After the tubing is attached to the pneumatic tourniquet, the side post is attached to the operative side of the OR table. The side post should be positioned about one handbreadth above the patient’s patella. The purpose of the side post is to allow a valgus force to be applied to the knee which allows arthroscopic access to the medial compartment. When the post is lowered, it can serve as a platform for the extremity to rest on while in varus position, exposing the lateral compartment.

The operative foot is temporarily placed in a sling while preparation solution is applied to operative extremity. The lower extremity is held with a sterile towel and removed from the sling, in order to apply preparation solution to the ankle (some surgeons prefer to include the foot as well). An impervious stockinette is used to cover the foot and is held in place by a Coban wrap.

Portal Placement

The standard utility knee portals include the anterolateral and anteromedial portals. They are located adjacent to the patella tendon and above the tibial plateaus. Appreciation of the location of the menisci, the femoral condyles and the intercondylar notch with its contents will assist the surgeon in successfully performing a knee arthroscopy and preventing iatrogenic injury.

Portal placement is key to performing arthroscopy successfully and ensuring that iatrogenic injury does not occur. Drawing out the surface anatomy is important for the beginner to understand the location of intra-articular structures to be examined arthroscopically. A marking pen is used to draw out the patella, patella tendon, and the medial and lateral tibial plateaus3 (Figure 1a-b). After locating the planned portals, confirmation can be confirmed by using the marking pen cap to palpate the medial and lateral femoral condyles (Figure 1c).

Supracondylar Humerus Fracture - Closed Reduction with Percutaneous Pinning (CRPP)

Position and Set-up

The patient is placed in the supine position on a regular operating room table. The operative extremity is propped on the x-ray receiver, allowing easy access to the humerus for elbow reduction and pin placement. The C-arm fluoroscope is placed at the foot of the operating table and positioned parallel to the patient. The fluoroscope x-ray source is positioned to emit x-rays to the floor and the receiver positioned to support the arm. An arm board is attached to the table and positioned adjacent to the C-arm receiver and support the head of the patient during surgery. For better visualization, the image intensifier screen is positioned directly across the OR table to facilitate a direct line of vision for the surgery team. The scrub tech and instruments are directly behind the surgeon and can readily provide instruments needed to complete the procedure.

Conclusion

In an effort to increase resident preparedness, the first step is creating a sturdy foundation. By
reviewing the basics, we hope that our residents will enter the operating room with confidence, and the mindset to make great surgical decisions.

References

Reliability Assessment of the EOS® Imaging in Clinical Evaluation of Lower Limb Deformity

Introduction
Blount’s disease is a developmental disorder associated with disordered growth of the proximal medial physis of the tibia—resulting in a progressive varus deformity. While the incidence rate in the U.S. is estimated to be less than 1% of the population, higher incidences are associated with the African American and Scandinavian races, early walking age, and obesity.

Diagnosis of Blount disease is based on a physical examination, history, and radiographs. Varus deformity is based on tibiofemoral varus angle on a standing hip-to-ankle anteroposterior radiograph. The treatment of Blount disease depends on the age of child, stage of disease, and severity of deformity. For children under the age of three, bracing is recommended while surgery is recommended for children over the age of three with a tibiofemoral angle greater than 13°.

Computed tomography technique is considered to be the gold standard in 3D measurement of bone deformity. However CT scans taken in the supine position can alter bone alignment while exposing patients to high radiation dose. The new slot scanning radiography technique (EOS imaging) allows upright standing X-rays with 20 times less radiation. Another feature of EOS imaging is synchronized AP and lateral X-rays to generate 3D reconstructions of bone.

Method
A total number of six lower limb sawbones with deformities (three models of tibia and three models of femur) were selected. The deformity of each bone is summarized in Table 1. These models were assembled into three leg models in a Plexiglas scaffold that permits axial rotation and flexion of the models (Figure 1). The scaffold was placed in the EOS machine and three posterior-anterior and lateral X-rays were taken from each model in 0, 15, and 30 degrees of axial rotation. Similarly bi-planar X-rays were taken in 0, 15, 30 degrees of knee flexion.

Computed tomography scans of the models were registered. Three different techniques were used to measure the geometrical parameters of the models i.e. femur mechanical length, tibia mechanical length, femur deformity, tibia deformity. In the first technique PA and lateral X-ray images were used. Geometrical parameters

<table>
<thead>
<tr>
<th>Model</th>
<th>Deformity Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibia Model 1</td>
<td>25° varus</td>
</tr>
<tr>
<td>Tibia Model 2</td>
<td>Blount disease &amp; tibial plateau oblique plane</td>
</tr>
<tr>
<td>Tibia Model 3</td>
<td>30° varus deformity of proximal end</td>
</tr>
<tr>
<td>Femur Model 4</td>
<td>10° external rotation, 25° distal valgus</td>
</tr>
<tr>
<td>Femur Model 5</td>
<td>Proximal neck malunion, distal valgus 30° malunion</td>
</tr>
<tr>
<td>Femur Model 6</td>
<td>20° distal valgus</td>
</tr>
</tbody>
</table>

Figure 1. Sawbone model mounted in the scaffold. The scaffold allows 55° of axial rotation 110° of flexion.
were measured in a DICOM viewer software (Philips iSite® Enterprise) using the method explained in Paley, 2002 (Figure 2a). These measurements were repeated by two observers. In the second and third techniques the 3D reconstruction of the X-ray images were generated in sterEOS (EOS imaging, Paris). Digitized landmarks were used to calculate the 2D and 3D geometrical parameters using the sterEOS software (Figures 2b & 2c). These measurements were compared with the data from the CT scans of the same bone. A linear mixed model was used to compare the three measurement techniques.

### Results

The 2D and 3D parameters *i.e.* length and deformity angles did not significantly vary as the measurement techniques changed \( p < 0.05 \). Leg deformity angle in the frontal view was significantly different between the CT measurements and 2D X-ray measurements only at the level of \( p < 0.1 \). The 2D EOS measurement on the AP X-rays showed higher variation in X-ray measurements 154.2° ± 8.1° than the CT measurements 160.5° ± 7.5°, \( p = 0.06 \). In the lateral view these measurement were 168.2° ± 9.2° and 174.5° ± 4.6° for EOS X-rays and CT scans, respectively \( p = 0.09 \). 2D and 3D EOS length measurement were not significantly different (\( p < 0.05 \)) (Figure 3) although a higher variation in the X-ray measurement was shown when the results were compared to the parameters calculated in sterEOS software.

### Discussion

The reliability of the EOS imaging system in measurement of leg deformity parameters, *i.e.* length and deformity angles, was assessed. The results showed no significant difference between the EOS measurements and CT scans. Using the sterEOS 3D software decreased the variation in measurement as the position of the sawbone models was changed inside the EOS machine. For future direction a numerical method will be developed to calculate the bone deformity angle from the EOS 3D reconstructions.

### Conclusion

The reliability of EOS system in 2D and 3D assessment of the lower limbs deformity was validated. The 3D reconstruction of the lower limb deformity decreased the intra-observer variability.

### References

Management of Distal Femoral Osseous Sarcomas using Expandable Endoprostheses

Introduction

Limb salvage surgery (LSS) is now the preferred treatment for bone sarcomas of the extremities at most institutions. Local control in children often necessitates resection of major growth plates; this makes LSS in the skeletally immature patient a challenge because of the need for maintenance of limb length. Around 75% of the reconstructions with expandable endoprostheses are performed at the distal femur. Because of the vast variety of options for expandable endoprosthesis, reports on their results are highly heterogeneous and those on the use of expandable endoprostheses in specific sites are rather few. The aim of this study is to report our experience on the management of distal femoral osseous sarcomas, using expandable endoprosthesis.

Methods

After obtaining Institutional Review Board’s (IRB) approval, a retrospective review was conducted on the patients who received expandable distal femur endoprostheses between January 2005 and September 2010. A total of 264 sarcoma patients were treated, among whom 28 were treated with a distal femur endoprosthetic reconstruction. Of those, eight patients (5 males and 3 females) were treated consecutively, by the senior author, using a second generation expandable endoprosthesis manufactured by Stryker-Howmedica. Data extracted is summarized in Tables 1 and 2. The small number of patients allowed us to report only descriptive statistics.

Results

The average follow-up time was 28 months. All surgical margins were negative. All the patients were alive at latest follow-up and there were no local recurrences. Five patients (62.5%) had undergone a total of 11 lengthening procedures with a mean of 2.2 lengthenings per patient. In these patients, the average total lengthening to date was 4.44 cm (range 1.2 cm- 9.1 cm). The average lengthening per session, per patient was 2.01 cm. There were no failures in lengthening. No cases of loosening, collapse of lengthening mechanism, mechanical failure of implant, and/or neurovascular damage or amputations were reported. Demographic data is presented in Table 1. Complications and functional outcomes are summarized in Table 2.

Discussion

In the present study, all 8 patients were treated according to the oncology division’s protocol with 3-4 cycles of neoadjuvant chemotherapy, after biopsy and definitive immunohistochemical diagnosis, and adjuvant chemotherapy after definitive local control.

All eight patients followed the institutional post-operative physical therapy protocol for distal femur reconstruction. They were placed in a continuous passive motion (CPM) device approximately two weeks postoperatively until they achieved knee flexion of more than 90°. Toe touch weight bearing was maintained for at least 4 weeks following surgery. Two weeks after the surgery, strengthening of the involved knee was initiated with the goal of obtaining knee strength of 4/5 within 8-12 weeks postoperatively.

Prediction of the ultimate LLD at skeletal maturity was measured using the Moseley straight-line graph. In cases where the length discrepancy was greater than 1.5 to 2 cm and knee flexion was at least 90°, endoprosthetic lengthening was performed under general endotracheal anesthesia via two small incisions; the first for releasing the locking mechanism and the second for the lengthening T wrench. Rehabilitation was started on the first postoperative day after each lengthening.

The reconstruction goal is to initially establish equality of extremity length. Dotan et al performed a 2 cm initial osteoplastic lengthening without any complications. In the present study, the average initial osteoplastic lengthening was 1.32 cm without any complications. Further, the initial lengthening was 24 months after initial implantation, in comparison to 15 months reported by Eckardt et al. The authors consider this a safer approach in that it has the advantage of delaying the first lengthening, thus decreasing the overall number of total procedures.

Multiple skip lesions and extensive femoral involvement without interruption merit consideration for total femoral resection, though it is not a complication-free procedure. In the present study, case 1 presented with
### Table 1. Demographic and surgical management characteristics of patients who underwent distal femoral reconstruction with an expandable endoprosthesis due to osseous sarcomas.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at initial surgery (years)</th>
<th>Gender</th>
<th>Follow up (months)</th>
<th>Sarcoma type</th>
<th>Localization of prosthesis</th>
<th>Survival at latest follow up</th>
<th>Number of procedures^</th>
<th>Number of Lengthenings</th>
<th>Time to 1^ lengthening (months)</th>
<th>Time in between lengthenings (months)</th>
<th>Initial osteoplastic lengthening (cm)</th>
<th>Bone stock (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>M</td>
<td>67</td>
<td>Osteosarcoma</td>
<td>Left</td>
<td>Alive</td>
<td>7</td>
<td>4</td>
<td>24</td>
<td>12 (8-15)</td>
<td>N/A</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>F</td>
<td>44</td>
<td>Osteosarcoma</td>
<td>Left</td>
<td>Alive</td>
<td>4</td>
<td>3</td>
<td>31</td>
<td>6.5 (6-7)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>F</td>
<td>38</td>
<td>Osteosarcoma</td>
<td>Right</td>
<td>Alive</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>10</td>
<td>2</td>
<td>11.6</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>M</td>
<td>28</td>
<td>Ewing Sarcoma</td>
<td>Right</td>
<td>Alive</td>
<td>2</td>
<td>1</td>
<td>23</td>
<td>0</td>
<td>1</td>
<td>8.8</td>
</tr>
<tr>
<td>5*</td>
<td>10</td>
<td>M</td>
<td>7</td>
<td>Osteosarcoma</td>
<td>Right</td>
<td>Alive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>16.2</td>
</tr>
<tr>
<td>6</td>
<td>8</td>
<td>M</td>
<td>16</td>
<td>Osteosarcoma</td>
<td>Left</td>
<td>Alive</td>
<td>2</td>
<td>1</td>
<td>14</td>
<td>0</td>
<td>0.8</td>
<td>16.5</td>
</tr>
<tr>
<td>7</td>
<td>12</td>
<td>M</td>
<td>12</td>
<td>Osteosarcoma</td>
<td>Right</td>
<td>Alive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>17.5</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>F</td>
<td>12</td>
<td>Osteosarcoma</td>
<td>Right</td>
<td>Alive</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Mean</td>
<td>9</td>
<td>-</td>
<td>28</td>
<td>-</td>
<td>Alive</td>
<td>2.6</td>
<td>2.2</td>
<td>24</td>
<td>10.4</td>
<td>1.32</td>
<td>13.68</td>
<td></td>
</tr>
</tbody>
</table>

*This patient has also a total femur reconstruction in the contralateral limb due to primary osteosarcoma.

^Includes initial implantation of the expandable endoprosthesis, lengthening, and surgical procedures to resolve complications.

### Table 2. Complications and functional outcomes of patients who underwent distal femoral reconstruction with an expandable endoprosthesis due to osseous sarcomas.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Functional Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>Infection</td>
</tr>
<tr>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Yes *</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>No</td>
</tr>
<tr>
<td>Mean</td>
<td>1/8=12.5%</td>
</tr>
</tbody>
</table>

*Superficial wound infection.

**Proximal migration of the femoral stem.

***Proximal periprosthetic fracture.
extensive femoral involvement. The authors believed that attempts should be made to preserve the hip joint so as to maintain the biomechanics. Due to proximal stem migration (Figure 1A-B), proximal femur bipolar hemiarthroplasty was performed (Figure 1C). In patients with an open triradiate cartilage, whose proximal femur was reconstructed with hemiarthroplasty, a progressive superior and lateral migration of the prosthetic femoral head may occur. To avoid this, acetabular osteotomy, as well as improvement of the abductor-adductor imbalance at the time of surgery may be needed.21 Also, as subsequent lengthenings can contribute to this issue, contralateral epiphysiodesis may be performed to stop the lengthenings and manage the LLD.

Oncologic complications are not infrequent and are reported in 14% to 71% of the cases.5,8,17,18 Non-oncologic complications have been reported in 23.5% to 81.8% of the cases in the literature; this discrepancy is mainly due to the usage of different types of devices and lengthening mechanisms. The most common reported complications are aseptic loosening, knee contractures and infection.8,19,22-26 There is no consensus on the management of knee flexion contractures. Some authors believe that surgical resection of the pseudocapsule is the right treatment.4,16 Recent studies show that aggressive physical therapy in the early stages maintains a good range of motion, prevents scar formation and allows subsequent expansions to be achieved with less force on the gearing mechanism.5,6,17,19 It is possible that, when a patient repeatedly develops contractures after each lengthening, a contralateral epiphysiodesis may become necessary. By doing this, one can manage the LLD and stop the lengthenings that trigger this problem.

The limitations of this study are the small number of patients and short follow up time; however, all the patients were treated by the senior author and with the same type of endoprosthesis, following a standardized protocol of management.

Conclusion

LSS, using expandable endoprosthesis in the distal femur, requires precise surgical planning. Even though the complication rate is relatively high, functional outcome is very good. Early and aggressive rehabilitation is crucial to the management of knee contractures.

References

Risk of Osteochondritis Dissecans (OCD) Lesions in Family Members of Patients with OCD: A Pedigree Analysis

Introduction

The exact etiology of osteochondritis dissecans (OCD) lesions remains undetermined, although repetitive microtrauma, ischemia, and genetics have all been proposed as likely contributors.\(^1\)\(^,\)\(^2\) Overall, the incidence of OCD in the general population is 1.2%, although this number appears to be higher in family members of those with OCD. Across the literature there have also been several case reports suggesting familial inheritance of OCD.\(^3\)\(^-\)\(^7\) In those reports with sufficient pedigree analysis, an autosomal dominant pattern has been suggested.\(^8\)\(^-\)\(^11\) However, as the families in these reports were all selected due to their unique histories that included a significant number of family members with OCD lesions, this may not accurately represent OCD inheritance patterns at large.

Anecdotally, we have observed that immediate relatives of patients with severe OCD lesions, which we defined as either bilateral lesions or those requiring multiple revision surgeries, were more likely to report a family history of OCD. Therefore, the primary objective of this study was to assess the incidence of OCD amongst family members of treated patients. Additionally, we sought to further subcategorize inheritance based upon the type/severity of lesion. Overall, we aimed to describe a broader, more representative pattern of OCD inheritance applicable to all affected patients.

Methods

Institutional Review Board approval was obtained prior to this prospective cohort study with a retrospective chart review component. The Children’s Hospital of Philadelphia (CHOP) patient databases, billing lists and surgical logs were queried in order to identify patients treated by the senior author between March 1\(^{st}\), 2004 and March 1\(^{st}\), 2014. Inclusion criteria included all patients aged 0 to 18 years at the time of initial visit and having a diagnosis of OCD. A questionnaire was designed that asked for the number, age, and gender of all immediate family members and the history of OCD lesions in any family member (immediate or extended). For all positive responses, patients were further queried regarding the age at diagnosis and relevant treatment details (e.g. surgical vs. non-surgical treatment, unilateral vs. bilateral lesions). All identified patients were contacted via mailed questionnaires with simultaneous phone calls in a retrograde consecutive fashion. Enrollment proceeded until approximately 486 total questionnaires had been completed. Retrospective chart review was further conducted for all enrolled patients. Patients were stratified into four categories of disease severity: successful conservative treatment, unilateral lesions requiring surgery, bilateral lesions (treated both conservatively and surgically), and those patients requiring multiple procedures for the same lesion.

To facilitate uniform comparison, only OCD lesions of the knee were considered, although patient reports of family members with lesions in other locations were included. Differences between the study groups were assessed using Chi-square tests (categorical variables) or \(t\)-tests/ANOVA (continuous variables). An alpha level of 0.05 was used for all tests.

Results

486 total patients were identified in the initial search. After all questionnaires were returned, 103 patients were included: 20 who were successfully treated conservatively and required no surgical intervention, 50 with unilateral lesions, 21 with bilateral lesions, and 12 who required multiple surgical procedures. There were no significant differences among the treatment groups in terms of baseline demographics. These included gender, lesion laterality, lesion location, number of secondary procedures at the time of the first surgical intervention, or average number of immediate family members (Table 1). Although of unclear clinical significance, patients in the unilateral group were marginally older. Additionally, there were no differences in these baseline characteristics when stratifying patients by family history status (data not shown).

In all, 14 patients (14%) were identified as having an immediate or extended family member with a history of OCD (Table 2). There was not a higher proportion of positive family history in any of the subgroups (\(p = 0.619\)). Only one patient had a family history notable for more than two successive generations positive for OCD, and no patients noted more than two other combined immediate and extended family members with a history of OCD. The cohort
### Table 1: Baseline Demographics in OCD Patients by Treatment Type

<table>
<thead>
<tr>
<th></th>
<th>Conservative*</th>
<th>Unilateral*</th>
<th>Bilateral*</th>
<th>Repeat*</th>
<th>p-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients (%)</td>
<td>20 (19)</td>
<td>50 (49)</td>
<td>21 (20)</td>
<td>12 (12)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>15 (75)</td>
<td>37 (74)</td>
<td>19 (90)</td>
<td>6 (50)</td>
<td>0.641</td>
</tr>
<tr>
<td>Female (%)</td>
<td>5 (25)</td>
<td>13 (26)</td>
<td>2 (10)</td>
<td>6 (50)</td>
<td>0.173</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>11 (55)</td>
<td>26 (52)</td>
<td>n/a</td>
<td>6 (50)</td>
<td>0.980</td>
</tr>
<tr>
<td>Right</td>
<td>9 (45)</td>
<td>24 (48)</td>
<td>n/a</td>
<td>6 (50)</td>
<td>0.978</td>
</tr>
<tr>
<td>Age, average years (±SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.000</td>
</tr>
<tr>
<td>(± 2.33)</td>
<td>12.45</td>
<td>14.16</td>
<td>12.04</td>
<td>13.60</td>
<td></td>
</tr>
<tr>
<td>Lesion Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial femoral condyle (%)</td>
<td>14 (70)</td>
<td>26 (52)</td>
<td>17 (81)</td>
<td>7 (58)</td>
<td>0.522</td>
</tr>
<tr>
<td>Lateral femoral condyle (%)</td>
<td>5 (25)</td>
<td>11 (22)</td>
<td>4 (19)</td>
<td>2 (17)</td>
<td>0.958</td>
</tr>
<tr>
<td>Trochlea (%)</td>
<td>0</td>
<td>9 (18)</td>
<td>0</td>
<td>2 (17)</td>
<td>0.063</td>
</tr>
<tr>
<td>Patella (%)</td>
<td>1 (5)</td>
<td>3 (6)</td>
<td>0</td>
<td>1 (8)</td>
<td>0.693</td>
</tr>
<tr>
<td>Unspecified (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>0.787</td>
</tr>
<tr>
<td>Number having secondary procedure*</td>
<td>n/a</td>
<td>18 (36)</td>
<td>3 (14)</td>
<td>8 (67)</td>
<td>0.049</td>
</tr>
<tr>
<td>(e.g. loose body removal, lat. meniscus repair, etc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of immediate family members, average # per patient (± SD)</td>
<td>3.75 (± 1.07)</td>
<td>3.94 (± 1.20)</td>
<td>3.90 (± 0.94)</td>
<td>3.67 (± 1.23)</td>
<td>0.845</td>
</tr>
</tbody>
</table>

n/a = not applicable; SD = standard deviation; * = at time of first procedure
* Groups correspond to successful conservative treatment, unilateral lesions requiring surgery, bilateral lesions (treated both conservatively and surgically), and those patients requiring multiple procedures for the same lesion.
* p values correspond to inter-group differences calculated via two-tailed Chi-square analyzes (categorical data) based upon the expectation of equal proportions between the groups or by ANOVA (continuous variables).

### Table 2: Patients with positive family history for Osteochondritis Dissecans

<table>
<thead>
<tr>
<th></th>
<th>Conservative</th>
<th>Unilateral</th>
<th>Bilateral</th>
<th>Repeat</th>
<th>Total</th>
<th>* p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients (%)</td>
<td>20 (19)</td>
<td>50 (49)</td>
<td>21 (20)</td>
<td>12 (12)</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Number with immediate family history (%)</td>
<td>4 (20)</td>
<td>1 (2)</td>
<td>2 (10)</td>
<td>0</td>
<td>7 (7)</td>
<td></td>
</tr>
<tr>
<td>Number with extended family history (%)</td>
<td>0</td>
<td>3 (6)</td>
<td>2 (10)</td>
<td>1 (8)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Number with immediate &amp; extended family history (%)</td>
<td>0</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Total:</td>
<td>4 (20)</td>
<td>5 (10)</td>
<td>4 (19)</td>
<td>1 (8)</td>
<td>14 (14)</td>
<td>0.619</td>
</tr>
</tbody>
</table>

Note: Siblings were tabulated as individual patients.
p values correspond to inter-group differences calculated via two-tailed Chi-square analyzes based upon the expectation of equal proportions between the groups.
Groups correspond to successful conservative treatment, unilateral lesions requiring surgery, bilateral lesions (treated both conservatively and surgically), and those patients requiring multiple procedures for the same lesion.
Discussion

Our report is the first to describe inheritance patterns across a broad, heterogenous population of OCD patients. Overall, our results did not support anecdotal evidence that patients with increased phenotypic disease severity are more likely to have a positive family history for disease.

In describing the potential influence of genetics on OCD, Gans et al identified 34 studies across the literature of suggesting a genetic component, including one from our institution describing two sets of monozygotic twins with identical knee lesions (one of which is included above). Multiple reports have also identified potential genetic defects responsible for OCD, with a recent genome wide linkage study by Statin and colleagues identifying a likely candidate gene. Furthermore, our 14% rate of positive family history is much greater than the estimated 1.2% incidence rate of OCD in the general population based upon knee arthroscopy, and consistent with the reported rate of 14.6% radiographically affected male relatives amongst men with OCD. All together, these studies suggest a genetic component to OCD, if at least for a subset of affected patients.

Our study has a number of limitations. The data was collected from a single, large urban institution. The chosen methodology using phone and mail surveys is vulnerable to a number of biases, including selection, recall, interviewer and response bias. Further, given the uncommon nature of an OCD diagnosis, not all patients are aware of the exact diagnosis of a given family member. Finally, our sample size may not have been large enough to adequately detect differences between the subsets.

Conclusion

Overall, 14% of treated patients had an immediate or extended family member with a history of OCD. Patients with a more phenotypically severe disease course were not more likely to have a positive family history than those with milder presentations. A large, multi-center and multi-national study may be required to adequately delineate differential inheritance patterns in OCD patients.

Disclosures

The authors of this work have no disclosures. There was no outside funding for this study.

References

Triceps Tendon Reconstruction in the Setting of Elbow Stiffness: A Surgical Technique

Mohit Gilotra, MD
G. Russell Huffman, MD, MPH

Introduction

Elbow stiffness may significantly interfere with activities of daily living. Loss of elbow flexion is particularly debilitating with respect to eating, personal hygiene, phone use and occupational specific tasks. An elbow contracture can result from trauma, burns, central neurologic spasticity and even prolonged immobilization. The etiology may broadly be classified as extra-articular or intra-articular and the treatment is adjusted accordingly. Specific intra-articular diagnoses include: joint incongruity; arthritis; loose bodies; capsular contracture; and osteophyte impingement. Extra-articular etiologies consist of: heterotopic ossification; contractures of skin, collateral ligament, peri-articular muscles and tendons.

Evaluation starts with a complete history and examination. Physical examination includes an assessment of range of motion and a neurovascular exam. The ulnar nerve location, sensory and motor function, and sensitivity to palpation are especially important in the evaluation.

Radiographic evaluation begins with orthogonal anteroposterior, lateral and oblique views. Computed tomography with three-dimensional reconstructions and, when appropriate, metal subtraction further characterizes bone that is essential to remove during surgery for full restoration of motion.

Non-operative treatment is the initial treatment for an elbow contracture in which a clear mechanical obstruction to motion is absent. In these patients, effective treatments include edema control, minimizing inflammation and the use of static progressive stretching and splinting. However, once an elbow contracture is established and is refractory to these measures, surgical contracture release, either arthroscopic or open, has been shown to be safe and effective. Traditionally, indications for surgery include inability of the patient to regain a functional flexion extension arc, which is most commonly defined as a 100-degree arc of motion (i.e., at least a 30° elbow contracture or inability to flex beyond 130°). Certain patients may require further range of motion based on occupational or sporting activities.

In this report, we describe the treatment of an extra-articular elbow contracture in which the patient lacked elbow flexion beyond 40 degrees. Restoration of elbow flexion was achieved through surgical lengthening of the triceps tendon using a tendon reconstruction technique after a complete capsulectomy. This step-wise approach is indicated for patients who have an extra-articular explanation for stiffness and a congruent non-arthritis joint.

Case

A 38 year-old male presented with a chief complaint of elbow stiffness and an inability to bend his arm. He originally sustained an open midshaft humerus fracture from a crush injury four years ago treated with an elbow-spanning external fixator. He then developed a chronic nonunion treated with a free vascular fibular graft and revision internal fixation 18 months prior to presentation. He had no complaints of elbow pain and no ulnar nerve symptoms. On examination, he had a 20° elbow extension contracture and lacked flexion beyond 40°. Radiographs of the humerus demonstrated a healed fracture with stable hardware (Fig 1a, 1b). Elbow imaging showed a congruent joint and no signs of arthritis. His lack of motion was attributed to both intra- and extra-articular contractures.

He underwent an open contracture release in the lateral decubitus position utilizing a posterior approach. The ulnar nerve was transposed in an anterior subcutaneous position and the posterior bundle of the medial collateral ligament was released. Complete anterior and posterior capsular excisions were performed and his motion was reassessed with an achieved flexion-extension arc from 5 to 90°. Elevation of the triceps tendon from the humeral shaft did not improve elbow flexion. The triceps insertion was then sequentially released from the medial aspect of the olecranon until elbow flexion reached 130 degrees. Approximately 75% of the tendon had been released at the triceps enthesis. The triceps insertion was then reconstructed using a previously published technique utilizing a non-irradiated semitendinosus allograft.
Operative Technique

Preoperatively, the patient is asked about ulnar nerve symptoms and examined for subluxation, pain and weakness. An ulnar nerve transposition is planned if there is a positive exam or if the patient lacks 90 degrees of flexion.

Prior to surgery, the patient receives either a supraclavicular or interscalene nerve block. A nerve block or an indwelling catheter helps reduce intraoperative narcotic requirements, postoperative nausea and aids in maintaining passive range of motion in the immediate postoperative period.

While the patient is under anesthesia, a full elbow exam is performed assessing range of motion and stability. The patient may be positioned supine with the arm extended on a hand table or lateral decubitus with the arm placed over a padded Mayo stand. A tourniquet is placed proximally and the arm is prepped and draped steriley.

Prior incisions around the elbow are assessed and a straight posterior incision is preferred. Limited medial and/or lateral approaches are options as well. A full thickness dissection is performed to the triceps tendon. The ulnar nerve is identified, protected and prepared for a transposition as indicated. It is released proximally to the Arcade of Struthers and distally to the first FCU branch. The intermuscular septum is excised and both the articular and motor branches to the FCU are sacrificed if needed to minimize nerve tension.

After the ulnar nerve is protected, the floor of the cubital tunnel or the posterior bundle of the MCL is released, particularly in patients lacking adequate elbow flexion.

Laterally, dissection is carried down to the lateral column of the humerus. The triceps is elevated posteriorly exposing the olecranon fossa where posterior capsule and scar are excised. Any osteophytes on the olecranon or the humerus blocking extension are removed.

Exposure anteriorly may be obtained medially or laterally. The author’s preferred technique is through a medial or Hotchkiss approach. The flexor pronator origin is longitudinally incised and the anterior two-thirds is reflected from the medial epicondyte with preservation of the anterior bundle of the medial collateral ligament. The brachialis and the anterior portion of the flexor pronator mass are elevated to visualize the anterior capsule. After the capsule is excised, the coronoid and radiocapitellar joint are debrided.

If flexion is still not obtained with the above maneuvers, then a triceps release is planned. While the elbow is placed in maximal flexion, the triceps is partially elevated from the olecranon medially with elevation continuing laterally as needed. When possible, the fascia contiguous between the triceps and anconeus is left intact to protect the remaining triceps tendon and remnant native extensor mechanism. Elbow flexion is re-examined after these steps to ensure satisfactory gains.

A triceps tendon reconstruction is then performed to augment the insertion site. A running locking stitch using non-absorbable braided suture is passed along both ends of either auto- or allograft tendon. Transosseous tunnels are drilled in a crossing fashion through the olecranon process.

Figure 1. (A & B) AP and lateral radiographs of the distal humerus show healed nonunion. There is no radiographic evidence of an intra-articular elbow pathology.
reconstruction tensioning is then assessed through full range of motion.

The tourniquet is then deflated and hemostasis achieved. The ulnar nerve is transposed into a subcutaneous position usually within an adipose sling. A submuscular transposition is an option as well. The wound is irrigated and a drain is placed prior to closure. When possible, the incision should

using a 4.0 mm cannulated reamer over guidewires with care taken to preserve the dorsal cortical integrity of the bone. The graft is passed through the bone tunnels and then through the triceps tendon using a Pulvertaft weave (Fig 2a-c). The graft is tensioned and sutured back to itself in 90 degrees of flexion. The graft is additionally sutured to the tendon in multiple places using non-absorbable suture on a tapered needle. The

Figure 2. (A) A semitendinosus allograft passed through bone tunnels. (B) A pulvertaft weave is woven through the triceps tendon. (C) A sketch diagram of the triceps reconstruction technique.
be placed medial or lateral to midline to avoid postoperative wound complications, particularly when the surgical goal is restoration of elbow flexion.

A splint is placed in 90 degrees of flexion and neutral forearm rotation for two days. Self-directed range of motion is started with active-assisted flexion and gravity-assisted extension. Active elbow extension is recommended at four to six weeks.

**Discussion**

Contracture release for elbow stiffness is effective regardless of an open or arthroscopic approach. A medial, lateral or posterior approach results in the same range of motion gains as long as all sites of pathology are addressed. Combined intra- and extra-articular contractures are particularly challenging and a myotendinous contracture of the triceps is one of the more difficult sites to treat. Options include a triceps slide and V-Y lengthening to gain flexion. All of these techniques can lead to extensor mechanism failure or lack of strength with active elbow extension. Most of the literature has focused on children with athrogryposis, where a posterior capsulotomy in addition to triceps lengthening had significant gains of passive flexion.

The technique of triceps reconstruction used in this case has been described for chronic triceps rupture. Hamstring autograft was used in two recent case reports. Other described tissue transfers include Achilles, plantaris, and latissimus. Anconeus and palmaris may be used from the same extremity. In another report, V-Y advancement with plantaris autograft was used to augment a repair.

In the setting of extra-articular elbow stiffness, a triceps contracture commonly reduces elbow flexion. The authors advocate consideration of a partial triceps release with allograft reconstruction. This technique provides gains in flexion while optimizing reconstruction strength and allowing early postoperative motion.

**References**

Neuropathic Arthropathy of the Glenohumeral Joint as the Presenting Symptom of a Cervical Syrinx: A Case Report

Introduction

Neuropathic arthropathy, also known as Charcot’s joint disease, is an extreme form of non-inflammatory osteoarthritis caused by disturbed sensory innervation and is typically asymmetric. Classically, neuropathic arthropathy is found in older male patients with an unstable, painless, and swollen joint. Radiographic manifestations of neuropathic arthropathy may include advanced destructive changes in the joint, scattered “chunks” of bone embedded in fibrous tissue, joint distension by fluid, and heterotopic ossification. Diabetes is the most common overall cause and typically affects the foot and ankle joints. In the upper extremity, the most common cause of neuropathic arthropathy is syringomyelia, accounting for 80% of cases. Syringomyelia leads to myelopathy due to compression or ischemia of the spinal cord. Myelopathy is usually characterized by weakness and clumsiness, more commonly affecting the upper extremity. The patient can experience decreased manual dexterity, gait disturbances, sensory changes and spasticity. Physical exam findings in myelopathy may include hyperreflexia, radicular signs, Hoffmann sign, inverted radial reflex, myelopathy hand, finger escape sign, clonus or Babinski sign. Myelomalacia, a radiographic hallmark of myelopathy, appears as an area of bright signal in the spinal cord on T2-weighted magnetic resonance imaging. In this case report, we present a patient who initially experienced symptoms of carpal tunnel syndrome but over several months developed, with increasing severity, many of the classic symptoms of neuropathic arthropathy associated with syringomyelia, demonstrating the importance of maintaining a broad differential diagnosis including cervical pathology.

Case Information

A 52-year-old man with hypertension and diabetes initially presented with severe left carpal tunnel syndrome in November 2013. After an open left carpal tunnel release in January 2014, the patient reported continued sensory changes in his fingertips and loss of manual dexterity in left hand. In May 2014, the patient reported worsening left shoulder discomfort that started while shoveling snow. Left arm weakness, acromioclavicular joint tenderness and limited range of motion were noted. Radiographs demonstrated advanced AC joint arthrosis as well as a chronic-appearing deformity of the humeral head (Figure 1). An MRI revealed a large glenohumeral joint effusion, posterior humeral head dislocation, humeral head deformity with bone marrow edema, and chronic rotator cuff tear (Figure 2). Despite immobilization, the patient’s discomfort worsened and he developed significant swelling about the shoulder. Multiple aspirations yielded bloody fluid. Analysis of this fluid revealed no signs of infection, no malignant cells, and trace amounts of extracellular monosodium urate crystals. Given the severe deformity of the humeral head, the extent of soft tissue damage to the shoulder and the relative lack of pain, concern for a neuropathic joint with cervical spine pathology as an etiology was raised. He also then reported repetitive fingertip burns to both hands when he was cooking, consistent with loss of pain and temperature sensation. An MRI of the cervical spine was obtained. The MRI (Figure 3), revealed a significant syrinx from the level of C2 to T6 with myelomalacia. From these findings, the patient was diagnosed with left shoulder neuropathic arthropathy secondary to syringomyelia. He was referred to a local neurosurgeon for treatment and subsequently underwent shunt placement into the syrinx. He is now in therapy with some resolution of his myelopathic gait but with continued diminished sensation in the hands.

Prior Reports & Relevant Literature

Neuropathic arthropathy secondary to syringomyelia is a rare condition. Fewer than 70 cases of Charcot’s shoulder have been reported in the literature. Syrinx is most highly associated with Charcot’s elbow, but it is important to include the involvement of the shoulder in a differential diagnosis. In many of the cases reported in the literature, there was a significant time lapse between the initial presentation and diagnosis of Charcot’s shoulder. The Charcot joint can resemble other diseases such as
inflammatory arthritis,9 cancer,10 or carpal tunnel syndrome,11 resulting in a misdiagnosis. Several of the reported cases have unique presentations12–14 but typical symptoms include pain, swelling, and loss in range of motion. Radiographic studies usually show osteolysis, fluid collection, and degeneration resembling septic arthritis. There is no established consensus on the treatment of neuropathic arthropathy secondary to syringomyelia. Treatment strategies have ranged from neurosurgical treatment of the syringomyelia and orthopaedic interventions such as arthrodesis or resurfacing procedures to physical rehabilitation and drug treatment, with varying degrees of success.15–19

Discussion
Establishing the diagnosis of neuropathic arthropathy and syringomyelia is often a prolonged process. This disease generally has a slow progression; the case presented above represents a relatively rapid symptom evolution over a 3-month period. There is concern that some of the neurologic changes that patients experience may become irreversible if not treated expeditiously, thus worsening the patient’s prognosis. The differential diagnosis for neuropathic arthropathy includes chronic septic arthritis, sarcoma,
idiopathic osteolysis, nephropathy, synovial chondromatosis, and Winchester syndrome in addition to cervical syrinx. Conversely, cervical pathology should be considered in the differential diagnosis of the aforementioned conditions. The definitive diagnosis of syringomyelia, made based upon the cervical MRI, raises the concern that the initial presenting symptoms were carpal tunnel syndrome-like, but in actuality due to syringomyelia.

Since diabetes leads to peripheral nerve damage, it is possible the patient’s diabetes contributed to his disease process. Although the exact pathophysiology of neuropathic arthropathy is unknown, there are two predominant theories.20,21 The neurotraumatic theory posits that an insensitive joint will be more prone to sustaining repetitive trauma, causing joint destruction. In the neurovascular theory, it is hypothesized that sympathetic dysfunction and sensory loss cause hyperemia and active bone resorption by osteoclasts.

Despite the wide variation in treatment of neuropathic arthropathy secondary to syringomyelia, optimal management should be focused on treating the underlying neurological cause before treating the secondary effects of syringomyelia. Aggressive orthopaedic intervention (e.g. arthrodesis and resurfacing operations) without first treating the underlying neurologic pathology has resulted in regression to the previous disease state.19

**Conclusions**

The orthopaedic surgeon will be the clinician most likely to encounter this rare disease, despite its neurological origin. A detailed history, a thorough and thoughtful physical exam including strength and sensory testing, neurological and pathological reflex provocation, as well as specialized maneuvers is paramount in diagnosing neuropathic arthropathy and identifying the underlying etiology. This will prevent unnecessary surgery and expedite definitive treatment. To avoid misdiagnosis of neuropathic arthropathy, the orthopaedic surgeon should be aware of the possibility of a neurological pathologic mechanism.

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**References**

Measurement of Adult Hill-Sachs Lesions on Magnetic Resonance Arthrography

Introduction

Posterosuperolateral compression fractures of the humeral head, eponymously described by Hill and Sachs in 1940,1 occur in 40-90% of anterior shoulder dislocations2 and typically occur in conjunction with anterior capsulolabral tears (Bankart and variant lesions).3,4 Repairing a Bankart lesion without simultaneously addressing significant Hill-Sachs lesions may result in repeated instability.5-7 However, identifying which Hill-Sachs lesions are clinically important remains challenging.

Although Hill-Sachs lesion size affects glenohumeral stability,8,9 no consensus exists on the best measurement technique. Recently, Kodali et al demonstrated that Hill-Sachs lesions could be measured on two-dimensional computed tomography. However, while depth of lesions could be reliably measured, width was consistently underestimated.10 Thus, additional work is needed to determine a more accurate and practical method of quantifying Hill-Sachs lesion size.

Magnetic resonance (MR) imaging provides improved visualization of intra-articular structures and soft tissues. MR has high sensitivity (96.3%) and high specificity (90.6%) for detecting Hill-Sachs lesions.11 Furthermore, Probyn et al showed that MR arthrography could detect Hill-Sachs lesions with 100% sensitivity and 93.3% accuracy compared to surgical findings.9

In this study, we describe two techniques for measuring the volume of Hill-Sachs lesions on MR arthrography that are reproducible and easy to perform.

Materials and Methods

This protocol received institutional review board approval. A custom data-mining tool called PRESTO12 was used to conduct a retrospective search of all MR arthograms performed at our institution from September 2010 through August 2012 whose reports included the text string “Hill-Sachs.” Scans were included for measurement if both measuring radiologists (ATR and ASW) agreed on the presence of a Hill-Sachs lesion and excluded if they had reverse Hill-Sachs lesions or sequelae of prior surgeries. Measurements were performed on 33 consecutive scans meeting the inclusion and exclusion criteria.

Hill-Sachs lesions were defined as contour irregularities on the posterosuperolateral aspect of the humeral head that demonstrated T1 shortening (T1 hyperintensity), indicating extension of gadolinium into the depressed defect. Bone marrow edema and subchondral impaction fractures subjacent to the Hill-Sachs deformities were not included in the measurements. The contour of the normal humeral head was assumed to be ellipsoid in shape to define the posterolateral margin of the Hill-Sachs defect for the measurements.

Volumetric measurements of the size of Hill-Sachs defects were performed from the axial fat saturated T1 sequence. The first measurement technique, the additive cross-sectional volume method, is essentially a Riemann sum method for determining volume of a shape. The area of the Hill-Sachs deformity was traced using the polygonal area measurement tool on each image demonstrating the defect (Fig. 1). These

Figure 1. Demonstration of the additive cross-sectional method. The contour defect of the Hill-Sachs lesion (top of panel) has been traced with the polygonal area measurement tool on this fat saturated T1-weighted image (bottom of panel). The process is repeated on all images demonstrating the contour defect.
Results

Hill-Sachs lesion volume was measured on 33 patients using both the additive cross-sectional and triaxial measurements. The range in Hill-Sachs lesion volumes was 37–2309 mm³. Spearman Rank Correlation Coefficients for both observers using the same method (inter-observer reliability) and for the same observer using both methods (intra-observer reliability) are shown in Table 1. Overall, Spearman Coefficients were greater than 0.8 in all cases, indicating strong overall reliability. All measurements reached significance.

Discussion

This study describes two methods to quantify the volume of Hill-Sachs lesions on MR arthrography. Spearman Correlation Coefficients for intra-observer reliability between the additive

<table>
<thead>
<tr>
<th>Table 1. Spearman Rank Correlation Coefficients for intra- and inter-observer reliability.</th>
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<tr>
<td><strong>Comparison</strong></td>
</tr>
<tr>
<td>Observer 1 Additive cross-sectional/Triaxial</td>
</tr>
<tr>
<td>Observer 2 Additive cross-sectional/Triaxial</td>
</tr>
<tr>
<td>Observer 1/Observer 2 Additive cross-sectional</td>
</tr>
<tr>
<td>Observer 1/Observer 2 Triaxial</td>
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measurements were multiplied by the slice spacing, including any interslice gap, and summed to give lesion volume. The second measurement technique, the triaxial volume method, is essentially the volume of an ellipse calculated from the maximum X, Y, and Z axes. This was performed by identifying the axial slice on which the Hill-Sachs lesion had the largest cross-sectional area and then obtaining a bi-axial measurement of the defect with perpendicular measurements (Fig. 2). The third axis was then obtained by triangulating to an orthogonal series, typically a sagittal oblique acquisition, and measuring the lesion height. The volume was calculated as the volume of an ellipsoid.

Intra-observer and inter-observer reliability were determined using the Spearman Rank Correlation Coefficient with p < 0.05 denoting significance.
cross-sectional and triaxial methods were greater than 0.9 for both observers (Table 1), demonstrating extremely high agreement between our method and the commonly used triaxial method. The Spearman Coefficient for inter-observer reliability of the additive cross-sectional method was also high (0.827), indicating that this method is reliable and produces similar results between users. Lower Spearman Coefficients for inter-observer reliability of the additive cross-sectional and triaxial methods can be attributed to observer differences in distinguishing between the outer margins of the Hill-Sachs lesion and surrounding bony edema. However, the intra-observer reliability was improved because measurements were made using the same definition of the lesion.

Both volumetric methods have limitations. First, the accuracy of the additive cross-sectional method is dependent on the slice thickness of the MR sequences, which are typically much thicker than high-resolution CT images. The triaxial method assumes the Hill-Sachs lesion is completely elliptical in shape and may lose accuracy in more irregular lesions. These irregular lesions may be more accurately measured using the additive cross-sectional method. Furthermore, we describe both methods using MR arthrography where gadolinium contrast within the lesion can be used to distinguish the contours of the depressed lesion from the subjacent marrow edema. However, not all patients with recurrent anterior instability are evaluated with MR arthrography. Additional investigation is needed to determine the accuracy of both methods in routine noncontrast shoulder MRIs.

The threshold size of Hill-Sachs lesions that requires operative intervention has yet to be determined. Many authors advocate surgical management of lesions greater than 20–40% of the humeral head. Voos et al found a significant association of Hill-Sachs lesions greater than 250mm³ with recurrent instability. It is therefore important to establish a consistent and reproducible method for measuring the size of such lesions. We have demonstrated two methods for MR arthrography, an additive cross-sectional method and a triaxial method that is standard practice amongst radiologists. The additive cross-sectional method has high concordance with the established triaxial method and both methods are reproducible and easy to perform. Reliable and accurate quantification of Hill-Sachs lesion volumes may offer a clinical benefit and help guide management of these lesions.

References

Failure of Cementless Total Hip Arthroplasty in a Patient with Contralateral Hip Arthrodesis: A Case Report

Abstract

A procedure once considered standard of care for end-stage degenerative joint disease of the hip, hip arthrodesis, has experienced decreased enthusiasm due to the enormous success of total hip arthroplasty (THA). Patients that have undergone previous hip arthrodesis may present with ipsilateral knee or contralateral hip pain due to altered biomechanics exhibited in the adjacent joints. Patients may be considered candidates for THA of the contralateral hip due to joint deterioration. Orthopaedic Surgeons must be aware of possible complications associated with performing a THA. We present a case of a cementless THA, contralateral to a long-standing hip arthrodesis, that failed within five years due to liner dissociation.

Introduction

The utilization of hip arthrodesis for the treatment of end-stage hip degenerative joint disease has significantly declined due to the success of total hip arthroplasty. In 2010, the Centers for Disease Control (CDC) reported that over 332,000 THA procedures were performed in the United States alone. Although fewer patients are undergoing primary hip fusion, patients that have previously undergone hip arthrodesis persist, and the risk of development of degenerative changes in ipsilateral and contralateral lower extremity joints increases over time.

A biomechanical study examining body kinematics following hip arthrodesis revealed that loss of motion in one hip resulted in increased rotation of the pelvis and increased flexion of the ipsilateral knee. The altered mechanics of these joints had been shown to lead to accelerated development of degenerative joint disease. Therefore, it is expected that adjacent joint deterioration will follow hip arthrodesis and will occur over varying time periods as a function of the individual.

Salvati and Insall published a case series in 1989 evaluating patients during the time period of 1972 to 1986 that had undergone total joint arthroplasty, contralateral hip or ipsilateral knee, following primary hip arthrodesis. In this study, patients that underwent THA for contralateral hip arthritis were treated with one of several different cemented THA components utilizing first generation cement technique. A total of 14 patients underwent THA and three (21%) patients required revision for mechanical failure of the implant. We report, to our knowledge, the first case of mechanical failure of a cementless acetabular highly cross-linked polyethylene liner in a patient having undergone total hip arthroplasty following previous contralateral hip arthrodesis.

Case Presentation

Pre-Operative Findings

The patient is a 64-year-old male who underwent right hip arthrodesis after a traumatic injury in Vietnam in 1976. He presented to the Veterans Affairs Medical Center in 2008, at age 59, with contralateral hip pain. Clinical and radiographic examination confirmed the diagnosis of end-stage degenerative joint disease with an infero-medial arthritic pattern (Figure 1). The patient was considered a candidate for THA following failure of conservative treatment, and underwent an uneventful Left THA, by a previous Orthopaedic team, in December 2008 through a posterior approach (Figure 1).

Five years following the index procedure, the patient presented to an outside hospital emergency department with complaints of left hip squeaking during ambulation and painful weight bearing. XR were obtained demonstrating an eccentrically positioned femoral head within the acetabular shell, suggestive of possible liner dissociation (Figure 1). The radiographs otherwise depicted well-fixed acetabular and femoral components, with no evidence of component migration, subsidence or loosening.

The patient was considered a candidate for revision left THA with the plan for isolated head and liner exchange versus possible acetabular component revision if it were determined...
Failure of Cementless Total Hip Arthroplasty in a Patient with Contralateral Hip Arthrodesis: A Case Report

Within the acetabular shell (Figure 3). Clinically at the 3 month follow-up appointment, the patient is without complaints and has returned to performing his activities of daily living without difficulties. New radiographs obtained at this time demonstrated a concentrically reduced total hip arthroplasty (Figure 3).

Discussion

Hip arthrodesis is an effective method to treat hip pain secondary to end-stage degenerative joint disease. However, arthrodesis may result in debilitating low back pain, ipsilateral knee and contralateral hip arthritis. Most commonly, hip arthrodesis take-down (conversion to THA) is indicated for end-stage lumbosacral degenerative disk disease.

Current literature supports favorable clinical outcomes following conversion of a previous hip arthrodesis to THA. However, in October 2013, Giannoudis et al. published a systematic review evaluating conversion of hip arthrodesis to THA. In this review, 11 studies were included accounting for 579 patients that underwent THA conversion. The authors concluded that the clinical results of hip arthrodesis take-down were mixed regarding reproducible pain relief and were associated with an overall complication rate as high as 54%.3
Figure 2. (A) Intra-operative images of original prosthesis reduced with a disengaged liner from the acetabular shell; (B) Intra-operative images of the acetabular component demonstrating adequate positioning; (C) Ceramic femoral head following explantation with evidence of a large metal stripe on the bearing surface; (D) Arrow indicates superior wear pattern within the polyethylene liner; (E) Arrow indicates superior wear pattern within the polyethylene liner.

Figure 3. (A) Intra-operative image with new liner engaged within the retained acetabular shell; (B) Post-operative left hip AP radiograph showing concentric reduction; (C) AP Pelvis radiograph at 3 months post-op showing concentric reduction.
Salvati et al. reported on a series of 14 patients following cemented Charnley or modified Charnley THA for hip arthritis in patients with contralateral hip arthrodesis. In this series, three (21%) patients required revision for mechanical failure while an additional three (21%) patients developed radiolucencies and component migration. Only two (14%) patients at final follow-up of eight years had excellent results without any complications. Clinical follow-up after cementless THA and contralateral hip arthrodesis using modern day THA technology has not been reported.

Our case demonstrates early failure (within five years) of cementless THA in a patient with contralateral hip arthrodesis. It is speculated that the excessive forces generated across the THA bearing articulation due to contralateral hip arthrodesis was responsible for the encountered liner dissociation. It is unclear whether this will recur after a short time interval due to continued increased loads, however, it is expected that this may occur again. Once THA has been performed, another solution is not available for treatment of polyethylene liner failure.

It is imperative that arthroplasty surgeons counsel patients regarding the risk of early failure of cementless THA planned for an arthritic hip contralateral to a previous hip arthrodesis. Patient expectations may also factor into longevity of the prosthesis, as this patient has been extremely active with his left THA following the index procedure.

Patients may also require counseling regarding hip arthrodesis take-down, as this is the only method by which to normalize the loading conditions across the contralateral THA bearing surface. However, take-down should still only be considered for the proper indications, end-stage lumbosacral degenerative disk disease. This is a complicated patient scenario without a long-term solution, and patients need to be aware prior to undergoing treatment for the contralateral arthritic hip.

**Literature Cited**

Operative Technique: Acetabular Distraction for Severe Acetabular Bone Loss with Associated Chronic Pelvic Discontinuity

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Introduction
Revision total hip arthroplasty (THA) coupled with severe bone loss is a challenging problem to address especially when associated with a pelvic discontinuity. The overall goal should be to restore hip biomechanics, achieve biologic fixation of a cementless device, implant a construct which yields adequate hip stability, and preserve limb function. The burden of revision THA is expected to increase over the next several years and with it the number of complex acetabular revisions will also rise.¹

A pelvic discontinuity defines a clinical situation where the inferior and superior hemipelvis is no longer in continuity (Figure 1). Numerous techniques have been described to address this problem including the use of a custom triflanged component, cup-cage construct, acetabular allograft with a cage, jumbo cup in conjunction with posterior column plating (in the case of an acute discontinuity), as well as acetabular distraction with porous tantalum augments. Each method intends to restore continuity between the ischium and the ilium by way of bridging the defect. In this technique guide, we describe the acetabular distraction technique using a jumbo cup and modular porous metal acetabular augments.

Background
Several classification systems have been described throughout the literature to categorize the pattern of bone loss that is present at the time of revision surgery. They include the Paprosky, Gross, and American Academy of Orthopaedic Surgeons.²³⁴ We advocate the use of the Paprosky classification, which is based on four radiographic factors: the integrity of Kohler’s line (ilioischial line), osteolysis of the tear drop and ischium, and the location of the hip center in relation to the superior obturator line.²

The incidence of pelvic discontinuity is very low. Berry et al., determined that the incidence at one high volume institution was 0.9%.⁵ Pelvic discontinuities can be present with IIC, IIIA, or IIIB defects; however, the highest association with chronic discontinuity is seen with IIIB defects. An “up and in” pattern is demonstrated in IIIB defects (i.e. the acetabular columns are not supportive and the hip center has migrated greater than 3cm superomedially).

The three key factors that influence the treatment of pelvic discontinuity are the amount of residual host bone stock available for reconstruction, the potential for biological ingrowth, and the potential for healing.⁶ In the setting of chronic pelvic discontinuity, the discontinuity is often thought of as a fibrous non-union, and the healing potential is significantly decreased as compared to an acute pelvic discontinuity.⁶ As a result, we do not recommend routine plating of the posterior column in the setting of chronic pelvic discontinuity.

Pre-operative Evaluation and Indications
Patients typically present with pain and often a leg-length discrepancy due to superior migration of the hip center. A thorough pre-operative history and physical exam should be performed. All operative reports should be acquired so that the treating surgeon has an understanding of all previously performed procedures as well as the implants that are currently in place. Infection must always be ruled out prior to performing a revision THA.⁷⁸ An elevated erythrocyte

Figure 1. Demonstration of chronic pelvic discontinuity prior to distraction.
OPMATIVE TECHNIQUE: ACETABULAR DISTRACTION FOR SEVERE ACETABULAR BONE LOSS WITH ASSOCIATED CHRONIC PELVIC DISCONTINUITY

Reamer is reached, the reamer typically disengages from the reamer handle and is used as a surrogate for the acetabular shell. At the correct size, the reamer will pinch between the anterosuperior and posteroinferior columns. Bone graft should be placed in the discontinuity prior to implanting the cementless shell.

A cementless trabecular metal TM revision acetabular (Zimmer, Warsaw, IN) shell is the implant of choice for treatment of pelvic discontinuity (Figure 4). A minimum of four screws should be placed through the cup into host bone, ensuring that at least one screw is placed inferiorly in the ischium or the superior pubic ramus (kickstand screw). At least 50% of the cup should be in contact with host bone; a cup placed against allograft alone will not achieve biologic fixation. The liner is then cemented in place with the proper version and abduction. If screw fixation through the cup is inadequate (e.g. less than four screws or screws with poor purchase), then a tantalum augment should be placed in the discontinuity prior to implanting the cementless shell.

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Post-operative Protocol

As previously described, our protocol following acetabular distraction includes touchdown weight bearing (10%) for 6 to 12 weeks to facilitate bone ingrowth. At three months, assuming there is no change in the position of the components, the patient is allowed to progress to weight-bearing as tolerated with a cane. Finally, no active abduction should be allowed for six weeks if an extended trochanteric osteotomy was performed to aid in femoral revision.6

Discussion

Revision THA with an associated chronic pelvic discontinuity is a difficult problem to treat. Results with an acetabular cage
alone, structural allograft with a cage and cemented liner, cup-cage construct,17,18 customized triflange have been mixed.2,10,11,12,13,14,15,16,19,20,21 To date, there has only been one study reviewing the results of acetabular distraction. Sporer et al. demonstrated excellent results with only one out of 20 patients being revised for aseptic loosening.9 Given the mixed results to date and the promising results reported by Sporer, acetabular distraction with a jumbo cup and modular porous metal acetabular augments appears to be a practical treatment option.

References


A Systematic Approach to Soft-tissue Balancing in Primary Varus Total Knee Arthroplasty

Introduction

More than 600,000 total knee arthroplasties (TKA) are currently performed annually in the United States and by 2030 the number is expected to reach 3.48 million per year.\(^1\) Advances in implant design, materials and cement technique have contributed to increased survivorship. However, long-term outcomes are primarily predicated on overall alignment, component stability, and soft-tissue balancing. The degenerative process of osteoarthritis leads to altered joint mechanics and deformity in both the coronal and sagittal planes, frequently producing varus malalignment with or without an associated flexion contracture. More severe varus deformities typically require more complex surgical techniques in order to achieve appropriate soft-tissue balance. This article discusses a systematic approach to evaluate and address soft-tissue balancing in a varus primary TKA.

Background

Accurate bone resection and precise soft-tissue release of the medial side are critical in achieving a well-balanced total knee arthroplasty in the setting of varus deformity. Although still controversial, algorithms for sequential ligamentous, capsular, and tendinous releases have been described to restore alignment and optimize implant stability.\(^2-12\)

Pre-operative Evaluation

Successful management of a degenerative varus knee requires careful pre-operative evaluation and planning. The surgeon should obtain a detailed history and perform a physical examination with a focus on overall knee/limb alignment, the quality of the soft-tissue sleeve surrounding the knee, the presence and location of previous incisions, the presence of a flexion contracture, stability to varus and valgus stress throughout the range of motion, and the ability to correct the varus deformity at 30° of flexion with a valgus directed force. Appropriate knee roentgenograms should be obtained. A complete set of X-rays includes a weight bearing anteroposterior (AP) view, a lateral view and a sunrise or merchant view (Figure 1). Radiographs should be carefully scrutinized for the presence of subchondral sclerosis and osteophytes, particularly medially and posteriorly where they may be impinging on capsular tissue, making the deformity worse. The lateral projection also provides information regarding the potential challenges of the exposure. In the setting of a short patellar tendon (patella baja) or a large inferior patellar nose or prominent tibial tuberosity (relative patella baja), surgical exposure of the knee is typically more challenging due to difficulty with subluxation or eversion of the patella. Full length weight bearing films also assist in determining the distal valgus resection angle (the difference between the mechanical axis and the anatomic axis of the femur), the correct point for cannulation of the femoral canal with intramedullary instrumentation and the level of bone resection both at the distal femur and at the proximal tibia (Figure 2). Based on physical exam and radiographic evaluation, the surgeon should determine the appropriate implant for planned TKA and determine whether a more constrained device should be available for backup.

Relevant Anatomy

When performing a TKA on a varus knee, the medial soft-tissues are tight and balancing therefore relies on appropriate releases of medial soft-tissue structures (Figure 3). Relevant structures include both static stabilizers (superficial fibers of the medial collateral ligament, posterior oblique ligament, posterior cruciate ligament and posterior capsule) and dynamic stabilizers (pes anserine tendons and semimembranosus tendon). Release of anterior structures primarily affects the flexion gap, while release of posterior structures affects the extension gap.

Procedure

There are two different schools of thought regarding TKA balancing: measured resection and gap balancing. In general, measured resection requires soft-tissue balancing after the bony cuts have been made, while gap balancing uses...
flexion and extension gaps. Soft-tissue balance can be assessed with spacer blocks, laminar spreaders, tensioning devices and/or trial implants and then applying a varus/valgus force in both flexion and extension. Generally, thorough removal of medial osteophytes in conjunction with a minimal soft-tissue medial sleeve release can result in a balanced knee; however, medial structures often enough remain tight, leading to unequal flexion and/or extension gap(s). When this happens, the surgeon must determine how to proceed.

As a part of the standard exposure for a TKA, the anterior capsule and deep MCL are released to aid in exposure. This release is more extensive (extends farther distal) in varus knees compared to valgus knees; however, it is equally important that this release be carried out medially around the tibia to the level of the posteromedial corner in both varus and valgus knees.

Following accurate femoral and tibial bony resections and removal of osteophytes, the surgeon should address soft-tissue balance with the goal of creating symmetric rectangular flexion and extension gaps. Soft-tissue balance can be assessed with spacer blocks, laminar spreaders, tensioning devices and/or trial implants and then applying a varus/valgus force in both flexion and extension. Generally, thorough removal of medial osteophytes in conjunction with a minimal soft-tissue medial sleeve release can result in a balanced knee; however, medial structures often enough remain tight, leading to unequal flexion and/or extension gap(s). When this happens, the surgeon must determine how to proceed.

After ensuring that the bony resections are accurate and the appropriate alignment has been obtained, attention should be given to additional medial soft-tissue release. We recommend addressing the extension space first. Initially, medial osteophytes will tether the medial soft-tissues; removal of any residual osteophytes will functionally lengthen the medial collateral ligament and result in further medial coronal

**Figure 1.** Standard radiographic evaluation of the knee. (A) A weight bearing AP view is critical to evaluate the degree of tibiofemoral joint space narrowing. (B) The lateral view, taken at 30° of flexion, allows for radiographic assessment of the patellofemoral compartment and is also particularly helpful for assessing posterior tibiofemoral wear patterns that are not readily apparent on AP views. (C) A weight bearing 45° PA (Rosenberg) flexion view is an alternative view to assess posterior wear patterns. (D) The Merchant view allows for radiographic assessment of the patellofemoral compartment.

the tension of the native soft-tissues/ligaments to determine the appropriate level of bone resection. Most surgeons use a combination of both techniques to achieve TKA balance. The authors prefer the use of gap balancing for the extension gap and then matching the flexion gap with the use of a measured resection technique.

As a part of the standard exposure for a TKA, the anterior capsule and deep MCL are released to aid in exposure. This release is more extensive (extends farther distal) in varus knees compared to valgus knees; however, it is equally important that this release be carried out medially around the tibia to the level of the posteromedial corner in both varus and valgus knees.

Following accurate femoral and tibial bony resections and removal of osteophytes, the surgeon should address soft-tissue balance with the goal of creating symmetric rectangular
plane balancing. If additional soft tissue release is required, the next step is to continue around the posteromedial corner to include the deep MCL, the posterior oblique ligament, the posteromedial capsule and fibers of the semimembranosus insertion. A Cobb elevator should be utilized in the posteromedial corner to perform a distal release of the tight soft-tissues. If adequate coronal plane balance has not been achieved at this point, we recommend completing the remaining cuts of the femur and then re-assessing the coronal plane balance.

In flexion, the remaining femoral cuts are performed after appropriate sizing and femoral component rotation have been achieved. Resection of the medial posterior femoral condyle will result in additional medial release in extension—the posterior capsule, which plays a bigger role in extension stability will no longer be “tented” over posteromedial osteophytes and will thus be functionally lengthened. If, after femoral cuts have been made, the knee is still not balanced in extension on the medial side, there are a few more surgical decisions that can be made to achieve balance.

Total knee arthroplasty procedures that are being performed as a cruciate retaining (CR) procedure may benefit from release of the PCL to gain additional medial release and balancing. The PCL, which is a medial based structure based on its insertions may contribute to the overall varus deformity. If PCL release is not enough, then the only other options remaining are to downsize the tibial component (resect a portion of the medial tibia for further MCL functional lengthening) or to “pie crust” the superficial MCL. Pie crusting the MCL involves either making a small horizontal incision in the ligament or (author’s preferred method) making multiple puncture holes using a large diameter (18- or 19-guage) hypodermic needle. At this point, a constrained TKA may be required and should be available as a backup prosthesis for all severe varus deformity cases.

If coronal plane balancing has been achieved in extension, then it must also be assessed in flexion. If the medial compartment is tight in flexion, then femoral component rotation should be assessed first—an internally rotated component will result in medial flexion tightness. If the femoral component is properly rotated, then release of the anterior fibers of the superficial MCL and Pes Anserine tendons will yield increased medial laxity in flexion.

A final note should be made regarding bony resections in TKA: extreme caution should be used and it is not advisable to resect additional bone from the distal femur or proximal tibia as a means to achieve soft tissue balance. Additional bone resection can alter the mechanical alignment of the TKA and lead to early implant failure. Increased distal femoral resection raises the joint line and can lead to mid-flexion instability due to laxity of the collateral ligaments throughout the range of motion, and can necessitate the use of a constrained implant or, if not identified intra-operatively, may result in early TKA failure.

Figure 2. Templating the varus TKA. (A) Full-length standing AP radiograph of the lower extremities. (B) The distal femoral valgus resection angle is determined by calculating the angle between the mechanical axis (line connecting center of femoral head and center of the distal femur) and the anatomic axis (line connecting the center of the distal femur and bisecting the femoral shaft) of the femur. (C) A higher magnification view at the level of the knee shows the planned distal femoral resection (90° to the mechanical axis) as well as the entry site for the intramedullary femoral cutting guide (point where anatomic axis exits in the intercondylar notch on the AP view, which is generally just medial to the center of the notch). (D) The tibial resection for a TKA is performed at an angle 90° to the tibial mechanical axis (line connecting the midpoint between the medial and lateral tibial eminences and the center of the ankle). (E) A higher magnification view at the level of the knee demonstrates a templated tibial cut; in a varus TKA, generally 9 mm is resected from the uninvolved lateral tibial plateau and 2mm is resected from the medial side.
Post-operative Protocol

Post-operatively, patients with a pre-operative varus deformity may be allowed to weight bear as tolerated (WBAT) without restrictions. In the setting of an iatrogenic MCL rupture or superficial MCL pie crusting, the operative extremity is braced in a hinged knee brace with unrestricted range of motion. Routine post-operative antibiotics and anticoagulation should also be utilized.

References

Patellar Dislocation after Total Knee Arthroplasty for Neglected Chronic Post-traumatic Patellar Dislocation: A Case Report

Abstract
Chronic post-traumatic patellar dislocation is a rare condition that presents a therapeutic challenge to the treating physician. The authors present the case of a 72-year-old female with a greater than 30-year history of neglected chronic post-traumatic patellar dislocation and resulting severe osteoarthritis who underwent total knee arthroplasty (TKA) and subsequently sustained a patellar dislocation after a fall. The patient was successfully treated with a revision soft-tissue procedure with post-operative immobilization in a cast and subsequently regained full range of motion.

This case highlights the importance of an adequate lateral retinacular release, the use of pants-over-vest imbrication as a technique to improve patellar tracking, post-operative immobilization, and the conservative course of rehabilitation to prevent recurrent patellar dislocation.

Level of Evidence: V

Keywords: total knee arthroplasty, chronic patellar dislocation

Introduction
Chronic post-traumatic dislocation of the patella is rare and results in persistent dislocation throughout the arc of motion of the knee.1 Whereas newborns with trochlear dysplasia may exhibit congenital patellar dislocation, typical delayed presentation in adults is often due to trauma and can progress to painful motion and secondary osteoarthritis. Although rare, recurrent dislocation is most commonly seen in females of late adolescence, is often familial, and approximately one-third are bilateral.2 Recurrent dislocation has been attributed to factors including inappropriate care following acute trauma, familial and/or anatomic predisposition, and ligamentous laxity.3 Miller et al. suggest that unilaterality, dislocation after adolescence, or adaptive changes could explain the delay in presentation and lack of significant functional changes.3 Treatment for chronic patellar dislocation focuses on restoration of native anatomic alignment and correction of any secondary destabilizing pathology, such as meniscal tears or loose bodies. Traditionally, treatment has included non-operative management with physical therapy, patellar realignment, or patellectomy.4 In the presence of osteoarthritis, a patellofemoral or total knee arthroplasty may be performed.5,6,7 We present a case of a patient with chronic post-traumatic patellar dislocation treated with total knee arthroplasty, who subsequently required a secondary soft tissue procedure for recurrent patellar dislocation.

Case Report
A 72-year-old-female presented to the clinic with right knee pain for over 30 years after sustaining an injury in 1977 and undergoing a procedure unknown to her at the time of presentation. She had been able to function reasonably well without limitation, but over the preceding months the pain had become more disabling. The patient ambulated with a cane at baseline but had difficulty with walking distances greater than one city block and ascending stairs. Her pain was primarily in the lateral compartment but was present in all three compartments. On inspection of her right knee she had a scar from a previous medial incision and her patella was dislocated laterally. Examination demonstrated an eight degree valgus deformity with passive range of motion from 10 to 90 degrees of flexion. She had a 45-degree extensor lag associated with 3/5 quadriceps strength and 4/5 strength of her extensor hallucis longus, flexor hallucis longus, and tibialis anterior. In addition to the lateral patellar dislocation, radiographs also demonstrated severe tricompartmental osteoarthritis and lateral subluxation of the tibia on the femur (Fig. 1).

After an in-depth discussion of the risks, benefits, and alternatives to surgical treatment, the patient elected to proceed with TKA. She
underwent a right TKA using a standard midline incision and medial parapatellar approach with a posterior-stabilized, fixed-bearing prosthesis (Fig. 2). A lateral release of the patella was performed to allow for medialization of the patella and proper patellar tracking. After surgery she was permitted full weight bearing and she was not immobilized. Continuous passive motion was also not instituted due to risk of re-dislocation.

Three weeks post-operatively, the patient returned to clinic with limited range of motion and visible deformity of the patella, though unaware of a possible dislocation (Fig. 3). She stated that she had a fall at her rehabilitation facility one week prior to her visit but with no resulting limitation in her progress. Examination revealed a lateral dislocation of the patella with passive range of motion from 10 to 110 degrees and a 50-degree extensor lag.

The patient was readmitted to the hospital and brought to the operating room. The recent midline incision, which was well-healed at the time of revision, was utilized. Following the medial parapatellar arthrotomy, the positioning of the femoral, tibial, and patellar components was carefully inspected. It was determined that the components were appropriately positioned. The previous lateral release was identified and reopened using blunt digital dissection. After this maneuver, the patella was easily relocated into the trochlear groove, and proper patellar tracking was confirmed with range of motion from 0 to 110 degrees using the no thumbs technique. A pants-over-vest imbrication of the medial retinaculum was then performed to further stabilize the patella. Prior to closure, adequate patellar tracking and positioning of the total knee components were once again confirmed. Post-operatively, a cylinder cast was applied to reduce the risk of recurrent patellar dislocation. Post-operative radiographs demonstrated...
acceptable alignment of the patella and positioning of the prosthetic components (Fig. 4).

The patient returned to clinic two weeks post-operatively. Radiographs demonstrated sustained location of the patella with no radiolucent lines or evidence of osteolysis. A new cylinder cast was applied. At one month post-operatively, the patient’s range of motion was 5–70 degrees, and she was able to ambulate with a walker. At this time, she was transitioned to a hinged knee brace locked in extension for four weeks, with the potential side effect of knee stiffness outweighing the risk of recurrent patellar dislocation. Two months post-operatively, the patient continued to do well. Her brace was discontinued and she began gentle range of motion and physical therapy. Four months post-operatively, the patient had full flexion and extension of her knee.

Discussion

Chronic, irreducible dislocations of the patella are rare and are seen most often in association with valgus knees deformities.\(^5^,^8\) Whether congenital or traumatic in etiology, patients may have considerable functional limitations in range of motion and mobility.\(^5\) For patients who undergo TKA to correct extensor mechanism insufficiency combined with osteoarthritis, special consideration should be given to ensure proper component alignment and stable patellar tracking.

Patellar complications have been cited as the most common complication after TKA, occurring at a rate of approximately 0.5–50%.\(^9^,^{10,11,12}\) Potential risk factors for instability include pre-operative valgus alignment, medial retinacular insufficiency, vastus medialis obliquus weakness, component malalignment, and trauma. Specifically, internal rotation of the femoral and tibial components is a common risk factor for dislocation. This configuration increases the Q angle, leading to patellar instability.\(^9\) Instability of the patella and altered patellar tracking due to femoral component misalignment and eccentric stresses can lead to increased polyethylene wear or aseptic loosening.\(^13\) If patellar dislocation occurs following total knee arthroplasty, additional revision procedures that lateralize the femoral component, medialize the patellar button, externally rotate the tibial and/or femoral components, or adjust the soft tissue balancing of the extensor mechanism can help to restore normal patellar tracking.\(^14,^15\)

While a lateral retinacular release has been shown to improve the tracking of the patellar component, no significant difference was found in rates of subluxation after this procedure alone.\(^16,^17\) Additionally, this technique can be complicated by patellar osteonecrosis or fracture and wound healing problems.\(^16,^{18,19,20}\) Therefore, several other techniques including proximal and distal realignment procedures as well as revision TKA have been attempted to improve outcomes.\(^21\) Kirk et al. performed a lateral release with a medializing tibial tubercle osteotomy, a modification of the Trillat procedure.\(^10\) In their case series of fifteen knees, they observed no recurrent patellar dislocations.\(^10\) Similarly, Nakajima et al. presented a case of recurrent patellar subluxation with well aligned components following TKA managed with the Elmslie-Trillat procedure.\(^22\) This procedure involves a lateral retinacular release and plication of the medial retinaculum, followed by a medializing tibial tubercle osteotomy. At one year post-operatively, the patient had no subluxation events and no patellar apprehension.\(^22\) In a retrospective review of five patients with subluxation following TKA, Price et al. performed a Fulkerson osteotomy in addition to lateral release and medial soft tissue imbrication. Patients had improved knee scores at one year post-operatively and had no dislocation/subluxation events.\(^21\) Despite the effectiveness of an osteotomy in improving recurrent dislocation due to its role in patellar lateralization restraint, Piedade et al. have described an increased incidence of skin necrosis and tibial tubercle fracture following such procedures.\(^23\) Therefore, tibial tubercle osteotomies should be reserved for recalcitrant cases where other soft tissue procedures have been ineffective.

Limited data are available regarding medial patellofemoral ligament (MPFL) reconstruction following TKA for a chronically dislocated patella. Gennip et al. showed that in nine patients, reconstruction and lateral release following patellar subluxation is an effective option to improve patellar tracking with or without tibial tubercle osteotomy.\(^24\) In their case report evaluation, Matsushita et al. also reported that MPFL reconstruction is a suitable surgical option for chronic patellar dislocation following TKA.\(^8\)

Conclusion

We present the case of a 72-year-old female with chronic patellar dislocation who traumatically re-dislocated her patella following TKA. This case demonstrates the utilization of soft tissue imbrication and careful attention to patellar tracking to recreate a properly tensioned extensor mechanism. The pants-over-vest technique identifies another alternative for surgical stabilization of chronic post-traumatic patellar dislocation combined with post-operative immobilization. It illustrates that despite adequate component alignment and patellar tracking, patients with prior patellar dislocation may be at higher risk for further dislocation following arthroplasty. Patients at higher risk should be managed with a hinged knee.
brace locked in extension or a cylinder cast for 6 weeks postoperatively to ensure adequate scar formation and extensor mechanism healing.

References

Dual Antibiotic Prophylaxis is Associated with Acute Kidney Injury after Primary Joint Arthroplasty

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Introduction
With increasing prevalence of MRSA in patients undergoing hip and knee replacement procedures, some have advocated a dual antibiotic prophylactic regimen including Vancomycin to minimize the risk of surgical site infections. Orthopaedic surgeons have studied several methods to reduce the infection rate following primary TJA. While preventing prosthetic joint infection is multifactorial, administration of prophylactic antibiotics one hour prior to surgical incision has become the standard of care in preventing SSI in primary TJA. The American Academy of Orthopaedic Surgeons (AAOS) currently recommends the use of cefazolin or cefuroxime prior to patients undergoing any orthopaedic procedure. With the increasing prevalence of methicillin-resistant staphylococcus aureus (MRSA), recent studies have suggested the addition of vancomycin to the prophylactic antibiotic regimen. Vancomycin has proven pharmacologic efficacy against gram-positive bacteria and particularly MRSA; its superiority over cefazolin or cefuroxime in reducing SSI after primary TJA continues to be debated in the literature. Administration of vancomycin is also not without adverse effects. Exposure to vancomycin has been shown to be a risk factor for development of vancomycin resistant enterococcus (VRE) and acute kidney injury (AKI). The purpose of this study is to determine if patients receiving antibiotic prophylaxis with Cefazolin and Vancomycin have a higher rate of postoperative acute kidney injury (AKI) compared to patients receiving Cefazolin alone prior to elective primary hip and knee replacement surgery.

Materials and Methods
We retrospectively reviewed a consecutive series of patients who underwent primary TKA or THA at a single high-volume academic institution between September 2008 and December 2012. The study was conducted according to guidelines set forth by our hospital’s Institutional Review Board (IRB). We included all patients who received cefazolin alone or cefazolin plus vancomycin as perioperative antibiotic prophylaxis prior to TJA. Patients were excluded from the study if they had a documented allergy to penicillins, cephalosporins, or vancomycin or if they received an antibiotic other than cefazolin or vancomycin prior to surgery. A SSI was defined according to Centers for Disease Control and Prevention (CDC) guidelines as an infection occurring at the surgical site within 30 days of the operation or up to 1 year if an implant was inserted and the infection appears related to the surgery. The SSI rate of both groups was previously published. We recorded patient variables that could impact postoperative renal function including American Society of Anesthesiologists (ASA) classification, age, surgical procedure, estimated blood loss (EBL), intraoperative fluid resuscitation, and preoperative kidney function. Each patient’s preoperative creatinine was documented in addition to creatinine on post-operative days 1 and 2 as per our hospital’s protocol. Preoperative kidney disease was defined as if the patient’s preoperative GFR was less than 60 mL/min/1.73 m². We defined and classified postoperative AKI according to the published, validated Acute Kidney Injury Network (AKIN) criteria. We first performed an a priori power analysis to identify an adequately powered sample size for our study. Univariate logistic regression analysis of all variables was performed to identify risk factors for postoperative AKI. To control for confounding variables, we analyzed the data using a multivariate logistic regression model to identify independent risk factors for acute kidney injury following primary joint arthroplasty.

Of the 2215 consecutive primary TJA patients during the study period, 1828 patients met inclusion criteria and were included in the final analysis. There were 500 patients in the cefazolin group and 1328 patients in the cefazolin plus vancomycin group. Complete demographic details of the patient population are shown in table 1.

Results
The overall incidence of patients with AKI following surgery was 11.3% (207 patients). Patients in the dual antibiotic prophylaxis
group were more likely to sustain AKI than patients receiving cefazolin alone (12.6% vs. 7.8%, p = 0.002). There was no statistical difference between the groups with respect to EBL, intraoperative fluid resuscitation, preoperative kidney function, or percent change in GFR postoperatively.

Patients returned to within 50 percent of baseline kidney function at an overall mean of 2.6 days (range 1-29 days). While there was no difference in the time to return to baseline kidney function (2.7 vs. 2.2 days, p = 0.155) between the dual antibiotic group and cefazolin alone (Figure 2), patients with dual antibiotic prophylaxis were more likely to have severe grade II or III kidney injury (3.1% vs. 0.0%, p < 0.001). Two patients required dialysis following joint replacement surgery, both in the cefazolin and vancomycin group, and both with multiorgan system complications in the intensive care unit.

Using multivariate logistic regression to controlling for confounding variables, we found that dual antibiotic prophylaxis is an independent risk factor for AKI after primary TJA (adjusted OR 1.82, 95% CI 1.25 - 2.64). ASA classification (adjusted OR 1.64, 95% CI 1.24 - 2.17) and preoperative kidney disease (adjusted OR 1.81, 95% CI 1.30 - 2.52) were also independent risk factors. Age, procedure, EBL, and intraoperative fluid resuscitation were not significant risk factors for development of AKI (Table 2).

### Table 1. Comparison of outcomes between patients receiving cefazolin alone and cefazolin plus vancomycin perioperatively.

<table>
<thead>
<tr>
<th>Patient Variable</th>
<th>Ancef Only (n = 500)</th>
<th>Ancef + Vancomycin (n = 1328)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury (%)</td>
<td>39 (7.8)</td>
<td>168 (12.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Surgical Site Infection (%)</td>
<td>7 (1.4)</td>
<td>15 (1.1)</td>
<td>0.636</td>
</tr>
<tr>
<td>Estimated Blood Loss in mL (SD)</td>
<td>277 (418)</td>
<td>223 (309)</td>
<td>0.476</td>
</tr>
<tr>
<td>Intraoperative Fluids in mL (SD)</td>
<td>1825 (890)</td>
<td>1837 (874)</td>
<td>0.576</td>
</tr>
<tr>
<td>Preoperative Kidney Disease (%)</td>
<td>128 (26)</td>
<td>283 (21)</td>
<td>0.050</td>
</tr>
<tr>
<td>Preoperative GFR in mL/min/1.73 m^2 (SD)</td>
<td>770 (26)</td>
<td>78.6 (26)</td>
<td>0.645</td>
</tr>
<tr>
<td>Preoperative Creatinine in mg/dL (SD)</td>
<td>1.00 (0.84)</td>
<td>0.92 (0.54)</td>
<td>0.844</td>
</tr>
<tr>
<td>Percent Change GFR</td>
<td>47.3</td>
<td>44</td>
<td>0.186</td>
</tr>
</tbody>
</table>

### Table 2. Univariate and multivariate logistic regression analysis of risk factors for AKI after primary hip and knee arthroplasty.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th></th>
<th>Multivariate Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
<td>p value</td>
<td>Odds Ratio</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.01</td>
<td>1.00-1.02</td>
<td>0.048</td>
<td>1.01</td>
</tr>
<tr>
<td>Knee Arthroplasty</td>
<td>1.03</td>
<td>0.76-1.38</td>
<td>0.871</td>
<td>1.23</td>
</tr>
<tr>
<td>EBL (per 100mL)</td>
<td>1.03</td>
<td>1.00-1.07</td>
<td>0.087</td>
<td>1.04</td>
</tr>
<tr>
<td>Intraoperative Fluids (per 100mL)</td>
<td>1.02</td>
<td>1.00-1.03</td>
<td>0.056</td>
<td>1.02</td>
</tr>
<tr>
<td>ASA</td>
<td>1.75</td>
<td>1.33-2.29</td>
<td>&lt; 0.001</td>
<td>1.64</td>
</tr>
<tr>
<td>Dual Antibiotic Prophylaxis</td>
<td>1.71</td>
<td>1.89-2.47</td>
<td>0.003</td>
<td>1.82</td>
</tr>
<tr>
<td>Preoperative kidney disease</td>
<td>1.87</td>
<td>1.37-2.55</td>
<td>&lt; 0.001</td>
<td>1.81</td>
</tr>
</tbody>
</table>

**Discussion**

This study suggests no difference in SSI between patients receiving cefazolin alone and cefazolin plus vancomycin prior and is in keeping with published infection rates for primary TJA in the literature. The effect of the addition of vancomycin...
on renal function, however, appears to be transient, as there was no difference in the number of days to return to baseline creatinine (2.7 vs. 2.2 days, p = 0.155). Only 1% of all patients in both groups met criteria for AKI after post-operative day six (Figure 1). The impact of dual antibiotic prophylaxis on kidney function is limited to the immediate post-operative period. Whether or not this transient renal insult will limit patients’ ability to deal with future renal injury is beyond the scope of this study.

There are several limitations to our study. Its retrospective design requiring a review of medical records has inherent limitations. A single surgeon treated the large majority of patients receiving cefazolin only for prophylaxis, leading to a potential selection bias, however there was no difference in age or ASA classification between the groups. While we controlled for multiple confounding variables such as age, medical comorbidities (ASA), preoperative kidney function, EBL, and intraoperative fluid resuscitation, we did not control for patients receiving other drugs with the potential for nephrotoxicity. Medications such as angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), or other non-steroidal anti-inflammatory drugs (NSAIDs) may have the potential to effect kidney function postoperatively.

Multivariate logistic regression analysis revealed dual antibiotic prophylaxis, ASA classification, and preoperative kidney disease to be independent predictors of AKI postoperatively. This finding agrees with data from Jafari et al who found that preoperative kidney disease and medical comorbidities predisposed patients to developing AKI after primary TJA. In patients at low risk for MRSA, the authors suggest avoiding the addition of vancomycin in patients with pre-existing renal dysfunction and multiple medical comorbidities. We should be cautious about decolonizing patients and furthering drug resistant bacteria with the widespread use of vancomycin. Further studies should determine the value of selective preoperative screening for MRSA to determine perioperative antibiotic prophylaxis.

References
The Effect of Malnutrition and Morbid Obesity on Complication Rates Following Primary Total Joint Arthroplasty

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Department of Orthopaedic Surgery
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Introduction
The association with malnutrition and obesity and its impact on outcomes after TJA is not clear. Some studies have shown an association with obesity and malnutrition leading to increased rates of periprosthetic infection and persistent wound drainage.1,2 While some orthopaedic surgeons consider both morbid obesity and malnutrition to be modifiable risk factors, however the effect of correcting these risk factors prior to elective TJA has yet to be addressed in the literature. Whether or not obesity and/or malnutrition independently predict complication rates is not well defined. What predisposes patients to short-term complications after primary TJA: low serum albumin, high BMI, or both?

We sought to further identify independent risk factors leading to complications after primary TJA and to correlate those factors with readmission rates and post-operative complications leading to a return to the operating room. The purpose of our study was to determine if any association between malnutrition and morbid obesity exists and if malnutrition and morbid obesity independently increase complications following primary TJA.

Materials and Methods
We retrospectively reviewed a consecutive series of patients who underwent elective primary hip or knee replacement surgery at a single high-volume academic center from June 2013 to December 2013. Nutritional markers are routinely obtained as part of each patient’s preoperative medical evaluation within 30 days of the procedure. Patients were categorized as malnourished if the preoperative serum albumin was less than 3.5 mg/dL and morbidly obese if their body mass index (BMI) was greater than 40 kg/m² based on the World Health Organization classification of obesity.3,4,5

Medical comorbidities, demographics, postoperative complications, and 90-day readmission rates were documented for each patient from the electronic medical record. We defined a postoperative complication based on the classification published by Sink et al.6 Grade I complications such as constipation, postoperative nausea, and fever that resolved without treatment were excluded. We also recorded reasons for return to the operating room for the duration of the study period, but limited follow-up for postoperative medical complications to 90 days, as any medical condition after this period was likely unrelated to the index surgery. Surgical complications were followed for a minimum of 6 months.

An a priori power analysis was conducted to determine the appropriate sample size for the study. Because our primary outcome variable of postoperative complication was binary, we analyzed the data with univariate and multivariate logistic regression. Univariate logistic regression analysis was then performed to identify risk factors for complications. To control for confounding variables, we then performed multivariate logistic regression to determine if morbid obesity and malnutrition are independent risk factors for complications after primary total joint procedures.

Results
Morbidly obese patients were more likely to be malnourished than non-morbidly obese patients (19% vs. 11%, p = 0.010). Among patients with normal nutritional status, morbidly obese patients had no significant difference in complication rates than non-morbidly obese patients (7% vs. 8%, p = 0.661). Malnourished morbidly obese patients also had no difference in complication rate than malnourished patients with a BMI < 40 kg/m² (29% vs. 25%, p = 0.726). Differences in complications grouped by morbid obesity and malnutrition are listed in table 2.

When compared to patients with normal nutritional status, malnourished patients were more likely to have a postoperative complication (27% vs. 8%, p < 0.001), ICU intervention (14% vs. 2%, p < 0.001), return to OR (8% vs. 3%, p = 0.008), and 90-day readmission (17% vs. 4%, p < 0.001). Patients who were malnourished were more also likely to return to the OR for infection than patients with normal nutritional status (6% vs. 0.3%, p = 0.004). Of patients sustaining complications after primary TKA requiring return to the operating room, 10
patients underwent manipulation under anesthesia and 4 patients underwent subsequent surgery for infection. Of the patients requiring surgical complications after THA, 3 patients sustained periprosthetic femur fracture, 3 patients required surgery for wound drainage or infection, and 4 patients required subsequent surgery for instability. Based on multivariate logistic regression analysis, malnutrition is an independent risk factor for complications following primary TJA (adjusted odds ratio 3.00, 95% CI 1.56 – 5.75). Our study did not detect a significant independent increase in complications in obese patients with BMI > 35, 40, 45, or 50 kg/m². Univariate and multivariate logistic regression analyses are detailed in table 3.
The link between malnutrition and obesity in total joint arthroplasty (TJA) has been linked to short-term complications following TJA as well. The increase in hospital complication or readmission rates, morbid obesity in the absence of malnutrition may not adequately power to detect this difference between the subgroups of morbidly obese hip and knee patients. While morbid obesity in the absence of malnutrition may not increase in hospital complication or readmission rates, other published studies. Obesity and morbid obesity has in joint replacement surgery is in agreement with several other published studies.4,15 Malnutrition, which was used in several published studies.3,15 Obesity and morbid obesity has also been linked to short-term complications following TJA as well.10,11,12 The link between malnutrition and obesity in TJA is not as clear, however. Our study sought to explain if short-term complications in morbidly obese primary total hip and knee arthroplasty patients are due to the patient’s high BMI, low serum albumin, or both.

This study has several limitations including its retrospective design. Follow-up for our study was limited. We can accurately report short-term complications, critical care intervention, and readmission rates, long-term complications such as revision arthroplasty for loosening, infection, and instability were not followed after 6 months. Our study was adequately powered to detect a difference in complications among all primary total joints patients, however it lacked adequate power to detect this difference between the subgroups of morbidly obese hip and knee patients. While morbid obesity in the absence of malnutrition may not increase in hospital complication or readmission rates, several studies have shown a negative effect of increased BMI on both infection and survivorship of total hip and knee arthroplasty.13,14 Another limitation is our definition of malnutrition. Serum albumin has been validated as a marker for nutritional status in orthopaedic surgery patients, but the orthopaedic literature is lacking in defining a strict cutoff for malnutrition.3,15 We used a threshold of 3.5 mg/dL to define malnutrition, which was used in several published studies.3,15 Other nutritional markers such as transferring, prealbumin, and absolute neutrophil count were not measured in our study.

Although the complication rate, ICU rate, and 90-day readmission was higher for all malnourished patients, there was no difference in complications between malnourished morbidly obese patients and malnourished patients with BMI under 40 kg/m² (29% vs. 25%, p = 0.726). Similarly, morbidly obese patients with normal nutritional status also had no difference in complications than non-morbidly obese patients with normal nutritional status (7% vs. 8%, p = 0.661). When controlling for other confounding variables with logistic regression, we did not find obesity or morbid obesity to be an independent risk factor in our series. Our data suggests that morbidly obese patients with normal nutritional status also had no difference in complications than non-morbidly obese patients with normal nutritional status at-risk patients for complications. Further study is needed to determine if correcting malnutrition prior to surgery will improve outcomes following primary TJA.

### Table 3. Multivariate logistic regression analysis of comorbid risk factors for complications after primary TJA.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>95% Confidence Interval</td>
<td>p value</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>4.14</td>
<td>2.34 – 7.33</td>
</tr>
<tr>
<td>BMI &gt; 50 kg/m2</td>
<td>1.09</td>
<td>0.25 – 4.85</td>
</tr>
<tr>
<td>BMI &gt; 45 kg/m2</td>
<td>0.57</td>
<td>0.20 – 1.63</td>
</tr>
<tr>
<td>BMI &gt; 40 kg/m2</td>
<td>1.12</td>
<td>0.60 – 2.09</td>
</tr>
<tr>
<td>BMI &gt; 35 kg/m2</td>
<td>0.92</td>
<td>0.54 – 1.57</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>1.27</td>
<td>0.61 – 2.58</td>
</tr>
<tr>
<td>Hip Arthroplasty</td>
<td>1.13</td>
<td>0.67 – 1.88</td>
</tr>
<tr>
<td>COPD</td>
<td>2.84</td>
<td>1.17 – 6.87</td>
</tr>
<tr>
<td>CAD</td>
<td>2.94</td>
<td>1.49 – 5.78</td>
</tr>
<tr>
<td>CHF</td>
<td>2.92</td>
<td>1.84 – 4.00</td>
</tr>
<tr>
<td>Intraoperative Vasopressors</td>
<td>1.44</td>
<td>0.87 – 2.37</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>6.01</td>
<td>3.45 – 10.47</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.78</td>
<td>0.39 – 1.54</td>
</tr>
</tbody>
</table>

### Discussion

Many surgeons consider both morbid obesity and malnutrition to be modifiable risk factors when selecting a patient for TJA. However, some factors may be more modifiable than others. Morbidly obese patients with debilitating osteoarthritis may find weight loss through exercise difficult, however nutrition can be modified with supplements prior to undergoing primary TJA. Our data demonstrating malnutrition as an independent risk factor for complications in joint replacement surgery is in agreement with several other published studies. Obesity and morbid obesity has also been linked to short-term complications following TJA as well.10,11,12 The link between malnutrition and obesity in TJA is not as clear, however. Our study sought to explain if short-term complications in morbidly obese primary total hip and knee arthroplasty patients are due to the patient’s high BMI, low serum albumin, or both.

This study has several limitations including its retrospective design. Follow-up for our study was limited. We can accurately report short-term complications, critical care intervention, and readmission rates, long-term complications such as revision arthroplasty for loosening, infection, and instability were not followed after 6 months. Our study was adequately powered to detect a difference in complications among all primary total joints patients, however it lacked adequate power to detect this difference between the subgroups of morbidly obese hip and knee patients. While morbid obesity in the absence of malnutrition may not increase in hospital complication or readmission rates, several studies have shown a negative effect of increased BMI on both infection and survivorship of total hip and knee arthroplasty.13,14 Another limitation is our definition of malnutrition. Serum albumin has been validated as a marker for nutritional status in orthopaedic surgery patients, but the orthopaedic literature is lacking in defining a strict cutoff for malnutrition.3,15 We used a threshold of 3.5 mg/dL to define malnutrition, which was used in several published studies.3,15 Other nutritional markers such as transferring, prealbumin, and absolute neutrophil count were not measured in our study.

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References

The Use of Press-fit Stems in Revision Total Knee Arthroplasty

Introduction

The routine use of stems has been shown to improve the outcomes and survival rate in revision total knee arthroplasty. Stems are widely used to supplement component fixation, acting to bypass bone defects, offload deficient bone, and reduce interface stresses of damaged bone in the distal femur and proximal tibia. The optimal method of stem fixation in revision TKA, however, continues to be debated in the literature. Several studies have demonstrated good long-term clinical results with cemented stems in revision TKA. Cemented stems provide immediate fixation with less intrusion into the intramedullary canal, however they can present a challenge to remove and theoretically increase stress shielding surrounding the metaphyseal bone.

More recently, some orthopaedic surgeons have advocated the use of a press-fit diaphyseal stem with cement in the metaphyseal portion of the implant. The use of a long stem that fills the intramedullary canal and engages diaphyseal bone has been shown to improve component alignment. In biomechanical studies, short, cemented stems have shown equivalent strength of fixation with longer press-fit stems. In this review, we will describe the indications, surgical technique, and clinical results of this hybrid technique for fixation in revision TKA.

Indications

Press-fit stems should be considered for all patients with a failed primary total knee arthroplasty. Patients must have structural integrity of both the femoral and tibial canals to accommodate a wider press-fit stem. The intramedullary canals should be correlated with the mechanical axis of the limb as the stem will dictate the position of the components. Care should be taken to make sure the components are appropriately lateralized for patellar tracking, as longer press-fit stems can result in improper component positioning, particularly the tibia where the canal is posteromedial relative to the plateau. Most manufacturers make offset stems to solve this problem. Those patients with large metaphyseal bone defects and soft tissue laxity are also good candidates for press-fit stems. Longer uncemented stems will bypass the bony defect and provide more support in both the rotational and bending planes.

There are several relative contraindications to the use of uncemented stems in revision TKA. Patients with wide, osteopenic intramedullary canals often require cement fixation. In the setting of infection, press-fit stems are unable to deliver local antibiotics as in the case of a fully cemented canal. End-of-stem pain has also been described with older cobalt chromium uncemented stems, however newer fluted titanium stems have experienced this problem less frequently.

Surgical Technique

Here we explain the surgical technique used by the authors for hybrid fixation in revision TKA. Regardless of the type of fixation that is chosen, adequate surgical exposure must be obtained in order to gain proper visualization and allow for safe removal of implants with minimal iatrogenic bone loss. Following implant removal, a thorough debridement of all fibrous tissue and remaining cement must be performed to allow for proper implant fixation to host bone and to avoid eccentric canal reaming and potential perforation due to retained cement. Femoral and tibial intramedullary canal debridement can be facilitated with using instruments such as the “back scraper” and cement removing osteotomes typically found in the Depuy Moreland set (Warsaw, IN). Attention should first be turned to reconstruction of the tibia, as tibial reconstruction can affect both the flexion and extension space and acts as a foundation for revision TKA.

Tibial component revision begins with a “freshen up” cut on the tibia. This resection can be performed using a “free-hand” technique, with the use of an extramedullary guide, or with an intramedullary guide and an attached resection guide. The author’s preference is to make tibial resection with an intramedullary guide with a 0 degree slope resection guide. The tibial canal is either reamed by hand or on power to determine the appropriate sizing of type of
canal. Once the canal diameter has been determined, a reamer handle is left in the canal and used as a guide for the resection. A common tendency is to undersize the femoral and tibial stems in order to avoid creating a periprosthetic fracture.

Typically, a tibial resection guide is secured in position over the intramedullary guide with two drill pins as the remaining anterior cortical tibial bone is often sclerotic making placement of mechanical pins with a mallet difficult and inaccurate. The 0 degree guide allows for the resection to be made from any position—medial or central, depending on the ability of the patellar tendon to be mobilized laterally. Guides that are sloped can result in a varus resection if the cut is made medial to lateral, resulting in a biplanar proximal tibial resection.

Following the tibial resection, the intra-medullary reamer is maintained in position and a tibial sizing tray of the appropriate size is placed in the proper external rotation. An offset bushing is often available from most manufacturing companies to determine the necessary amount of offset needed for reconstruction. Most revision TKA systems offer anywhere from 4-8 mm of offset. Most commonly, the tibial tray sits posterior and lateral from the intra medullary tibial canal. Drill pins are used to secure the tray in its final position and the degree of offset is recorded. A drill and a punch are used for final preparation of the proximal tibia. All instrumentation is removed and the trial tibia with the appropriate diameter offset stem in the proper offsets position is assembled and placed on the tibia. A 100 mm length stem is typically used for the tibial reconstruction (Figure 1).

Attention is now turned to the femur for reconstruction. In the setting of revision TKA, it is typical to be looser in flexion than in extension and often times, the tendency is to raise the joint line. Most commonly, the femoral component that was removed is upsides one size and an augment is placed posterolaterally (to assist with component external rotation) with an augment placed both distal medial and distal lateral (to avoid creating excessive patella baja). The femoral canal
is again reamed either by hand or on power to determine the appropriate canal diameter. Once the diameter has been chosen, one diameter smaller is often selected for the purpose of trialing. The offset stem is typically placed in a posterior position; however, the stem is placed on the trial femur in a loose manner so the canal and the remaining host femoral condyles can assist in finding the correct alignment and component position, respectively. The stem length on the femoral side is typically longer and is in judge range of 150 mm.

Once the final component sizes have been chosen for both the femur and the tibia, all trial components are removed and the final components are assembled on the back table. Typically two batches of cement, with a total of 2 grams of antibiotics per batch of cement, are used for cementation of each component. The tibial component is cemented in position first—the cement is placed under the tibial tray to include the modular junction and slightly beyond. The same cement technique is used for the femur. All excess cement is removed and a trial polyethylene of the appropriate thickness of each component. The tibial component is cemented in a loose manner so the canal and the remaining host metaphysical bone stock. The stems are assist with construct alignment as well as protection of the extension during the cement curing process.

The stems in this type of reconstruction are used to assist with construct alignment as well as protection of the remaining host metaphysical bone stock. The stems are NOT in-growth surfaces, however act as a “deep nice-post” to perform the functions previously stated (Figure 2). This technique demonstrates why undistinguished placement of the stem on both the femoral and tibial sides is suboptimal, as an undersized stem may not result in appropriate stability of the construct and lead to early loosening.

### Clinical Results

Clinical results have demonstrated favorable mid-term clinical outcomes for press-fit stems in revision TKA. Table 1 summarizes the clinical studies. In a retrospective series of consecutive patients undergoing revision TKA with a hybrid technique, Sah et al reported 92% survivorship at 5 years and 84% survivorship at 10 years. Wood et al reported similar results with a survivorship from aseptic loosening of 98% at 12 years. Patients in both series reported good functional outcomes. Although prospective studies comparing cemented stems and hybrid fixation with long follow-up are still needed, press-fit stems are a reliable option for fixation in revision total knee arthroplasty.

### References


### Table 1. Summary of clinical results of studies for the use of press-fit stems in revision total knee arthroplasty.

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients</th>
<th>Knee Society score (preop-postop)</th>
<th>Aseptic revision rate</th>
<th>Survivorship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hass et al (1995)</td>
<td>76</td>
<td>49-76</td>
<td>2.6% at 3 yrs</td>
<td>83% at 8 yrs</td>
</tr>
<tr>
<td>Gofton et al (2002)</td>
<td>89</td>
<td>40-52</td>
<td>4.5% at 5.9 yrs</td>
<td>93.5% at 8.6 yrs</td>
</tr>
<tr>
<td>Shannon et al (2003)</td>
<td>63</td>
<td>56-81</td>
<td>10% at 5.7 years</td>
<td>84% at 6 years</td>
</tr>
<tr>
<td>Fehring et al (2003)</td>
<td>95</td>
<td></td>
<td>71% “stable”</td>
<td></td>
</tr>
<tr>
<td>Bottner et al (2006)</td>
<td>33</td>
<td>42-83</td>
<td>6% at 3 yrs</td>
<td></td>
</tr>
<tr>
<td>Wood et al (2009)</td>
<td>135</td>
<td>55-86</td>
<td>1.5% at 5 yrs</td>
<td>87% at 12 yrs</td>
</tr>
<tr>
<td>Sah et al (2011)</td>
<td>88</td>
<td>46-85</td>
<td>90% at 40 months</td>
<td>92% at 5 yrs, 84% at 10 yrs</td>
</tr>
<tr>
<td>Manopoulos et al (2012)</td>
<td>46</td>
<td>42-84 (IKS score)</td>
<td>4.3% at 8.5 yrs</td>
<td>90% at 10 yrs</td>
</tr>
<tr>
<td>Iamaguchi et al (2013)</td>
<td>34</td>
<td>35-81</td>
<td>100% at 2.2 yrs</td>
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</table>
Heart Murmurs as a Predictor for Post-arthroplasty Complications and Performance

Introduction

By 2033, demand for total knee arthroplasty is predicted to rise by 174% and total hip arthroplasty by 673%. Patients report good satisfaction with these procedures, however adverse event rates as high as 7.4%, and large numbers of patients requiring discharge to rehabilitation centers continue to negatively affect outcomes and add to expense. With new Medicare and Medicaid pay-for-performance programs rewarding better outcomes, there is pressure to reduce complication rates and rehabilitation requirements without increasing cost. Finding cost-effective, early-detection tools to identify patients at risk of post-arthroplasty complications is therefore an important topic of study.

The post-operative cardiac exam is a low-cost screening method that is often overlooked by orthopedic surgeons. It has been noticed at our institution that a high number of arthroplasty patients have post-operative heart murmurs, but to our knowledge, there is no orthopaedic literature assessing the significance of this. The purpose of this study was to assess the correlation between post-operative heart murmurs and post-operative outcomes in hip and knee arthroplasty patients. We hypothesized that heart murmurs would be associated with increased complications, decreased physical therapy capacity, and increased need for discharge to rehabilitation facilities following primary joint arthroplasty.

Materials and methods

This was a single institution prospective cohort study. Inclusion criteria were patients who underwent a primary hip or knee replacement surgery between 4/1/14 and 5/30/14, were over the age of eighteen, did not have a planned ICU admission, spoke English, and gave informed consent. Exclusion criteria were patients who were pregnant or incarcerated. Data was recorded from time of surgery to time of discharge. Every patient received a physical and cardiac exam by a resident and a hospitalist attending within 24 hours of surgery to detect the presence of a heart murmur.

Patient characteristics included age, sex, body mass index (BMI), past medical history, and procedure type. Post-operative complications included myocardial infarction, atrial fibrillation, stroke, DVT, pulmonary embolism, acute kidney injury, and blood transfusion. Other measured post-operative variables included distance walked with physical therapy and whether a patient was discharged to home versus a rehabilitation facility. All patients had a CBC and BMP checked each morning for at least 48 hours following surgery. Acute kidney injury was defined as an increase in creatinine of 50 percent or of 0.3 mg/dL within 24 hours. Heart murmurs were recorded whether or not the patient had a murmur preoperatively.

Chi-square tests and T-tests were used to compare group demographics and to test for correlation.

Results

151 of 181 (89.5%) patients who underwent a primary hip or knee arthroplasty met inclusion requirements. Fifty-five (36.4%) of procedures were hip arthroplasties. Fifty three (35%) of patients were male and the average BMI was 32.5. Twenty eight (18.5%) of patients had murmurs post-operatively. All murmurs were systolic. Thirty (19.9%) patients had a total of 32 complications. Acute kidney injury and need for blood transfusion comprised the majority of complications. (Table 1) Other complications included hypotension and partial small bowel obstruction.

The murmur and non-murmur groups were comparable in age, BMI, and type of procedure. Past medical history between groups were comparable except for cardiac history (32.1% versus 13%, p = 0.014). There was a significantly lower proportion of males compared to females with post-operative murmurs (10.7% versus 40.7% p = 0.003).

Patients with post-operative murmurs had a significantly higher rate of acute kidney injury (22% versus 5.7%, p = 0.03). The groups did not have a significantly different rate of blood transfusion (7% versus 8.9% p = 0.3). The number of other measured complications was

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Josh Steere, MD
Jaimo Ahn, MD PHD
Eric Hume, MD
not high enough to compare the two groups. Patients with murmurs walked 21.1 feet less than those without (67 versus 45.9, \( p = 0.12 \)), and they were half as likely to be discharged home (14.3\% versus 29.3\%, \( p = 0.1 \)). (Table 2)

### Discussion

In this prospective cohort of hip and knee arthroplasty patients, 18\% of patients had a post-operative heart murmur, and patients with post-operative murmurs were over three times as likely to develop acute kidney injury. Decreased ability to participate with physical therapy and increased rate of discharge to a rehabilitation facility trended towards significance.

Current orthopaedic literature is vague about the significance of post-operative murmurs. The American Heart Association and American College of Cardiology (AHA/ACC) recommend echocardiography if there is ‘moderate probability’ for structural heart disease associated with a murmur.\(^6,7\) However, because concern for acute structural changes of the heart is usually low, and post-operative workup for murmurs can be expensive, post-operative murmurs are usually ignored as no workup is indicated.\(^6\)

This study lends evidence that auscultating for heart-murmurs post-operatively may represent a cost effective strategy for identifying patients at risk of developing post-operative acute kidney injury and may identify those with

### Table 1: Patient demographics.

<table>
<thead>
<tr>
<th>Total</th>
<th>151</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hip Athroplasty</td>
<td>55 (36.4%)</td>
</tr>
<tr>
<td>Age</td>
<td>61.2 ± 10.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>53 (35%)</td>
</tr>
<tr>
<td>BMI</td>
<td>32.5 ± 7.8</td>
</tr>
<tr>
<td>PMH</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (11.3%)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>25 (16.6%)</td>
</tr>
<tr>
<td>Renal</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td>Pulmonary (Asthma/COPD)</td>
<td>28 (18.5%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>9 (6.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>61 (40%)</td>
</tr>
<tr>
<td>Complications</td>
<td>32</td>
</tr>
<tr>
<td>AKI</td>
<td>12 (7.9%)</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>13 (8.6%)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>0</td>
</tr>
<tr>
<td>Afib/Stroke/MI</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (0.66%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (4.0%)</td>
</tr>
<tr>
<td>Murmur</td>
<td>28 (18.5%)</td>
</tr>
</tbody>
</table>

### Table 2. Comparison of patients with and without murmurs.

<table>
<thead>
<tr>
<th></th>
<th>With post-operative murmur</th>
<th>Without post-operative murmur</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>28</td>
<td>123</td>
<td>n/a</td>
</tr>
<tr>
<td>Age</td>
<td>63.8 ± 9.9</td>
<td>60.57 ± 10.6</td>
<td>( p = 0.15 )</td>
</tr>
<tr>
<td>Male sex</td>
<td>3 (10.7%)</td>
<td>50 (40.7%)</td>
<td>( p = 0.003 )</td>
</tr>
<tr>
<td>BMI</td>
<td>33.1 ± 7.4</td>
<td>32.4 ± 7.9</td>
<td>( p = 0.66 )</td>
</tr>
<tr>
<td>Procedure (Hip arthroplasty)</td>
<td>7 (25%)</td>
<td>48 (39%)</td>
<td>( P = 0.16 )</td>
</tr>
<tr>
<td>PMH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>3 (10.7%)</td>
<td>14 (11.4%)</td>
<td>( p = 0.9 )</td>
</tr>
<tr>
<td>Cardiac</td>
<td>9 (32.1%)</td>
<td>16 (13%)</td>
<td>( p = 0.014 )</td>
</tr>
<tr>
<td>Renal</td>
<td>1 (3.5%)</td>
<td>6 (4.9%)</td>
<td>( p = 0.7 )</td>
</tr>
<tr>
<td>Pulmonary (Asthma/COPD)</td>
<td>5 (17.9%)</td>
<td>23 (18.7%)</td>
<td>( p = 0.9 )</td>
</tr>
<tr>
<td>Vascular</td>
<td>1 (3.5%)</td>
<td>8 (6.5%)</td>
<td>( p = 0.56 )</td>
</tr>
<tr>
<td>Other</td>
<td>15 (53.6%)</td>
<td>46 (37.4%)</td>
<td>( p = 0.11 )</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>5 (17.9%)</td>
<td>7 (5.7%)</td>
<td>( p = 0.03 )</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>2 (7.1%)</td>
<td>11 (8.9%)</td>
<td>( p = 0.3 )</td>
</tr>
<tr>
<td>MI/Afib/Stroke/DVT/PE</td>
<td>1 (3.6%)</td>
<td>0 (0%)</td>
<td>n/a</td>
</tr>
<tr>
<td>Distance walked (feet)</td>
<td>45.9</td>
<td>67</td>
<td>( p = 0.12 )</td>
</tr>
<tr>
<td>Discharged Home</td>
<td>4 (14.3%)</td>
<td>36 (29.3%)</td>
<td>( p = 0.1 )</td>
</tr>
</tbody>
</table>
decreased ability to perform with physical therapy. Heart murmurs have been associated with increased cardiac output, increased strain of the heart, and decreased physiologic reserve. Arthroplasty patients, who are often older with multiple comorbidities, may have a lower tolerance for increased heart strain. This could explain the relationship between a post-operative murmur, increased acute kidney injury, and a reduced ability to participate with physical therapy.

Weaknesses of this study included a relatively small sample size which barred analysis of many complications. A larger sample size would be needed to examine correlations between heart murmurs and other complications. Ten and one-half percent of arthroplasty patients did not meet requirements or chose not to participate in the study. We do not believe that there was a pattern to which patients were not included and do not believe that these omissions significantly affected analysis.

Conclusion
In summary, we have found evidence that auscultating for heart murmurs within 24 hours of hip and knee arthroplasty surgery may represent a cost-effective strategy for identifying those at higher risk of developing acute kidney injury. There is limited evidence that murmurs may also predict those at risk of acute decreased performance with physical therapy and increased need for discharge to a rehabilitation facility.

References
Musculoskeletal Health Literacy in patients with Carpal Tunnel Syndrome: Pilot Results of a Cross-sectional Study

Introduction
Health literacy is a measure of an individual's ability to obtain, process, and understand basic health information and services needed to make appropriate health decisions and is the most important predictor of one's health status. Those with inadequate health literacy are more frequently associated with decreased medical knowledge, infrequent use of preventative services, increased hospitalization and use of emergency care, worse control of chronic diseases, and bad disease outcomes. Conversely, patients with adequate health literacy experience more effective and meaningful interactions with their physicians and are better equipped to make informed and appropriate treatment decisions.

In the United States, studies of health literacy have estimated that between 33% and 48% of Americans possess inadequate health literacy. This is troubling, as the annual cost of low health literacy is estimated to range from $106 to $238 billion.

In this study, the Literacy in Musculoskeletal Problems (LiMP) questionnaire was used to evaluate the prevalence of limited musculoskeletal health literacy in patients undergoing elective carpal tunnel release, a common procedure associated with significant health and socioeconomic implications. In this study, the Literacy in Musculoskeletal Problems (LiMP) questionnaire was used to evaluate the prevalence of limited musculoskeletal health literacy in patients undergoing elective carpal tunnel release, a common procedure associated with significant health and socioeconomic implications. It is crucial that we identify individuals with limited musculoskeletal health literacy, as they may be susceptible to inferior outcomes and a more complicated recovery following surgery.

Methods
Setting and Study Sample
This cross-sectional study was approved by the Institutional Review Board at our medical center. A convenience sample of 65 English-speaking adults (age ≥ 18) was obtained from our institution’s orthopaedic surgery outpatient practice between 03/01/2014 – 05/31/2014. Inclusion was limited to patients presenting for their routine pre-surgical office visit prior to elective, primary carpal tunnel release from a single surgeon. Patients were excluded if they didn’t meet the aforementioned criteria, were unable to read English, or unable to sign their own consent.

Data Collection and Literacy Assessment
Participants first completed a five-minute demographic questionnaire, followed by the nine question, self-administered LiMP survey, which took five to seven minutes to complete. The LiMP scores ranged from 0-9, with scores ≥ 6 indicative of adequate musculoskeletal health literacy. This cutoff was determined in a validation study based on the methodology of Pendlimari et al.

Statistics
Performance on the LiMP survey was evaluated as a function of the mean score and the prevalence of adequate and inadequate musculoskeletal literacy amongst participants. A chi-squared analysis was performed to assess whether demographic parameters significantly correlated with categorical outcome variables (limited or adequate musculoskeletal health literacy), with p-values < 0.05 considered significant.

Results
A total of 65 participants completed both the demographic and LiMP surveys. Participants were predominantly Caucasian (94%), female (62%) and had some college education (74%). Additionally, 69% reported that they had been seen in the past for a non-carpal tunnel related musculoskeletal complaint. Less than one-third of the participants were either currently or previously employed in the healthcare industry (29%).

The mean LiMP score was 6 ± 1.4. The prevalence of inadequate musculoskeletal literacy amongst participants was 34% (22/65). There was no significant correlation between the prevalence of adequate musculoskeletal health literacy and participants’ gender, race, level of education, or history of healthcare employment (p > 0.05, Table 1). However, females, Caucasians, participants with a level of education ≥ college, and those with a current or prior occupation in healthcare experienced higher rates of adequate musculoskeletal

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Adequate health literacy is required for patients to make informed decisions regarding their care. Further, patients with limited health literacy have been shown to experience inferior outcomes. Health literacy in patients with CTS has never been assessed, so we sought to evaluate the prevalence of and factors related to inadequate health literacy in patients undergoing elective CTR in order to help orthopaedic surgeons identify “at risk” populations who may be undergoing CTR.

This investigation demonstrated a 34% prevalence of inadequate musculoskeletal literacy among patients undergoing elective, primary CTR. This is consistent with the lower end of national estimates of limited general health literacy and greater than that seen in other specialty-specific literacy studies related to diabetes and heart disease, which found 15.1% and 17.5% of afflicted patients to have low health literacy, respectively. We believe that the actual rate of limited musculoskeletal literacy may be even higher, as the participants in our study were predominantly Caucasians and had received at least partial college education. Several studies...
have identified increased rates of adequate health literacy in such individuals, supporting our hypothesis.\textsuperscript{22,23}

There was a statistically significantly higher proportion of adequate musculoskeletal literacy observed in those participants who had previously seen a physician for an orthopaedic-related problem. This is consistent with the added familiarity one would presumably have with the musculoskeletal system and orthopaedic conditions after such an interaction.

This study has several limitations. As a cross-sectional study utilizing a convenience sample, selection bias is a significant concern. Our high rates of Caucasian, female and college educated participants might not accurately approximate the general population afflicted with CTS and a larger scale study is warranted to confirm our findings. The homogeneity of our sample across multiple demographics makes comparative analysis difficult. A larger sample size may identify statistically significant demographic risk factors. As with other patient-reported questionnaires, response and volunteer bias are potential confounders.

**Conclusions**

Our study suggests that approximately at least one-third of patients scheduled for elective, primary CTR may lack the necessary skills required for making informed decisions regarding their care. These patients may be at risk for suboptimal outcomes given their poor health literacy. Although patient education materials are widely available for patients with carpal tunnel syndrome through the American Academy of Orthopaedic Surgery (AAOS) and American Society of Surgery of the Hand websites, it has been shown that the readability of these materials may be too difficult for many to comprehend.\textsuperscript{24} It is therefore essential that revised education campaigns be developed and geared toward those individuals most at risk for limited musculoskeletal health literacy.

**References**

The life of an orthopaedic surgeon is filled with excitement, personal satisfaction, and daily anxiety. I manage two operating rooms, see approximately 125 patients a week, and do what I can to educate the next generation of surgeons. I would not trade my vocation for any other; yet, stress abounds each and every day. My wife of 27 years, Marie, my trusted colleagues, friends, and staff all help buoy my emotions and it is with them whom I share my professional journey. We all need the trusted support of a significant other—whether a spouse, close personal friend, or family member—to help navigate the daily stressors that accompany the life of a surgeon.

Relationships, not material things, determine our personal happiness. In fact, the quality of our lives is directly proportional to the quality of our relationships. The deeper each relationship, the more influence it has on our well-being.

This article will focus chiefly on the importance of our significant other, spouse, or partner. It will embrace important questions. Are physicians more prone to divorce? How does a physician balance family obligations with his or her commitments in the workplace? What role do trusted friends and family play, beyond that served by the significant other or spouse?

The Data: A Mixed Bag

I am one of those fortunate few who loves his job. My occupation, however, requires considerable time away from home. The average physician works approximately 54 hours per week. An orthopaedic surgeon works a bit longer, averaging 58 hours per week. Add the travel to conferences (occasionally to different countries) and the time dedicated to papers and peer-reviewed studies, one could easily draw a straight line from physicians being away from home to higher divorce rates compared to the national average (often stated between 40-50%). The data backing up this claim, however, varies. In 1997, Rollman and colleagues assessed the specialty choices and marriage histories of 1118 physicians who graduated from The Johns Hopkins University School of Medicine from 1948 through 1964; they found that surgeons had a divorce rate of 33%. The authors acknowledged that today’s medical school graduates may have a different acceptance of divorce, and so the proportion may change over time. In fact, in the book *The Medical Marriage: Sustaining Healthy Relationships for Physicians and Their Families*, author and physician Wayne M. Sotile, MD argues that the divorce rate is 10% to 20% higher than the percentage given in the study by Rollman and colleagues.

Relationships—especially one’s choice of spouse—are complicated, and given the stresses endured by surgeons, the data show that these relationships do not all end well. Even so, there are some principles that can help support a fulfilling and lasting relationship: commitment, compassion, and other-centeredness.

Commitment

Most of the data on physician relationships come from the perspective of the physician. A 2013 study by Shanefelt and colleagues evaluated physician relationships from the perspective of their spouses/partners. Of the 891 survey responders, most (86.8%) said they were satisfied with their relationship with their physician spouse or partner. According to the study, the strongest predictor of relationship satisfaction was the mean time spent with their partners each day. Although the large majority of the spouses/partners in the survey appeared content with their relationship, the data also indicated that physicians often came home irritable, too exhausted to perform home activities, or remained preoccupied with work. It is not merely an issue of ‘quality time’. Rather, relationships require both quality and a sufficient quantum of time in order to flourish.

Healthy relationships blossom in the presence of commitment. The more important the relationship, the more important is the role of commitment. When an easy escape is available, many opt to leave, rather than do the real work of personal growth. When we decide to leave, we simply transfer our “stuff” to the next relationship. Only in the context of a committed and loyal relationship is the safety and assurance provided to risk new behaviors and strategies. In addition, when we commit, we are more inclined to look at our partner’s positive attributes and make the most out of the situation. Commitment applies to lasting friendships as well. Single and divorced surgeons will need trusted friends in order to ease the stressors a busy practice will generate.
Compassion

Healthy relationships thrive on compassion. The antithesis of compassion is judgment. Judging another leads to anger, frustration, and discontent. Healthy couples see one another as imperfect beings, each bearing old hurts and merely doing the best they can. When we change our core beliefs about another, our entire perspective is transformed. For example, if our partner is having a bad day and displays moodiness, it is easy to believe that he or she is inconsiderate and are willfully trying to upset us. If instead we interpret our partner's actions through a lens of compassion, we will then see our partner as someone who is merely acting out of his or her own pain. His or her internal suffering is manifest outwardly as complaints, irritability, or fault-finding. When we are compassionate, we extend loving kindness and see others as they really are: imperfect creatures carrying old wounds, and doing the best they can.

This is not to say that boundaries can’t be protected. We need never tolerate verbal or physical abuse, and we must always uphold our own personal dignity. However, episodic bouts of discourteous behavior can usually be neutralized with compassion and acts of kindness.

Other-Centeredness

Happy couples and good friends continually seek to help and please each other. This behavioral mindset, called other-centeredness, may result in tremendous personal growth. Further, other-centered individuals are generally happier. When we focus outward on the needs of another, we leave our own concerns and troubles behind. We become more engaged in the present moment and our anxieties and guilt dissipate. For surgeons, a draining wound, a post-op fever or a partner is having a bad day and displays moodiness, it is easy to believe that he or she is inconsiderate and are willfully trying to upset us. If instead we interpret our partner's actions through a lens of compassion, we will then see our partner as someone who is merely acting out of his or her own pain. His or her internal suffering is manifest outwardly as complaints, irritability, or fault-finding. When we are compassionate, we extend loving kindness and see others as they really are: imperfect creatures carrying old wounds, and doing the best they can.

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Friends and Family

Those who spend their lives in social isolation endure more illness and emotional strife and do not live as long as those with a healthy social circle. A sound relationship more illness and emotional strife and do not live as long as those with a healthy social circle. A sound relationship more illness and emotional strife and do not live as long as those with a healthy social circle. A sound relationship and please each other. This behavioral mindset, called other-centeredness, may result in tremendous personal growth.

Healthy relationships thrive on compassion. The antithesis of compassion is judgment. Judging another leads to anger, frustration, and discontent. Healthy couples see one another as imperfect beings, each bearing old hurts and merely doing the best they can. When we change our core beliefs about another, our entire perspective is transformed. For example, if our partner is having a bad day and displays moodiness, it is easy to believe that he or she is inconsiderate and are willfully trying to upset us. If instead we interpret our partner's actions through a lens of compassion, we will then see our partner as someone who is merely acting out of his or her own pain. His or her internal suffering is manifest outwardly as complaints, irritability, or fault-finding. When we are compassionate, we extend loving kindness and see others as they really are: imperfect creatures carrying old wounds, and doing the best they can.

This is not to say that boundaries can’t be protected. We need never tolerate verbal or physical abuse, and we must always uphold our own personal dignity. However, episodic bouts of discourteous behavior can usually be neutralized with compassion and acts of kindness.

Suggestions for a More Peaceful Life

• Commit for the next 30 days to be the best spouse/partner you can be. Expect nothing in return.
• Write a vision statement for your important relationships and refer to it often. A relationship vision statement is a written summary describing in detail your vision of your life with another person. Capture, in words, your conception of the ideal relationship and use specifics. What activities, habits, attitudes and atmosphere do you seek?
• Change your core belief that the offensive behavior of others is directed at you personally. Rather, see your partner or friend as another wounded soul on life’s journey.
• Develop compassion for your partner and yourself. If you have failed in other relationships, it is never too late to grow. If you are divorced and you harbor sustained anger toward your “ex,” enlist the help of a therapist so that old wounds can be healed. You will be doing more than you can imagine for the happiness of your ex-spouse, your children, and most importantly, yourself.

References

Who Should not Undergo Short Stay Hip and Knee Arthroplasty? 
Risk Factors Associated with Major Medical Complications Following Primary Total Joint Arthroplasty

Introduction 
Improved anesthesia and rehabilitation protocols have made outpatient or short stay (less than 24 hours) total hip arthroplasty (THA) and total knee arthroplasty (TKA) possible. However, the optimal candidate for either outpatient or short stay THA or TKA remains to be defined. Furthermore, hospitals and surgeons are wary of the financial and safety impact of readmissions following short stay THA/TKA. Nausea, bleeding, urinary retention, and pain can all result in early readmissions. Therefore, the purpose of this study is to identify which risk factors would preclude patients from undergoing short stay THA/TKA. We sought to identify the medical comorbidities associated with an increased risk of complication and develop a predictive model to identify patients who should not be considered for either outpatient or short stay joint arthroplasty.

Materials and Methods 
We retrospectively reviewed a consecutive series of 1012 patients who underwent primary total hip and knee arthroplasty at a single high volume academic institution from February 2013 to December 2013. Medical comorbidities, demographics, and timing of postoperative in-hospital complications were documented for each patient. Each post-surgical complication was classified and stratified based on published definitions by Sink, et al. Grade I complications involving no intervention were excluded from the study. A subgroup of patients who experienced a later in-hospital complication after 24 hours post-operatively was identified. Length of stay, rates of return to the operating room, and readmission at 90 days were also noted. We chose 24 hours postoperatively as a cutoff because we only wanted to look at later in-hospital complications, as urgent complications prior to 24 hours postoperatively would be identified by most short stay TJA protocols.

Results 
Of the 1012 consecutive primary THA and TKA patients included in the study, 70 patients (6.9%) experienced a perioperative complication during their index hospital admission. Fifty-nine (84%) of these complications occurred greater than 24 hours post-operatively.

When comparing the patients who experienced a complication after 24 hours postoperatively and those who did not, there was no statistical difference in BMI (31.8 vs 32.8 kg/m^2, p = 0.425), surgical procedure (36% vs. 35% THA, p = 0.857), or incidence of diabetes mellitus (18% vs. 18%, p = 0.989). Patients experiencing a complication after 24 hour postoperatively were more likely to be older (mean age 63.6 vs. 60.1 years, p = 0.045), and have a history of chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), or coronary artery disease (CAD) (all p < 0.001).

Results comparing the two groups are listed in Table 1.

Based on multivariate analysis, independent risk factors for in-hospital complications included COPD (adjusted OR 4.16, 95% CI 1.86 – 9.32), CHF (adjusted OR 9.71, 95% CI 4.55 – 20.71), CAD (adjusted OR 2.80, 95% CI 1.38 – 5.69), and liver cirrhosis (adjusted OR 8.43, 95% CI 1.63 – 43.59). Results of univariate and multivariate analyses are detailed in Table 2.

We then performed a forward, stepwise, multiple logistic regression analysis to generate a model to identify the ideal patient for outpatient or short-stay primary TJA. Results of this analysis are shown in Table 3. A 6-point risk score was created appropriately weighting these independent variables including COPD, CHF, cirrhosis, and CAD. Patients with a score of zero had a probability of complications after 24 hours postoperatively of 3.1% (Figure 1). The receiver operating characteristic curve demonstrated a good fit of this model with area under curve of 0.738.
shown no difference between the readmission rates in patients undergoing outpatient THA/TKA compared to controls, the patient characteristics best suited for these types of procedures remain undefined. Therefore, we examined the timing and severity of complications as well as ultimate interventions in

Discussion

As the drive to decrease the length of stay following primary THA/TKA continues to strengthen, concerns regarding patient safety and the financial impact of unexpected readmissions due to early discharge remain. While some studies have

Table 1. Comparison of patients who experienced a complication after 24 hours postoperatively and those who did not.

<table>
<thead>
<tr>
<th>Complication &gt; 24 hours post-operatively (n = 59)</th>
<th>No Complications after 24 hours (n = 953)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.6</td>
<td>60.1</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>31.8</td>
<td>32.8</td>
</tr>
<tr>
<td>Total Length of Stay (days)</td>
<td>6.95</td>
<td>3.12</td>
</tr>
<tr>
<td>Risk Score</td>
<td>1.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Hip Arthroplasty</td>
<td>21 (36)</td>
<td>329 (35)</td>
</tr>
<tr>
<td>Age &gt; 75 years</td>
<td>10 (20)</td>
<td>90 (11)</td>
</tr>
<tr>
<td>BMI &gt; 35 kg/m^2</td>
<td>19 (35)</td>
<td>277 (35)</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (18)</td>
<td>47 (5)</td>
</tr>
<tr>
<td>CAD</td>
<td>19 (32)</td>
<td>78 (8)</td>
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<tr>
<td>CHF</td>
<td>18 (31)</td>
<td>28 (3)</td>
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<td>Intraoperative Vasopressors</td>
<td>30 (51)</td>
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<td>Diabetes</td>
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<td>177 (18)</td>
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<tr>
<td>Cirrhosis</td>
<td>3 (9)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>90-day Readmission</td>
<td>16 (27)</td>
<td>53 (6)</td>
</tr>
<tr>
<td>Return to OR</td>
<td>7 (12)</td>
<td>38 (4)</td>
</tr>
</tbody>
</table>

Table 2. Univariate and multivariate logistic regression analysis to identify independent risk factors for in-hospital complications after 24 hours postoperatively.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Univariate Analysis</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
<td>p value</td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
<td>p value</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>1.73</td>
<td>0.88 – 3.45</td>
<td>0.113</td>
<td>1.15</td>
<td>0.53 – 2.59</td>
<td>0.713</td>
</tr>
<tr>
<td>BMI &gt; 35</td>
<td>0.52</td>
<td>0.23 – 1.16</td>
<td>0.111</td>
<td>0.52</td>
<td>0.22 – 1.23</td>
<td>0.136</td>
</tr>
<tr>
<td>Hip Arthroplasty</td>
<td>1.05</td>
<td>0.61 – 1.82</td>
<td>0.867</td>
<td>0.96</td>
<td>0.51 – 1.81</td>
<td>0.902</td>
</tr>
<tr>
<td>COPD</td>
<td>4.42</td>
<td>2.16 – 9.06</td>
<td>&lt; 0.001</td>
<td>3.98</td>
<td>1.74 – 9.07</td>
<td>0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>5.33</td>
<td>2.94 – 9.64</td>
<td>&lt; 0.001</td>
<td>2.71</td>
<td>1.32 – 5.57</td>
<td>0.007</td>
</tr>
<tr>
<td>CHF</td>
<td>14.5</td>
<td>7.42 – 28.33</td>
<td>&lt; 0.001</td>
<td>9.27</td>
<td>4.20 – 20.44</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intraoperative Vasopressors</td>
<td>1.78</td>
<td>1.05 – 3.02</td>
<td>0.032</td>
<td>1.45</td>
<td>0.80 – 2.65</td>
<td>0.22</td>
</tr>
<tr>
<td>Chronic Kidney Disease</td>
<td>2.39</td>
<td>1.31 – 4.39</td>
<td>0.004</td>
<td>1.10</td>
<td>0.52 – 2.31</td>
<td>0.799</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.00</td>
<td>0.51 – 1.98</td>
<td>0.989</td>
<td>0.90</td>
<td>0.42 – 1.94</td>
<td>0.79</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>5.62</td>
<td>1.48 – 21.33</td>
<td>0.011</td>
<td>8.06</td>
<td>1.85 – 35.11</td>
<td>0.005</td>
</tr>
</tbody>
</table>
WHO SHOULD NOT UNDERGO SHORT STAY HIP AND KNEE ARTHROPLASTY?

VOLUME 25, JUNE 2015

Disease (COPD), congestive heart failure (CHF), coronary artery disease (CAD), and cirrhosis were not surprisingly associated with complications, interestingly, age, body mass index (BMI), diabetes, and chronic kidney disease were not independent risk factors. These results are not completely consistent with prior published reports. Parvizi and colleagues reported that old age, increased body mass index and ASA score were associated with complications.9 Patients with these risk factors should therefore not be recommended to have short stay THA/TKA.

Finally, we developed an easy-to-use 6-point scale with good predictive accuracy (AUC = 0.738) that orthopedic surgeons can use to determine a patient’s candidacy for short stay total joint arthroplasty (TJA). However, this model is not fully predictive and there are other factors such as operative time or intraoperative events that can affect events postoperatively. Our model is intended for preoperative use in order to help facilitate and determine perioperative resources such as bed

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Weighted Score</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF</td>
<td>2</td>
<td>9.71</td>
<td>4.55 – 20.71</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2</td>
<td>8.19</td>
<td>1.97 – 34.15</td>
<td>0.004</td>
</tr>
<tr>
<td>COPD</td>
<td>1</td>
<td>4.16</td>
<td>1.86 – 9.32</td>
<td>0.001</td>
</tr>
<tr>
<td>CAD</td>
<td>1</td>
<td>2.8</td>
<td>1.38 – 5.69</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Figure 1. Probability of complications after discharge 24 hours postoperatively based upon risk score.

Table 3. Forward, stepwise, multiple logistic regression analysis to generate a model to identify the ideal patient for outpatient or short-stay primary TJA. A weighted 6-point score was generated.
management, hospital vs. ambulatory surgery utilization, and patient guidance. The threshold for risk should be adjusted according to institutional or individual preference.

This study has several strengths and limitations. We did not quantify the severity of medical comorbidities such as CAD, COPD, obesity, or diabetes mellitus. These were considered binary variables and thus may affect the final analysis. However, our data represents the detailed data set for a large, consecutive number of unselected patients undergoing primary THA/TKA. The sample size exceeded our power analysis and therefore minimizes type II error. We also did not take into account intraoperative factors such as operative time or blood loss, and we did not assess readmissions at 30 or 90 days. While this can bias our analysis, the intent of this study was to determine who would be a candidate for short stay TJA (less than 24 hours), not to predict the need for readmissions. Future prospective studies are necessary to validate these findings. The strengths of this study include the large sample size, the unselected nature, and the detailed documentation analysis of patient comorbidities. Patients with a history of COPD, CHF, CAD, and cirrhosis are at higher risk for developing a late in hospital complication following primary THA/TKA. Most postoperative complications occur beyond 24 hours. Thus, patients with these risk factors should not undergo short stay or outpatient primary TJA.

References
Are There Identifiable Risk Factors and Causes Associated with Unplanned Readmissions Following Total Knee Arthroplasty?

Introduction

Prevention of unplanned hospital readmissions has become a major focus in cost containment efforts by healthcare payers, policy makers, and providers. Under the Patient Protection and Affordable Care Act (PPACA) of 2009, the Center for Medicare & Medicaid Services (CMS) has begun instituting reimbursement penalties for 30-day readmissions associated with certain conditions. In August 2013, CMS announced an expansion of this policy to elective total knee arthroplasty (TKA) for fiscal year 2015. Since private insurers often emulate Medicare’s payment methods, we can expect many insurers to follow suit. Therefore, if this proposal is successfully implemented, hospitals will have a strong financial incentive to decrease such readmissions.

While unplanned readmission rates have received increasing attention recently, there are a relatively limited number of studies focusing on readmissions after primary TKA. Recent work has suggested an association with black race, increased length of stay (LOS), decreased age, and male gender. Overall, however, current literature on the subject is mixed and inconclusive. A better understanding of the factors associated with such readmissions will be essential in efforts to identify and prevent potential future readmissions. The purpose of this study is to identify the risk factors and causes for unplanned readmissions following TKA.

Methods

A retrospective review of 3,218 primary TKAs performed over two years from July 1, 2009, to June 30, 2011, at a large urban academic hospital network was conducted using clinical and administrative data. We used a sample of convenience composed of patients admitted to the institution under review. Patients who had undergone primary TKA during the study period were identified using the corresponding ICD-9 procedure code (81.54). Unplanned 30-day readmissions were identified using ICD-9 codes and patient-specific identifiers. Planned readmissions, most commonly for in-house acute inpatient rehabilitation or skilled nursing facility, and revision TKA procedures were excluded.

Results

We identified 3,218 patients who had a TKA during the observation period. The average age at time of surgery was 63 years and the average BMI was 32.8 kg/m². Sixty-six percent of patients were female. The 30-day readmission rate at our institution was 5.53%, comprised of 178 readmissions among 165 patients. Readmission was associated with increased LOS (p < 0.001). Age, BMI, gender, race, and staged bilateral procedures were not associated with readmissions (Table 1). Average MS-DRG weight among readmitted patients was 2.57 versus 2.48 among non-readmitted subjects (p = 0.074).

Similar associations were demonstrated by bivariate logistic regression (Table 2); LOS is significantly associated with a 10% increased odds of readmission. This association is unchanged after adjusting for gender and race in multivariate regression.

The most common diagnoses associated with readmissions were post-operative infection (22.5%), hematoma (10.1%), pulmonary embolus (7.9%), deep venous thrombosis (5.6%), and uncontrolled pain (5.6%). Surgical causes constituted 53.9% while medical causes constituted 46.1% of all readmissions (Table 3).
### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (N = 3,218)</th>
<th>Readmitted (N = 165)</th>
<th>Not Readmitted (N = 3,053)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N or mean % or SD</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>63.0 10.9</td>
<td>63.9 12.6</td>
<td>62.9 10.8</td>
<td>0.100</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2125 66.0%</td>
<td>112 67.9%</td>
<td>2013 65.9%</td>
<td>0.608</td>
</tr>
<tr>
<td>Male</td>
<td>1093 34.0%</td>
<td>53 32.1%</td>
<td>1040 34.1%</td>
<td>-</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2152 66.9%</td>
<td>100 60.6%</td>
<td>2049 67.1%</td>
<td>0.084</td>
</tr>
<tr>
<td>Black</td>
<td>908 28.2%</td>
<td>55 33.3%</td>
<td>851 27.9%</td>
<td>0.129</td>
</tr>
<tr>
<td>Native American</td>
<td>3 0.1%</td>
<td>0 0.0%</td>
<td>3 0.1%</td>
<td>0.687</td>
</tr>
<tr>
<td>Asian</td>
<td>48 1.5%</td>
<td>2 1.2%</td>
<td>46 1.5%</td>
<td>0.761</td>
</tr>
<tr>
<td>Other</td>
<td>63 2.0%</td>
<td>4 2.4%</td>
<td>58 1.9%</td>
<td>0.633</td>
</tr>
<tr>
<td>Unknown</td>
<td>50 1.6%</td>
<td>4 2.4%</td>
<td>46 1.5%</td>
<td>0.353</td>
</tr>
<tr>
<td>BMI</td>
<td>32.8 7.6</td>
<td>33.4 8.2</td>
<td>32.7 7.6</td>
<td>0.329</td>
</tr>
<tr>
<td>LOS (days)</td>
<td>3.8 2.1</td>
<td>4.70 4.12</td>
<td>3.75 1.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staged bilateral procedures</td>
<td>69 2.1%</td>
<td>5 3.0%</td>
<td>64 2.1%</td>
<td>0.420</td>
</tr>
</tbody>
</table>

### Table 2. Bivariate logistic regression (readmitted vs non-readmitted patients)

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 55</td>
<td>1.01</td>
<td>0.99 – 1.02</td>
<td>0.30</td>
</tr>
<tr>
<td>56-65</td>
<td>0.97</td>
<td>0.63 – 1.49</td>
<td>0.88</td>
</tr>
<tr>
<td>66-75</td>
<td>1.26</td>
<td>0.82 – 1.94</td>
<td>0.3</td>
</tr>
<tr>
<td>≥ 76</td>
<td>1.44</td>
<td>0.87 – 2.39</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male</td>
<td>0.94</td>
<td>0.68 – 1.31</td>
<td>0.73</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Black</td>
<td>1.28</td>
<td>0.92 – 1.80</td>
<td>0.15</td>
</tr>
<tr>
<td>Other</td>
<td>1.11</td>
<td>0.47 – 2.57</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>LOS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>1.1</td>
<td>1.06 – 1.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>25 – &lt; 30</td>
<td>0.7</td>
<td>0.41 – 1.21</td>
<td>0.2</td>
</tr>
<tr>
<td>30 – &lt; 35</td>
<td>1.08</td>
<td>0.64 – 1.81</td>
<td>0.78</td>
</tr>
<tr>
<td>≥ 35</td>
<td>1.00</td>
<td>0.61 – 1.65</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Staged bilateral procedures</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*The event rate was too low for logistic analysis*
Implementation of standardized care pathways contributed in readmissions. Furthermore, multiple studies of TKA and hospital volumes were associated with a reduction in discharge disposition;\(^2\)\(^1\),\(^2\)\(^2\) however, Riggs, et al demonstrated illustrating the benefit of process standardization. Mixed socioeconomic factors. Prior literature has shown black race among white patients likely represents the impact of numerous previous literature.\(^5\)-\(^7\) Prior literature has suggested that elevated rate of readmission as well as the relatively high MS-DRG weights among these patients.\(^8\)-\(^1\)\(^0\)\(^1\) Likewise, these studies demonstrate that despite many readmissions for medical reasons, most patients are readmitted for post-surgical issues. These complications differ in treatment costs; surgical infections tend to be relatively more expensive to treat because they frequently necessitate multiple subsequent procedures, extended courses of intravenous antibiotics, prolonged rehabilitation, and frequent follow-up.\(^1\)\(^4\)

In order to improve care and prevent financial losses, providers should strive to reduce unplanned readmissions. One method to consider is the consolidation of care at large healthcare centers. Bozic, et al identified a volume-outcomes relationship associated with TKA.\(^1\)\(^5\) That is, increased surgeon and hospital volumes were associated with a reduction in readmissions. Furthermore, multiple studies of TKA patients, as well as other surgical patients, have shown that implementation of standardized care pathways contributed to reduced LOS\(^1\)\(^5\)-\(^1\)\(^7\) and improved short-term outcomes,\(^1\)\(^6\)-\(^2\)\(^0\) illustrating the benefit of process standardization. Mixed findings exist for an association between readmission and discharge disposition;\(^2\)\(^1\),\(^2\)\(^2\) however, Riggs, et al demonstrated that identifying patients who may benefit from inpatient rehabilitation before discharge may be a crucial step in preventing hospital readmissions.\(^2\)\(^1\) Interdisciplinary home care programs provide a non-medical intervention aimed at reducing readmissions and costs for outpatients by providing informal care from providers and friends, and has demonstrated lower readmissions rates than traditional inpatient alternatives.\(^2\)\(^3\)-\(^2\)\(^7\)

Limitations of this study include using a single institution’s data and no analysis of discharge disposition for our patient population.

**Discussion**

Patients with increased LOS were more likely to be readmitted in this population, which is consistent with previous literature.\(^5\)-\(^7\) Prior literature has suggested that extended LOS is associated with increased levels of comorbidity and complications, which likely explains the elevated rate of readmission as well as the relatively high MS-DRG weights among these patients.\(^8\)-\(^1\)\(^0\)

Race may be correlated with socioeconomic status in the study population, so the trend towards decreased readmissions among white patients likely represents the impact of numerous socioeconomic factors. Prior literature has shown black race associated with higher rates of readmission following TKA than white race.\(^9\)

The most common causes of readmission in our study parallel previous findings, where infection remains one of the major causes of readmission.\(^4\)-\(^8\),\(^1\)\(^0\)-\(^1\)\(^5\) Likewise, these studies demonstrate that despite many readmissions for medical reasons, most patients are readmitted for post-surgical issues. These complications differ in treatment costs; surgical infections tend to be relatively more expensive to treat because they frequently necessitate multiple subsequent procedures, extended courses of intravenous antibiotics, prolonged rehabilitation, and frequent follow-up.\(^1\)\(^4\)

In order to improve care and prevent financial losses, providers should strive to reduce unplanned readmissions. One method to consider is the consolidation of care at large healthcare centers. Bozic, et al identified a volume-outcomes relationship associated with TKA.\(^1\)\(^5\) That is, increased surgeon and hospital volumes were associated with a reduction in readmissions. Furthermore, multiple studies of TKA patients, as well as other surgical patients, have shown that implementation of standardized care pathways contributed to reduced LOS\(^1\)\(^5\)-\(^1\)\(^7\) and improved short-term outcomes,\(^1\)\(^6\)-\(^2\)\(^0\) illustrating the benefit of process standardization. Mixed findings exist for an association between readmission and discharge disposition;\(^2\)\(^1\),\(^2\)\(^2\) however, Riggs, et al demonstrated that identifying patients who may benefit from inpatient rehabilitation before discharge may be a crucial step in preventing hospital readmissions.\(^2\)\(^1\) Interdisciplinary home care programs provide a non-medical intervention aimed at reducing readmissions and costs for outpatients by providing informal care from providers and friends, and has demonstrated lower readmissions rates than traditional inpatient alternatives.\(^2\)\(^3\)-\(^2\)\(^7\)

**References**


**Table 3. Most common causes of readmission**

<table>
<thead>
<tr>
<th>Readmitting Diagnosis</th>
<th>Count</th>
<th>% of Readmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep Wound Infection</td>
<td>21</td>
<td>11.8%</td>
</tr>
<tr>
<td>Superficial Cellulitis</td>
<td>19</td>
<td>10.7%</td>
</tr>
<tr>
<td>Hematoma</td>
<td>18</td>
<td>10.1%</td>
</tr>
<tr>
<td>Pulmonary embolus</td>
<td>14</td>
<td>7.9%</td>
</tr>
<tr>
<td>DVT</td>
<td>10</td>
<td>5.6%</td>
</tr>
<tr>
<td>Pain control</td>
<td>10</td>
<td>5.6%</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>9</td>
<td>5.1%</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>6</td>
<td>3.4%</td>
</tr>
<tr>
<td>Chest pain (MI work up)</td>
<td>5</td>
<td>2.8%</td>
</tr>
<tr>
<td>Swelling</td>
<td>5</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

*Total: Surgical causes = 53.9%; Medical causes = 46.1%*


27. Cryer L, Shannon SB, Van Amsterdam M, et al. Costs for ‘hospital at home’ patients were 19 percent lower, with equal or better outcomes compared to similar inpatients. Health Aff (Millwood) 31(6):1237-1243 (2012).
Altered Force Sensing and Cell-cell Adhesion by Mutant ALK2 FOP Cells—Implications for Heterotopic Ossification

Introduction
The rare genetic disease fibrodysplasia ossificans progressiva (FOP) dysregulates progenitor cells to form heterotopic bone in soft tissues. Microenvironment rigidity modulates lineage specification to direct cell fates. Soft substrates induce mesenchymal progenitor cells towards neuro-/adipogenic fates while stiff substrates promote chondro-/osteogenesis. Pathologic tissue stiffening occurs in fibrotic diseases when damaged tissue aberrantly acquires increased rigidity during wound healing. Similarly, injury-induced FOP lesions exhibit excessive fibroproliferation. Gain-of-function R206H mutations in the BMP receptor ALK2/ACVR1 cause FOP. Since BMP signaling both regulates and is regulated by cell tensional force, we hypothesized that altered ALK2 signaling as a consequence of the FOP mutation alters mechanical force sensing in progenitor cells and lowers the threshold for bone formation.

Methods
We used immortalized mouse embryonic fibroblasts (iMEFs) from ACVR1R206H knock-in and WT embryos on varied matrix elasticity (soft/5kPa; moderate/15kPa, stiff/55kPa) and analyzed cell size, aspect ratio (AR), circularity, and solidity at low cell density.

Results
WT cells responded to increasing stiffness as expected with increased cell size and AR, and decreased circularity and solidity. However, FOP cells on soft substrates were similar to WT on stiff substrates, and FOP cells were overall less responsive to substrate rigidity. FOP iMEFs also showed a loss of contact inhibition, reduced cell-cell contacts, and loss of β-catenin at cell membranes.

Discussion
These data support that the combination of increased BMP signaling and misinterpretation of biomechanical signals in FOP cells lowers their threshold for commitment to chondro-/osteogenic lineages, resulting in an aberrant tissue repair response that leads to ectopic bone formation.
Heterozygous Inactivation of \textit{Gnas} Alters Skeletal Development and Bone Quality

\textbf{Introduction}

Progressive osseous heteroplasia (POH), Albright hereditary osteodystrophy (AHO), osteoma cutis (OC), and pseudohypoparathyroidism 1a/1c (PHP) form a spectrum of disorders that are caused by heterozygous inactivating mutations in \textit{GNAS}, a gene that encodes multiple transcripts including the \(\alpha\)-subunit of the stimulatory G-protein (G\(_s\alpha\)) of adenylyl cyclase. All these disorders exhibit subcutaneous heterotopic ossification (HO), however, POH has the most severe HO, characterized by HO progression into deeper connective tissues including muscle and fascia. The \textit{GNAS} gene shows genomic imprinting, and POH and AHO are associated with paternal and maternal inheritance of the mutation respectively. Mice with paternally- and maternally-inherited deletion of \textit{Gnas} exon 1 exhibit different phenotypes although both develop subcutaneous ossifications. But whether reduced \textit{Gnas} expression leads to alterations in the formation or maintenance of skeletal bone and how paternal and maternal inheritance of the mutation affects skeletal bone quality remains undetermined.

\textbf{Methods}

We performed \(\mu\)CT and mechanical testing in young (2 week old – P14) and adult (9 months) mice with heterozygous inactivation of paternal (Ex1\(^{p/-}\)) or maternal (Ex1\(^{m/-}\)) allele of \textit{Gnas} exon 1.

\textbf{Results}

For both mutants, trabecular bone parameters, analyzed through \(\mu\)CT scans of the distal femoral epiphyses in P14 mice, revealed dramatic reductions in total volume (~20%) and bone volume (>25%) with marginal reduction in bone volume fraction (~12%) compared to wildtype littermates. Trabecular microarchitecture was altered with a significant decrease (~9%) in trabecular thickness and a concomitant increase in the structure model index (>10%), suggesting that trabecular bone is more rod-like in \textit{Gnas} deficient mice. In addition, \(\mu\)CT analyses of the femoral mid-diaphysis showed reduced cortical thickness (15%), cortical bone volume (>25%) and bone volume fraction (>13%) in P14 mutants vs. wildtype. Femurs from both P14 mutants exhibited significantly lower strength (stiffness and peak load) by 3-point bending. Although the differences between wildtype and either Ex1\(^{p/-}\) and Ex1\(^{m/-}\) mice were the same at P14, \(\mu\)CT of adult mice revealed differences dependent on the parental origin of the mutation. At 9 months of age, both Ex1\(^{p/-}\) and Ex1\(^{m/-}\) mice showed trabecular bone properties that were now similar to wt. However, cortical bone parameters including bone volume fraction (>10%) and cortical thickness (~14%) and biomechanical strength were significantly lower in mice with paternal inactivation of the \textit{Gnas} at 9 months of age, while mice with maternal inheritance of the \textit{Gnas} mutation showed no differences vs. wildtype in cortical bone.

\textbf{Discussion}

These results indicate that G\(_s\alpha\) signaling plays an important role in skeletal bone formation and maintenance and that inheritance of the mutation paternally vs. maternally differentially effects bone remodeling with age. Currently studies are focused on understanding the interaction between G\(_s\alpha\) and other signaling pathways and the effects of \textit{Gnas} inheritance in regulating bone quality.
The FOP R206H Acvr1 Mutation is Sufficient to Cause Heterotopic Ossification in Mouse Limbs and is Inhibited by a Selective RARγ Agonist Treatment

Introduction
Fibrodysplasia ossificans progressive (FOP) is a rare autosomal dominant genetic disorder characterized by extensive heterotopic ossification (HO). Most cases of FOP are caused by the same gain-of-function mutation of the ACVR1/ALK2 type I BMP receptor (R206H).

Methods
In the present study, we conditionally-activated the Acvr1 R206H mutation in skeletal mesenchymal progenitor (Prrx1⁺) cells in mice to examine the effects of this cell population on HO and skeletal development. We also tested palovarotene, a phase II selective RARγ agonist, as an inhibitor of Acvr1 R206H-induced heterotopic ossification.

Results
Heterozygous Prrx1-Cre;Acvr1 R206H (Prrx1⁺;R206H) mice are viable, but show reduced body length at birth. Histology revealed shorter growth plates with increased proliferative cells and a decreased hypertrophic chondrocyte zone. Consistent with FOP patients, Prrx1⁺;R206H mice at P0 had hind-limb specific great toe malformations and no HO. Soft x-ray and microCT analyses showed that all Prrx1⁺;R206H mice spontaneously developed HO within 2 weeks, with most occurring in the hind limbs. By 4 weeks, HO formation occurs in both hind limbs and fore limbs where Prrx1 is most highly expressed, then progressed to severely impair movement over time. Histological examination confirmed that the HO occurs through endochondral ossification, as in FOP patients. Of note, when the Acvr1 R206H mutation was globally expressed post-natally by a doxycycline-inducible system beginning at P5, all mice developed HO, however the onset and progression were substantially delayed compared to mice with embryonic expression of Acvr1 R206H in Prrx1⁺ cells. Palovarotene, a RARγ agonist that inhibits chondrogenesis, was administered to Prrx1⁺;R206H mice from P3-P14 and significantly reduced spontaneous HO in a dose dependent manner, rescued longitudinal bone growth, and improved limb movement.

Discussion
Our data demonstrate that Acvr1 R206H expression in skeletal progenitor cells supports the induction and progression of heterotopic endochondral ossification as well as being sufficient to induce the characteristic great toe malformations that are characteristic of FOP. While Prrx1⁺ cells appear to be major contributors to HO formation, given the localized expression of Prrx1, additional cell populations likely also contribute to HO in patients. Palovarotene was able to inhibit both the skeletal and HO effects of Acvr1 R206H, providing strong preclinical data for RARγ agonists in clinical trials for FOP.
Notch Signaling is Required for Osteoclast Differentiation and Function

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Introduction

Osteoclasts are multinucleated giant cells responsible for the resorption of bone.\(^1\) As such, they are a critical component along with bone-forming osteoblasts and bone-regulating osteocytes in the process of bone remodeling. For this reason, osteoclasts are an attractive target in instances where increased bone mass is desired. In particular, anti-resorptive agents, which are chemicals and biologicals that inhibit osteoclast differentiation and/or activity are the most commonly proscribed treatments for the prevention of fractures in patients with osteoporosis, a disease marked by decreased bone mineral density. Side-effects and limited improvements in bone quality under current anti-resorptive therapies highlight the need for better, more nuanced control over osteoclast function. One promising potentially targetable pathway is mediated by the mammalian homologues of Notch.

Regulated signaling from Notch is recognized as an important regulator of tissue patterning during development and stem cell niche maintenance. Notch signaling results from interaction with a membrane-bound Notch family receptor with a membrane-bound ligand such as Jagged1 or Delta-like1. After binding, the intracellular domain of Notch (NICD) is released from the membrane by a gamma-secretase complex (targeted inhibition by DAPT).\(^1\) NICD then translocates to the nucleus where it engages in transcription in a complex containing CSL and Mastermind-like (targeted inhibition by SAHM1) (Fig. 1). Notch signaling also impacts the differentiation of osteoblasts.\(^{1,2,3}\) As such, there is growing interest in manipulation of Notch signaling to improve outcomes in fracture healing. Notch signaling, however, may also influence the differentiation and function of osteoclasts, and understanding of the manner in which osteoclasts, which are essential both in physiological bone turnover and remodeling of a healing fracture callus, may be affected by therapies manipulating Notch signaling is essential for proper exploitation of this pathway. The role of Notch signaling in osteoclasts and its utility in bone loss disorders such as osteoporosis, however, are controversial as there is evidence for both stimulatory and inhibitory effects.\(^{1,2,3,4,5,6}\)

Studies of specific activation of Notch family members with antibodies have provided strong evidence for a positive role for Notch signaling in osteoclastogenesis. Because of this, we hypothesized that Notch signaling is necessary for osteoclastogenesis and stimulation of Notch signaling will result in increased osteoclast formation and function.

Methods

Notch signaling was stimulated by plating bone marrow macrophages on goat anti-human IgG (control), Jagged1-Fc (JAG), or Delta-like1 (DLL) immobilized on the culture surface at 10µg/mL. Notch signaling was inhibited by adding DMSO (control), DAPT, or SAHM1 to the culture medium at a final concentration of 10µM. Osteoclastogenesis was performed by culturing bone marrow macrophages in

Figure 1. Summary of Notch signaling.
medium containing 35ng/mL M-CSF and 100ng/mL RANKL. After differentiation, cells were stained for tartrate-resistant acid phosphatase (TRAP) activity and quantified for osteoclast size, osteoclast number, osteoclast precursor number, nuclei per cell, and TRAP-stained area. Osteoclastic resorption was measured by differentiating osteoclasts on hydroxyapatite-coated culture surfaces; cells were cultured for 4 or 6 days, and resorbed areas were quantified.

**Results**

Under M-CSF/RANKL-stimulated osteoclastogenesis, JAG, but not DLL, promoted a significant increase in osteoclast size and TRAP-stained well area compared to IgG. Conversely, both DAPT (inhibition of NICD cleavage activation) and SAHM1 (inhibition of NICD mediated transcriptional activation) significantly reduced osteoclast size and stained area compared to DMSO control. As measured by quantitative RT-PCR, JAG stimulation resulted in a significant increase in TRAP, cathepsin K, and MMP9 expression, while DAPT significantly decreased in cathepsin K expression. Both JAG and DLL significantly increased resorbed area compared to IgG control at day 4. At this time, DMSO control, DAPT, and SAHM1 groups were similar. At 6 days, however, IgG resorption matched JAG resorption, though DLL stimulation still showed significantly higher resorption than IgG control. DAPT and SAHM1 groups had significantly less resorption than DMSO control. In partial explanation for the enhanced osteoclast size and resorption seen in JAG and DLL stimulated osteoclasts, JAG and DLL both significantly increased expression of pro-fusion genes CD200 and DC-STAMP. DAPT significantly reduced expression of both CD200 and DC-STAMP, and SAHM1 significantly reduced expression of CD200.

**Discussion**

These data indicate that Notch signaling is necessary for normal osteoclast maturation and function, and Notch stimulation by JAG and DLL can increase osteoclast formation and function potentially by enhancing the fusion of osteoclast precursors.

**Significance**

Dysregulated osteoclastic resorption resulting in bone loss and insufficiency fractures represents a costly challenge both in terms of financial and quality-of-life considerations. While current anti-osteoclast therapies are effective in preventing further bone loss, they are often insufficient in promoting new bone growth. Controlling the Notch pathway may provide the advantage of being able to simultaneously regulate bone growth (osteoblast and chondroblast lineages) and resorption for positive therapeutic effect.

**References**


Intermittent PTH after Prolonged Bisphosphonate Treatment Improves Bone Structure by Inducing Substantial New Bone Formation with Decoupled, Inhibited Bone Resorption in Ovariectomized Rats

Introduction

Bisphosphonates (BP) are an osteoporosis treatment that acts to prevent bone loss by inhibiting bone resorption. While this adequately slows or stops further bone loss, it does not promote new bone formation. In addition, recent evidence has suggested that long-term bisphosphonate use may increase the risk of atypical femoral fractures.\(^1\) Intermittent parathyroid hormone (PTH) is the only FDA approved anabolic agent, which promotes bone formation. Using PTH in conjunction with bisphosphonates would provide the maximum benefit to severely osteoporotic individuals, both inhibiting resorption and promoting bone formation. Early studies showed conflicting results regarding the efficacy of combined treatment of bisphosphonate and PTH therapy, leading to the hypothesis that PTH’s anabolic effect may be dependent on prior resorption to initiate bone formation.\(^2,3\) However, recent studies have shown a positive effect of combined or tandem BP and PTH therapies, attesting to PTH’s anabolic effect in the absence of resorption.\(^4-7\) Therefore, we hypothesized that PTH is able to act through a resorption-independent pathway to promote modeling-based bone formation. A better understanding of this pathway would be advantageous for both understanding combined PTH and bisphosphonate therapy, as well as designing new treatments which could more directly target modeling-based formation.

In this study, the efficacy of PTH following 12-weeks of alendronate (ALN, a BP) treatment was tested in ovariectomized (OVX) rats. While current methods of investigating bone remodeling over time are limited to cross-sectional animal studies or indirect biomarkers, the current study employed a novel in vivo imaging technique to assess bone formation and resorption rate simultaneously and longitudinally. This allowed for an evaluation of the coupling between bone resorption and formation. We hypothesized that prolonged ALN prior to PTH treatment does not blunt PTH’s anabolic potential to activate new bone formation. Thus, PTH can be considered as a treatment for patients with a history of long-term BP treatment.

Methods

Animals: \(n = 6\) female SD rats received surgery at 4-mo of age; 24 received a bilateral OVX, and 6 received a sham OVX surgery. The study began when all rats were 6-mo-old, after a 2-mo development of osteoporosis in the OVX rats. The treatment plan consisted of 2 phases (phase 1: weeks 0-12, and phase 2: weeks 12-16). The OVX rats were assigned to 4 groups: (1) a Veh group treated with saline for both phases; (2) an ALN group treated with ALN (28µg/kg 2x/wk) for both phases, (3) a Veh + PTH group treated with saline for phase 1, then switched to PTH (40 µg/kg 5x/wk) for phase 2, (4) an ALN + PTH group treated with ALN for phase 1, then PTH for phase 2.

In Vivo \(\mu\)CT Scans: The right proximal tibia of all rats were scanned (Scanco VivaCT40, 10.5 µm) at week 0 (2 mo post surgery), then weekly from weeks 11-15 corresponding with phase 2. New bone voxels were used to calculate the bone formation rate (BFR/BS), and lost voxels to calculate bone resorption rate (BRR/BS) weekly over phase 2.

In Vivo Dynamic Histomorphometry: A bone sub-volume \((1.575 \times 1.575 \times 1.05 \text{mm}^3)\) of each week in phase 2 was subtracted from the registered sub-volume of the previous week (weeks 11-15) to identify the newly formed bone voxels (green) and resorbed voxels (red) during each week (Fig 1). Trabecular microstructure of subsequent scan images was precisely aligned to baseline using an iterative registration method to identify the same volume of interest (VOI). Bone microstructure was analyzed for the same VOI for weeks 0, 12, 14, and 16.

Femur 3-Point Bending: The right femoral midshaft was scanned ex vivo for evaluation.
Intermittent PTH after prolonged bisphosphonate treatment improves bone structure by inducing substantial new bone formation. Switching to PTH resulted in a dramatic increase in BV/TV by week 16 compared to week 12 (40% and 42%) driven by increased Tb.Th (33% and 25%) in both Veh+PTH and ALN+PTH groups (Fig 2).

In Vivo Dynamic Histomorphometry: During phase 2, the Veh+PTH group had a dramatic increase in BFR/BS by week 14, which began to stabilize by week 16. The ALN+PTH group had a similar increase in BFR/BS which remained elevated throughout phase 2 (Fig 3a). BRR/BS was low in all treatment groups after the onset of PTH therapy. This was further confirmed by TRAP serum ELISA (Fig 3b). Fig 3c showed that SHAM and ALN treated groups had highly coupled remodeling, with similar BFR/BS and BRR/BS. Resorption outpaced formation for the Veh group. Bone resorption and formation were decoupled in both Veh+PTH and ALN+PTH groups as shown by a substantially greater BFR/BS than BRR/BS.

Finite Element (FE) Analysis: The trabecular bone subvolume of weeks 12 and 16 were converted to voxel-based FE models to estimate axial stiffness under compression.

Statistical Analysis: Longitudinal measures were compared over time and between groups using repeated measures ANCOVA adjusted for baseline, and cross-sectional measures were compared using ANOVA.

Results

Tibia Microstructure: 2-mo after surgery, OVX resulted in an average BV/TV of 0.13, in contrast to 0.50 in the SHAM group at week 0. BV/TV continued to drop in the Veh and Veh+PTH to 0.06 by week 12 (Fig 2). ALN treatment effectively stabilized BV/TV for ALN and ALN+PTH groups. Switching to PTH resulted in a dramatic increase in BV/TV by week 16 compared to week 12 (40% and 42%) driven by increased Tb.Th (33% and 25%) in both Veh+PTH and ALN+PTH groups (Fig 2).

Spine: Lumbar vertebra, L2 was scanned ex vivo (Scanco µCT35, 3.5 µm) for microstructural and tissue mineral density (TMD) analysis. TMD was calculated for bone tissue at trabecular surface layers (sTMD), and central bone tissue (cTMD).

Spine Microstructure: Compared to the tibia, OVX resulted in less reduced vertebral BV/TV (0.21 in Veh vs. 0.33 in SHAM). All 3 treatments groups resulted in BV/TV that was...
In healthy bone, resorption and formation are coupled and balanced to sustain bone mass. Their uncoupling due to OVX results in resorption outpacing formation, and subsequent trabecular bone loss which compromises the mechanical competence of the bone. ALN treatment effectively re-couples this balance, preventing additional bone loss. PTH, however, uncouples the balance in favor of formation, resulting in thickened bone and greater structural stiffness. Resorption activities after ALN, Veh, and ALN + PTH treatments were not different and remained significantly lower than those of Veh and Sham. While we may have expected a higher BRR/BS or TRAP in the Veh compared to Sham group, the resorption-formation balance of OVX had been re-adjusted to the slower formation rate 6 months after OVX. In summary, our investigation across multiple skeletal sites suggests that ALN followed by PTH is a viable treatment strategy to maintain and improve bone quality by stimulating substantial new bone formation.

**Figure 2.** Invivo tibial trabecular microstructure parameters. Left panel: percent change from baseline, right panel: value at the study endpoint. Letters (left) indicate significant differences between groups: a: ALN to ALN+PTH, b: ALN to OVX, c: ALN to Veh+PTH, d: ALN+PTH to OVX, e: ALN+PTH to Veh+PTH, f: OVX to Veh+PTH. Symbols (right) indicate significant change from baseline (%) or week 12 ($).
Significance

Long term ALN therapy following OVX can be further augmented by subsequent PTH treatment. This increases the BFR/BS to thicken the existing trabeculae while inhibiting bone resorption. The novel in vivo dynamic histomorphometry analysis provides direct evidence for PTH’s anabolic effect in the absence of bone resorption, further confirming its capacity for modeling-based bone formation.

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References


Role of Canonical Wnt/β-catenin Pathway in DNA Repair and Osteoblast Survival as a Novel Anabolic Treatment for Radiotherapy Associated Bone Damage

Introduction

A preventive or curative treatment for bone damage caused by radiation therapy targeting neighboring tumor is still elusive. Understanding the mechanisms behind these adverse effects of radiation and exploring new treatments for such bone disorders that will inevitably lead to fractures is imperative to improve the quality of life for these cancer patients. We recently established a clinically relevant radiation model using skeletally mature rats and a newly available small animal radiation research platform (SARRP) that replicates focal clinical radiotherapy in rodents. With this model, we reported that focal radiation on rat bone causes a loss of small trabecular elements with decreases in bone mass and strength and that diminished bone formation, but not enhanced bone resorption is a major contributor to such bone loss. Interestingly, daily injections of parathyroid hormone (PTH1-34, teriparatide), a FDA-approved anabolic treatment for severe osteoporosis, blocks post-radiation bone damage via protecting osteoblasts and osteocytes from apoptosis. Further cell culture studies delineated that the survival effect of PTH is mediated through a PKA/β-catenin pathway. In this study, we investigated the molecular mechanism by which activating canonical Wnt/β-catenin pathway protects osteoblasts from radiation damage and explored whether Sclerostin antibody (Scl-Ab), a treatment that specifically stimulates β-catenin activity in bone, is efficient in preventing radiation induced-bone damage.

Material and Methods

Radiation on osteoblast lineage cells and Wnt3a treatment. Xrad 320i was used to deliver a dose of 8 Gy for osteoblastic (UMR106-01) and osteocytic (Ocy454) cells and 24 Gy for primary calvarial osteoprogenitors. Wnt3a conditioned medium was collected from Wnt3a overexpressing L cells and applied to osteoblast lineage cells at 30 min after radiation. Cell death detection. Ethidium Bromide (EB)/Acridine Orange (AO) staining was used for detection of apoptotic cells. Immunofluorescence. After radiation, cells were fixed with 4% paraformaldehyde and incubated with antibodies against γ-H2AX, caspase 3 and Ku70 followed by Alexa-conjugated fluorescent secondary antibodies and DAPI staining. Single cell gel electrophoresis. To measure the extent of DNA damage at a single cell level, comet assay was performed using the alkaline conditions of the Trevigen Comet Assay® kit. SARRP radiation and Scl-Ab treatment in mice. Two-month-old male C57BL6 (n = 7/group) received a total of 16 Gy radiation, fractionated as two 8 Gy doses delivered on days 1 and 3 to the distal metaphyseal region of the right femurs using SARRP (Xstrahl, Suwanee, GA). This was designed to mimic the typical femur dose constraints for whole pelvis intensity modulated radiotherapy for patients with prostate, rectal, or endometrial cancers. Following radiation, mice were intraperitoneally injected with either vehicle or Scl-Ab (100 mg/kg/week) for 4 weeks. µCT. Bilateral femurs were harvested on d28 for µCT measurement of trabecular structural parameters and stiffness based on finite-element modeling.

Results

To study the survival effect of Wnt signaling on osteoblast lineage cells, UMR106-01, Ocy454, and primary osteoprogenitor cells were radiated and cultured in Wnt3a-containing medium. Apoptosis assay using either EB/AO (Fig. 1A-C) or cleaved caspase-3 staining (Fig. 1D, E) revealed that Wnt3a strongly suppressed radiation-induced cell death in those cells. Further cell culture studies showed that the survival effect of PTH is mediated through a PKA/β-catenin pathway. In this study, we investigated the molecular mechanism by which activating canonical Wnt/β-catenin pathway protects osteoblasts from radiation damage and explored whether Sclerostin antibody (Scl-Ab), a treatment that specifically stimulates β-catenin activity in bone, is efficient in preventing radiation induced-bone damage.
Figure 1. Wnt protects osteoblasts from radiation-induced apoptosis through canonical β-catenin pathway. (A) Quantification of EB/AO staining of UMR cells at 2 days after radiation. (B) Cells transfected with or without siRNA against β-catenin were radiated and treated with or without Wnt3a-CM. Apoptotic cells were quantified. (C) Cells treated as in (B) (D) Quantification of apoptotic rat calvaria osteoprogenitors (left) and osteocytes (right) after radiation and Wnt3a treatment. (E) Immunofluorescence of cleaved-caspase3 after radiation and Wnt3a treatments. (F) Quantification of cells with nuclear cleaved casp3+. NR: non-radiated; R: radiated. & p < 0.001 vs NR; δ: p < 0.001 vs R; %: p < 0.01, #: p < 0.001 vs R-Wnt.

Figure 2. The canonical Wnt-signaling promotes DNA repair in radiated osteoblastic cells. (A) Immunofluorescence images of γ-H2AX foci in UMR cells after radiation. (B) Quantification of γ-H2AX foci number after radiation with or without Wnt3a and β-catenin siRNA(C). Comet assay shows amount of damaged DNA in UMR cells with or without siRNA against β-catenin. & p < 0.001 vs NR; δ: p < 0.001 vs R; %: p < 0.001 vs R-Wnt-mock-siRNA. (E, F) Immunoblots show that Wnt3a increases Ku70 amount in UMR cells via β-catenin pathway. (G-I) siRNA against ku70 was transfected in UMR cells followed by radiation and treatment with Wnt. γ-H2AX foci number (G), damaged tail DNA (%) (H) and cell apoptosis (I) were quantified. & p < 0.001 vs NR; δ: p < 0.001 vs R; $: p < 0.01; ^: p < 0.001 vs Wnt mock-si-RNA.
protect osteoblast lineage cells from radiation damage. To translate these in vitro findings into in vivo studies, we focally irradiated adult mice at distal femoral metaphysis followed by weekly injection of Scl-Ab for 4 weeks. As shown in Fig. 3, 16 Gy radiation generated from SARRP induced a significant trabecular bone loss and structural deterioration in irradiated femurs compared to contralateral ones in vehicle-treated mice (BMD: −20%; BV/TV: −21%; Tb.N: −10%; SMI: +30%; Stiffness: −75%). Remarkably, Scl-Ab injections increased trabecular BMD, BV/TV, Tb.N, decreased SMI and increased stiffness to a similar level regardless of radiation, implying that Scl-Ab treatment is able to reverse radiation-induced bone damage in a clinical setting.

**Discussion**

This study provides proof-of-principle evidence that anabolic therapy is efficient for radiation-induced osteoporosis. Radiation damage on bone is mainly caused by its genotoxic damage and subsequent cell death in osteoblast lineage cells. Our in vitro studies delineate that one underlying mechanism for the survival effect of activating Wnt/β-catenin pathway is through up-regulation of Ku70 and accelerating the repair of DSBs. Subsequent animal study demonstrate that injections of Scl-Ab are capable of blocking bone loss and microarchitecture deterioration after radiation.

**Significance**

Fractures in tumor neighboring bones is a significant side effect of radiotherapy that poses major health threats for those cancer patients, most of them are elderly and with a greater risk of age related osteoporosis. Scl-Ab is currently under clinical trial for postmenopausal osteoporosis and could be an alternative and better treatment for radiotherapy-induced bone loss compared to PTH1-34 because of its black box warning.

**References**


A Comprehensive Study of Long-term Skeletal Changes after Spinal Cord Injury in Adult Rats

Introduction

Osteoporosis is a well-known secondary complication of spinal cord injury (SCI).1-3 Shortly after the injury, sublesional bone density and mass decline rapidly and linearly. This is particularly deleterious within cancellous bone located in metaphysal-epiphysial areas of the distal femora and proximal tibiae, which experience a decline in bone mass of 1-4% per month for the first 6-12 months. This bone loss rate is 4, 10, and 30-fold greater than that observed during microgravity, prolonged bed rest, and early menopause, respectively. Hence, severe osteoporosis, with at least a 40% reduction in bone mineral content, is common in SCI patients. In the present study, we performed a comprehensive analysis of long-term structural and mechanical changes in axial and appendicular bones in skeletally mature SCI adults. Olfactory ensheathing glia (OEG) transplantation recently emerges as one of the most promising approaches for nervous system repair, in particular, in the various forms of SCI. Preclinical and clinical data have demonstrated the efficacy and robustness of this treatment in promoting motor function recovery after transection of spinal cord. In this study, we also investigated whether this OEG transplantation treatment has beneficial effects on bone after SCI.

Material and Methods

SCI surgery and tissue harvest: T13 spinal cord of four-month-old male Fischer 344 rats received modest injury delivered by a 10-gm rod dropped from a 25 mm height. After injury, rats (n = 5/group) were randomly assigned to receive either vehicle (DMEM) or OEG (400,000 cells/rat) injection at 1 mm rostral and caudal to the contusion site. Sixteen weeks later, sublesional bones, including femurs and tibiae, and supraspinal bones, including 4th lumbar vertebrae (L4) and humeri, were collected and fixed further in 4% PFA for subsequent measurements.

Evaluation of bone microarchitecture by micro-computed tomography (µCT): All bones were scanned by a compact fan-beam-type tomograph µCT 40 (Scanco Medical AG, Bassersdorf, Switzerland) at 15 µm nominal voxel size.

Bone histology analysis: After µCT scans, right tibiae were decalcified for 21 days followed by paraffin embedding. Five-µm longitudinal sections were stained either by hematoxylin and cosin (H&E) for counting the plump bone lining osteoblast number or the number of TRAP-positive multinucleated osteoclasts within secondary spongiosa.

Serum chemistry: Osteocalcin and TRACP 5b level were determined by Rat Osteocalcin EIA Kit and RatTRAPTM Assay.

Results

To study the SCI effects on the knee joint in details, we scanned all three regions using high-resolution µCT. In the distal femoral site, as shown in Fig. 1A, we observed that the most drastic bone loss occurred in the secondary spongiosa immediately followed by the primary spongiosa at 16 weeks post-surgery, while, surprisingly, there was only modest bone loss in the subchondral region (data not shown). 3D analysis of µCT data revealed striking 54% and 65% reductions in vBMD and BV/TV, respectively, in the secondary spongiosa of SCI-vehicle group compared to controls (Fig. 1B). In the primary spongiosa, similar but relatively reduced changes in vBMD (47%) and BV/TV (56%) were observed in SCI-vehicle rats compared to controls (Fig. 1C). Among all regions, OEG-treated rats had comparable trabecular bone phenotypes as vehicle-treated ones (Fig. 1). We next analyzed sublesional axial bones and to clarify this, L4 vertebrae were harvested for µCT analysis. Compared to controls, SCI rats apparently lost a lot of trabecular bone, specifically in the central region of the L4 (Fig. 2A). Trabecular vBMD and BV/TV in L4 from vehicle-treated SCI rats were 31% and 37%, respectively, less than those from controls (Fig. 2B). Injection of OEG marginally but significantly improved several parameters, such as vBMD and BV/TV. To understand the underlying cellular mechanisms of long term SCI damage on bone, we performed histological analysis on right tibiae of all three groups. As shown in Fig. 3A, even after 16 weeks, SCI still strongly suppressed the number of osteoblasts by 71% and enhanced the number of osteoclasts by a 3.7-fold. The effects of long term SCI on bone formation and resorption were further
might be the more suitable therapy to promote bone health and to prevent bone fracture in SCI patients.

References

Pregnancy, Lactation, and Weaning Induce a Physiological Redistribution of Bone Mass at Multiple Skeletal Sites with Minimal Impact on Bone Quality

Introduction

In addition to its mechanical role, the skeleton also plays an important role in calcium homeostasis. As a result, the increased calcium requirements during reproduction induce substantial changes in maternal bone structure. In rodents, pregnancy and lactation result in significant bone loss, which recovers partially, but not fully, after weaning. However, clinical studies have suggested no negative effect of lactation or parity on future risk of osteoporosis or fracture. These conflicting results, combined with recent findings that the extent of lactation-induced bone loss varies depending on the skeletal site, led to our hypothesis that the skeletal changes undergone during reproduction represent a physiological redistribution of bone mass with minimal impact on bone quality.

The objective of this study was to investigate patterns of reproductive bone loss and recovery and their effects on mechanical integrity of the bone at multiple skeletal sites.

Methods

Longitudinal Study: 4-month-old rats (n = 5) underwent 3 cycles of pregnancy, lactation, and weaning; 6 age-matched, virgin rats were used as controls. Each reproductive cycle consisted of a 3-week pregnancy, 3-week lactation, and 3-6 week post-weaning recovery. Using µCT, the right proximal tibia of each rat was scanned weekly at 10.5µm (vivaCT 40, Scanco Medical) during the first cycle, and every 3 weeks thereafter. The trabecular microstructure in the secondary spongiosa was quantified for each scan, and µCT-based finite element analysis (FEA) was performed to estimate whole-bone stiffness of the rat tibia at the end of recovery after three reproductive cycles and for age-matched, virgin controls.

Cross-sectional Study: Rats (aged 6 month at sacrifice) underwent 1 reproductive cycle, and were euthanized at parturition (“Pregnancy”, n = 6), after 2 weeks of lactation (“Lactation”, n = 5), and 2 weeks post-weaning (“Weaning”, n = 5). Virgin controls (n = 6) were sacrificed at age 6 months. Each rat was injected with calcein prior to sacrifice for dynamic histomorphometry.

At sacrifice, blood was collected for analysis of serum levels of TRAP. Tibiae were harvested, embedded in MMA, and sectioned for histology. L4 vertebrae and femurs were harvested and µCT scanned at 10.5 µm resolution to allow for analysis of trabecular and cortical bone, respectively. Femurs were loaded to failure in 3-point bending to assess stiffness and peak load. Then, the stiffness, µCT-derived moment of inertia, and bone area were used to estimate Young’s modulus.

Statistics: Repeated-measures ANOVA, adjusted for baseline values, and 1-way ANOVA were used for longitudinal and cross-sectional comparisons, respectively. Bonferroni corrections were applied to all post hoc tests. Significant differences were considered when p < 0.05.

Results

During each reproductive cycle, trabecular bone loss at the tibia induced by pregnancy and lactation was partially recovered after weaning. This negative net change accumulated over multiple cycles, resulting in a dramatically altered trabecular microstructure, which persisted even 5 months after the end of the last reproductive cycle (Fig 1). While trabecular bone volume fraction (BV/TV) remained 52% lower for reproductive rats than for controls, there was no difference between groups in cortical bone area. Since cortical bone bears much of the load at the tibia, this resulted in no significant difference between the 2 groups in whole-bone stiffness. Dynamic histology indicated that bone formation rate and mineralizing surface were 581% and 337% greater in the proximal tibiae of rats in the Weaning group as compared to controls, and serum levels of bone resorption marker TRAP were 56% lower at 2 weeks post-weaning than during lactation (Fig 2). Cortical structure of the femur midshaft had deteriorated as early as the end of pregnancy, as illustrated by the 10-12% lower cortical bone area (Ct.Area) in the Pregnancy, Lactation, and Weaning groups, compared to controls (Fig 3A). However, reproduction had a beneficial effect on bone’s material properties, as evidenced by the 32-

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Discussion

The combined effects of pregnancy and lactation resulted in dramatic changes in bone structure, which persisted long after weaning. Similar to previous studies, these changes and their duration varied based on the skeletal site that was assessed.¹ This study also investigated the effects of reproduction on mechanical competence of the bone: FEA of the tibia resulted in a measurement of structural stiffness, whereas 3-point bending of the femur allowed measurement of the mechanical consequences of both structural and material properties of the bone. The effects of reproduction on the mechanical properties of the spine are currently being investigated. Results demonstrate that the mechanical integrity of the load-bearing regions of bone, such as the vertebral trabecular bone or the cortical bone in the femur midshaft, appeared to be preserved either through maintenance of structural integrity (as in the vertebrae) or improved material properties (as in the femur). On the other hand, trabecular bone microarchitecture in the proximal tibia plays a less crucial role in mechanical function, as the cortex of the long bones bears the majority of the bone’s load. This may explain why reproduction caused greater calcium release from tibial trabecular bone, resulting in dramatic and irreversible deterioration. These results indicate that reproduction induces a shift in bone structure, which persists long after weaning. The lack of change in tibial

Figure 1. (A) A profile plot indicating changes in the percentage of the baseline trabecular BV/TV that remains at the proximal tibia at each reproductive stage, and (B) representative renderings of the proximal tibia of reproductive and virgin control rats, made 5 months after the end of the third reproductive cycle. *: different from measurement made 3 weeks prior (p < 0.05). #: different from pre-pregnancy measurement of the same cycle (< 0.05).

Figure 2. Effects of reproduction on bone remodeling parameters, including (A) BFR/BS, (B) MAR, (C) MS/BS, and (D) serum TRAP.

Figure 3. Effects of reproduction on (A) Ct. Area, (B) Young’s modulus, (C) Peak load, and (D) Stiffness at the femur midshaft. *: p < 0.05.

38% greater Young’s modulus in rats from the Pregnancy, Lactation, and Weaning groups, compared to controls (Fig 3B). Additionally, reproduction had no effect on femoral stiffness or peak load (Fig 3). A comparison of the effects of reproduction at two different trabecular sites (the L4 vertebra and proximal tibia) indicated that although both sites underwent decreases in BV/TV as a result of pregnancy and lactation, the structural adaptations of L4 were dramatically different from those of the tibia (Fig 4). BV/TV recovered more fully at L4, and there were minimal changes in trabecular number (Tb.N) and connectivity density (Conn.D) at L4 as compared to the tibia (Fig 4), while both sites underwent similar, reversible changes in trabecular thickness (Tb.Th).
whole-bone stiffness and femoral peak load and stiffness, combined with previous clinical studies which showed that reproduction has no adverse effect on osteoporosis risk, suggest that reproduction does not diminish the mechanical integrity of bone.\(^3\)\(^4\) Instead, it appears that the body responds to increased calcium demands during pregnancy and lactation by selectively degrading bone structure, resulting

in an alternate skeletal composition where bone structure may be optimized at the more load-bearing regions to allow maintenance of similar quality to non-reproductive bone.

**Significance**

Although reproduction constitutes a physiological process that has minimal impact on bone quality, dramatic, irreversible changes in bone structure and composition do occur. By characterizing these changes and assessing the mechanical integrity of the post-reproductive skeleton, this study establishes reproductive bone as a new model of an altered skeletal status where bone quality remains intact.

**Acknowledgements**

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**References**

Simultaneous Measurement of Changes in Bone Remodeling and Microvasculature in Response to Estrogen Deficiency-Induced Bone Loss and Intermittent PTH-Induced Bone Gain

Introduction

Bone is a dynamic, highly vascularized tissue that is involved in regulating calcium-phosphate metabolism and hematopoiesis. Osteogenesis and angiogenesis are closely coupled in bone remodeling process. Changes in bone remodeling are accompanied by changes in the microvascular network within bone marrow. Because of the drastic effects on bone remodeling, it is likely that both ovariectomy (OVX) and intermittent parathyroid hormone (iPTH) treatment will also affect bone vasculature. However, little is known about the impact of the relationships between bone remodeling and bone vasculature on OVX and iPTH treatment. Also, simultaneous visualization of the trabecular and vascular microstructures remains challenging. Therefore, it is of importance to understand the morphology of the bone vasculature. We hypothesized that the volume and number of blood vessels are associated with those of trabeculae. In this study, we used a well-described bone loss model by inducing estrogen deficiency in ovariectomized (OVX) rats and a bone gain model by administering intermittent parathyroid hormone (PTH) in intact rats.\(^1\)\(^2\) We developed a novel vascular network perfusion technique combining standard \(\mu\)CT, image processing techniques and \(\mu\)CT-based \textit{in vivo} dynamic bone histomorphometry technique to allow for simultaneous visualization of the trabecular and vascular microstructures and longitudinal and simultaneous assessment of changes in bone remodeling in the rat tibiae. The overall goal was to develop a platform to investigate the changes in bone remodeling and microvasculature in response to estrogen deficiency-induced bone loss and iPTH-induced bone gain in rat tibiae.

METHODS

\textbf{Study Design:} 10 intact and 9 ovariectomized (OVX) female Sprague-Dawley rats (10-wk old) were purchased and housed at the animal facility (IACUC approved). The 9 OVX rats developed osteopenia for 6 weeks. The 10 intact rats were divided into saline-treated (VEH) and PTH-treated groups (PTH 1-34, 60\(\mu\)g/kg/day, Bachem). Starting at 14-week old, both VEH and PTH groups received subcutaneous injections 5 days a week for 2 weeks.

\textbf{Pre-perfusion scans:} At age 15 and 16 weeks, 2 sequential scans of the proximal tibia were performed \textit{in vivo} using the vivaCT 40 scanner (Scanco) for 3 groups of rats: OVX (n = 9), VEH (n = 5), and PTH (n = 5). A 4.4-mm region at week 15 and a 10-mm region at week 16, respectively, located distal to the proximal growth plate was acquired from each tibia at 10.5\(\mu\)m resolution.

\textbf{Perfusion:} Right after the week 16 scan, rats were perfused with Microfil\textregistered (MV122, Flow Tech), a radiopaque contrast agent, to form a vascular cast inside bone. Briefly, a heat pad was used to keep the animal’s body temperature at 37\(^\circ\)C. All perfusion solutions were prepared and maintained at 37\(^\circ\)C in water bath except the Microfil\textregistered mixture. A catheter was inserted into the abdominal aorta, and an incision was made in the right atrium. Using a perfusion pump, heparin sodium (30 units/mL) followed by 100 mL of 0.9% saline and 50 mL of 4% paraformaldehyde was infused at 4.4 mL/min through the rat. Next, using a syringe pump, 5 mL of freshly mixed Microfil\textregistered was infused into the aorta at 1 mL/min. Once the mixture reached the common iliac arteries, the flow rate was decreased to 0.3 mL/min. The Microfil\textregistered mixture was prepared by diluting a silicone rubber injection compound 4:1 with medium-viscosity diluent and mixing the result with 3\% curing agent. The perfused animals were stored at 4 \(^\circ\)C for 24 hours. Tibiae were harvested and fixed in 10\% formalin.

\textbf{Post-perfusion Scans:} A 10-mm region located distal to the proximal growth plate was scanned at a 6\(\mu\)m resolution using the \(\mu\)CT 35 scanner (Scanco). Post-decalcification Scans: The tibiae were then decalcified by 10\% EDTA for three weeks. After the decalcification, the region distal to the proximal tibial growth plate, same as post-perfusion scans, were acquired at a 6\(\mu\)m resolution.
**Registration:** A registration procedure was employed using a landmark-initialized, mutual-information-based registration kit (ITK, NLM). First, the pre-perfusion scans (containing bone structure only) were registered to the post-perfusion scans (containing bone structure and bone vasculature) to derive the first transformation matrix $T_1$ since bone structure was contained in both image sets. Next, the post-perfusion scans were registered to the post-decalcification scans (containing bone vasculature only) to derive the second transformation matrix $T_2$ since bone vasculature was contained in both image sets. Finally, transformation matrices $T_1$ and $T_2$ were combined to generate $T_3$ ($T_3 = T_2·T_1$), the transformation matrix which aligned the pre-perfusion scans to the post-decalcification scans which allowed the same region of interest to be analyzed in both scans.

**Standard bone microstructure and blood vessel microstructure analyses:** A volume of interest (VOI) in the secondary spongia of the pre-perfusion scans at 10.5µm resolution was segmented and evaluated for bone microstructural parameters including bone volume fraction (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th), and trabecular spacing (Tb.Sp). The registered VOI of the post-decalcification scans at 6µm resolution was segmented and evaluated for blood vessel microstructural parameters including vessel volume over marrow volume (Ves.V/Mar.V), vessel number (Ves.N), vessel thickness (Ves.Th), and vessel spacing (Ves.Sp).

**µCT-based in vivo dynamic bone histomorphometry:** Bone resorption (BRR/BS) and formation (BFR/BS) were identified and measured based on the sequential in vivo µCT scans.

**Statistics:** A one-way analysis of variance (ANOVA) with a Tukey Honestly Significance Difference (HSD) was performed to determine the between-group difference in bone and blood vessel microstructural parameters and dynamic bone parameters with $p < 0.05$ indicating significance and $p \leq 0.1$ indicating trends.

**Results**

**OVX vs. VEH:** As expected, trabecular bone in the OVX group had 76% lower Tb.BV/TV ($p < 0.05$), 71% lower Tb.N ($p < 0.05$), 321% higher Tb.Sp ($p < 0.05$) compared to that of the VEH group. There was no measurable difference in Tb.Th (11%, $p < 0.1$). Vessels in the OVX group were 82% thicker than those in the VEH group ($p < 0.05$, Fig 2). Blood vessel in the OVX group had 43% higher Ves.V/Mar.V ($p < 0.05$), 81% higher Ves.N ($p < 0.05$), 30% lower Ves.Th ($p < 0.05$), and 48% lower Ves.Sp ($p < 0.05$) compared to that of the VEH group.

**PTH vs. VEH:** There was no significant difference in Tb.BV/TV, Tb.N or Tb.Sp between PTH and VEH groups, with a significant increase in Tb.Th in the PTH group (12%, $p < 0.05$). To confirm PTH’s anabolic effect on bone, trabecular bone measurements after PTH treatment were also compared with those at the beginning of treatment measured by in vivo µCT. Longitudinal comparisons confirmed that there was a 22% increase in Tb.BV/TV and 18% increase in Tb.Th ($p < 0.05$) due to a 2-week PTH treatment. Moreover, compared to the VEH group, the PTH group had 29% lower Ves.Sp ($p < 0.05$). There was no significant difference in Ves.V/Mar.V, Ves.N and Ves.Th between PTH and VEH groups.

**Discussion**

In this study we developed an imaging framework to simultaneously visualize 3D trabecular microstructure and microvasculature inside the tibiae of both OVX rats and iPTH-treated rats. The resorption and formation map with vessels provides a platform for our future comparison between vessels and bone formation and resorption. Following a 6-week development of osteoporosis, OVX rats showed deteriorations in trabecular bone microstructure and a significant increase in vessel volume fraction and vessel number compared to the VEH rats. However, our vasculature results were inconsistent with Ding et al’s and Peng et al’s report. The discrepancy may be due to use of different animal models and different perfusion techniques. In case of iPTH treatment, we did not find improved angiogenesis after 2-week iPTH treatment compared to saline-treated rats, which was consistent with Prisby et al’s report. Both OVX and iPTH treatment result in accelerated bone remodeling, but with opposite net balance towards resorption and formation, respectively. Our results showed that in estrogen deficiency-induced bone loss there may be a possible association between bone remodeling and angiogenesis while with iPTH-induced bone gain there may be not. More studies need to be done to test this hypothesis.
Significance
This study establishes a novel technique that simultaneously visualizes the 3D microstructures of bone and microvasculature using standard μCT. Combined with measures of bone formation and resorption, this may help improve our understanding of the effects of OVX and iPTH on the bone-blood vessel function unit.

Acknowledgments
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References
Impaired Chondrocyte Hypertrophic Differentiation is Associated with Failed Vertebral Bone Formation in Mucopolysaccharidosis VII Dogs

Introduction

Mucopolysaccharidosis (MPS) VII is associated with severe musculoskeletal manifestations, which are particularly prevalent in the spine. Vertebral dysplasia and accelerated intervertebral disc degeneration lead to kyphoscoliosis and spinal cord compression, directly impacting patient mortality and quality of life. A defining feature of spine disease in MPS VII is the presence of cartilaginous lesions in the vertebral bodies, indicative of failed cartilage-to-bone conversion during postnatal development; however, the underlying molecular mechanisms are poorly understood. During normal vertebral bone formation, cartilaginous rudiments form a template where resident chondrocytes undergo distinct stages of differentiation (resting, proliferative, hypertrophic, terminal) regulated by a highly orchestrated pattern of growth factor signaling, culminating in ossification by osteoblasts. Glycosaminoglycans (GAGs) perform critical roles in regulating the activity of these growth factors. We hypothesize that abnormal GAG accumulation in MPS VII disrupts chondrocyte differentiation by interfering with growth factor signaling, thus preventing normal cartilage-to-bone conversion. Our objectives were to: 1) identify the earliest developmental age where altered bone formation is evident in MPS VII, and 2) establish the stage at which epiphyseal chondrocyte differentiation is impaired, using the naturally-occurring canine model.

Methods

We collected thoracic vertebrae from 9 day (n = 2) and 14 day old (n = 5) litter-matched MPS VII heterozygote and affected dogs for quantitative PCR and micro-computed tomography (microCT) analyses. This age range was selected based on previous radiographic, longitudinal studies of vertebral bone formation in MPS VII dogs.

Results

Comparison of mRNA expression of chondrocyte differentiation (SOX9, RUNX2, COL10A1) and osteoblast (ALPL, BGLAP) markers, and microCT visualization of vertebral bodies of heterozygote and MPS VII affected dogs showed striking differences in bone formation (Figure 1) at 14 days whereas at 9 days, no significant differences besides a trend towards lower RUNX2 expression were detected (Figure 2). Interestingly, SOX9 expression was downregulated at 14 days for both heterozygote and affected dogs suggesting that both chondrocyte populations receive regulatory signals for proliferation but that MPS VII chondrocytes fail to progress into hypertrophy. Furthermore, bone volume fraction and bone mineral density quantification of the vertebral bone primary ossification centers showed no differences between heterozygote and affected dogs suggesting that at this time point, the most affected developmental pathways involve activation of secondary ossification centers. Since the epiphyses at these early ages are composed of cartilage and therefore high in GAG content, aberrant GAG accumulation in MPS VII is likely playing a role in failed ossification. Indian Hedgehog signaling plays a crucial role in regulating chondrocyte differentiation and is regulated in a highly GAG-dependent manner.

Discussion

Our preliminary data showed differences in Hedgehog pathway mRNA expression levels between heterozygote and affected animals at both 9 and 14 days implicating this pathway in disease etiology. The results of this study lay the foundation for future mechanistic investigations into bone disease in all MPS subtypes.
Acknowledgements
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References


Reduction Epidermal Growth Factor Receptor (EGFR) Signaling Enhances Cartilage Destruction in Mouse Osteoarthritis Model

Introduction

Osteoarthritis (OA) is a degenerative joint disease primarily characterized by the destruction of articular cartilage. Growth factors, such as TGF-β, IGFs, BMPs, and FGFs, regulate synthesis and maintenance of cartilage ECM and therefore, play important roles in cartilage homeostasis and OA development. Our recent work demonstrated that EGFR signaling is important for cartilage matrix degradation during endochondral ossification, and deficiency of EGFR activity either globally or specifically in chondrocytes causes expansion of the hypertrophic zone in the growth plate and delayed formation of secondary ossification center in long bones at early postnatal stage.1,2 We hypothesize that EGFR is important for cartilage homeostasis and OA development. In this study, we performed destabilization of the medial meniscus (DMM) to induce OA in mouse models with reduced EGFR activity.

Methods

Three mouse models with reduced EGFR activity were used in this study. In the first model, we compared OA development between EgfrWa5/− (n = 9) and their WT siblings (n = 10) after DMM surgery. Egfr wa5 codes for a kinase-dead, dominant negative receptor. Mice homozygous for Wa5 are embryonic lethal but the heterozygotes are viable and show no major pathological changes. In the second model, we compared OA development in WT mice treated with either vehicle (n = 8) or gefitinib (100 mg/kg, n = 9), an EGFR kinase inhibitor, once every other day, for 12 weeks. In the third model, we generated cartilage-specific EGFR inactivation mice (Col2-cre EgfrWa5/+; n = 5) and their control siblings (Col2-Cre Egfr+/+ and Egfr+/−, n = 6) by breeding Col2a1-Cre with EgfrWa5/− followed by breeding Col2-Cre EgfrWa5/+ with Egfr+/−. In all these models, 3-month-old animals received DMM surgery in the right knees and sham operation in the left knees. Bilateral knee joints free of soft tissues were harvested 12 weeks post-surgery for histological and immunohistochemical analysis. OA changes were evaluated by Mankin’s method.

Results

Histological analysis showed that total cartilage area and thickness, particularly the uncalcified area and thickness, at both medial femoral condyle and medial tibial plateaus were reduced in EgfrWa5/− and gefitinib-treated mice in comparison with WT and vehicle-treated mice, respectively. Further scoring by Mankin’s method revealed significant 19% and 36% increases of OA scores at medial femoral condyle and medial tibial plateaus, respectively, in EgfrWa5/− mice compared to those in WT mice (Figure 1A). In gefitinib-treated mice, OA damage on the articular cartilage was relatively milder than those in EgfrWa5/− mice, but still more...
To clarify whether global reduction of EGFR signaling by gefitinib treatment or a dominant negative allele Egfr$^{Wa5/+}$ might act on cells other than chondrocytes to affect OA development, we specifically reduced EGFR activity in chondrocytes by generating Col2-cre Egfr$^{Wa5/+}$ mice (CKO). Our previous data has shown that chondrocytes from these CKO mice exhibit much lower EGFR activity than those from Egfr$^{Wa5/+}$ mice. Interestingly, after DMM surgery, these mice developed a very severe OA phenotype with a complete loss of articular cartilage layers at femoral condyle and tibial plateau at 3 months post-operatively (Figure 3). In addition, the affected sites showed thickening of subchondral bone plate and contained less subchondral bone marrow in both femurs and tibiae.

Discussion

We provide the first direct evidence that chondrogenic EGFR signaling and its cognate ligands, most likely TGF-β, is essential for articular cartilage homeostasis and is critical for OA development. Our data demonstrate that reduction in EGFR activity, particularly in articular chondrocytes, increases apoptosis and amounts of cartilage matrix degradation enzymes such as ADAMTS5 and MMP13, eventually leading to accelerated articular cartilage destruction. Further investigations are underway to understand how EGFR pathway regulates the crosstalk between articular cartilage and subchondral bone during OA development.

Figure 2. The protein amounts of ADAMTS5, MMP13 and HIF2α are increased in osteoarthritic cartilage from mice with reduced EGFR activity. A: Immunostaining of ADAMTS5, MMP13 and HIF2α in DMM-operated knee joints from Egfr$^{Wa5/+}$ mice and gefitinib-treated mice and their respective controls. B: The percentages of ADAMTS5-, MMP13- and HIF2α-positive articular chondrocytes were quantified. a: p < 0.05; c: p < 0.001.

Proteolytic cleavage of aggrecan weakens the cartilage matrix and is a key event in OA pathogenesis. Immunohistochemistry showed that aggrecan degradation products generated by either aggrecanases or MMPs were significantly increased in both femoral and tibial articular cartilage areas in Egfr$^{Wa5/+}$ mice and gefitinib-treated mice compared to their respective control mice. These results indicate that activation of EGFR signaling pathway suppresses cartilage matrix degradation during OA development. Further study revealed elevated amounts of ADAMTS5 and MMP13, the critical proteinases responsible for cartilage degradation during OA development, in articular cartilage after DMM surgery in both mouse models with reduced EGFR activity, compared to those in their respective control mice (Figure 2), which coincides with the increased aggrecan degradation in these mouse models. Interestingly, we found elevated expression of hif2a, a transcription factor highly expressed in OA development and essential for Mmp13 expression in chondrocytes, in the articular cartilage of those mouse models after DMM surgery, compared to their respective control mice (Figure 2).

Significance

Our studies reveal a novel role of EGFR signaling in the protection of articular cartilage during OA development.
and therefore identify this signaling pathway as a potential therapeutic target for OA treatment.

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**References**

Population Average T2 MRI Maps Reveal Quantitative Regional Transformations in the Degenerating Rabbit Intervertebral Disc that Vary by Lumbar Level

Introduction

Lumbar intervertebral disc degeneration has been implicated as a cause of low back pain as the natural, age-related degenerative process is closely related to deficiencies in disc function. Magnetic resonance imaging (MRI) allows for the quantitative, non-invasive assessment of the disc and might be used to identify pathological changes associated with back pain. Clinical assessment of disc abnormalities is typically conducted through visual inspection of MR images or by qualitative evaluations on an integer scoring system. While these scoring systems provide some level of discrimination between degenerative states, they do not provide quantitative information on the MR signal or positional information regarding the location of compositional changes. Rigorous spatial quantification of T2 MR images may allow for improved discrimination between age-based sub-populations or degenerate sub-populations (populations with early versus advanced degeneration) by identifying changes in disc shape, structure and regional composition. The objective of this study was to spatially map changes in T2 relaxation time as a result of puncture-initiated degeneration in the rabbit lumbar spine. Rabbits were imaged before and after puncture to generate population average T2 maps of the healthy and post-injury state.

Methods

Surgical Procedure: New Zealand White rabbits (n = 20, age = 3mos.) underwent a procedure in which four lumbar discs (L3/L4 to L6/L7) were injured by needle puncture to induce degeneration. Using a retroperitoneal approach, an 18G needle was inserted through the lateral AF to a depth of 5 mm. Rabbits were returned to normal cage activity after surgery.

MRI Acquisition In vivo: T2 mapping was performed on each rabbit pre-injury and 4 weeks post-injury with a 3.0 T MRI spectrometer (Figure 1a). Coronal T2 maps were generated with the following parameters: three 2mm-thick slices, 17 Echoes, TE/TR = 7.55ms/2000ms, FOV = 16.5x16.5cm², matrix = 384x384, 2 averages.

Population Average T2 Maps: Discs were manually segmented from coronal slices and mapped to a grid normalized to disc dimensions (Figure 1b). Population Average T2 Maps were developed by averaging the T2 values of discs from the Week 0 or Week 4 groups at each grid point. T2 Difference Maps were constructed by subtracting T2 values of individual or population average post-injury T2 maps from the pre-injury population average T2 map at each grid point.

NP Auto-Segmentation: An automatic procedure was developed to enable non-biased segmentation of the nucleus pulposus (NP) (Figure 1c). The area surrounding the NP was first manually segmented and then T2 values at each point were fit to a bimodal, bivariate Gaussian distribution function, given the natural bimodal distribution the T2 signal in the NP. NP boundaries were demarcated where 50% of the max NP T2 signal had dissipated, defined by the means/standard deviations of the Gaussian function. After segmentation, disc, NP and annulus fibrosus (AF) geometry were measured.

Results

Population average T2 maps showed quantitative differences in T2 values across healthy discs and revealed specific transformations following injury (Figure 2a–b). Before injury, T2 relaxation time was lowest in the AF and increased gradually towards the NP. The pre-injury map identified that the intranuclear cleft (bilateral T2 peaks at the center of the NP) is a consistent anatomical feature preserved across all discs. At Week 4, NP T2 values decreased and the T2 difference map showed that this reduction occurred at the periphery of the NP. The T2 relaxation time decreased in the NP but not in the AF. Between Weeks 0 and 4, the mean T2 decreased in the NP and the whole disc, while there was no change in the AF.

Needle injury also resulted in changes in disc shape (Figure 2c–e). Whole disc area remained...
constant from Week 0 to Week 4, while NP area decreased and AF area increased. Whole disc width increased, while NP width decreased and AF width increased. In addition, whole disc and AF heights decreased, while there was no change in NP height. While MRI measurements showed a disc height decrease in the sagittal plane, radiographs demonstrated that disc height decreased in the coronal plane.

T2 difference maps revealed how discs at different lumbar levels responded to injury (Figure 3). With progression along the spine, the T2 difference in individual discs decreased in magnitude and increased in variability, indicating that the response to injury was not only less severe, but was less repeatable at these lower levels. The mean NP T2 signal in the L3/L4 and L4/L5 discs decreased significantly between Weeks 0 and 4, while the mean NPT2 value in both the L5/L6 and L6/L7 discs did not change over the same time period, and was significantly greater than the L3/L4 NPT2.

### Discussion

Rabbit lumbar discs were injured by needle puncture, a standard model for inducing degeneration. We generated population average T2 maps before and after injury that demonstrated that the reduced T2 signal occurred primarily in the NP. Geometric changes following needle puncture included decreases in disc height and NP width. Additionally, the increase in the coronal disc width following puncture supports the idea that disc bulging occurs in this model, a common finding in human epidemiological studies. The heterogeneity in response to injury by anatomic location suggests that, to produce a consistent degenerative response, puncture depth should be adjusted as a function of disc level. Future work will determine whether these population average T2 and corresponding T2 difference maps are useful in a clinical population to assess the degree of degeneration, to predict pain/disability, and to quantify adjacent segment degeneration.

### Significance

This study outlines a method for analyzing T2 MRI maps to improve clinical diagnosis of intervertebral disc disease. Heterogeneity in the rabbit needle injury model, a standard disc degeneration model, must be considered when planning future studies.
Acknowledgement
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References
In Vitro Growth Trajectory and In Vivo Implantation of a Cell-Based Disc-like Angle Ply Structure for Total Disc Replacement

Introduction
Surgical strategies for treating intervertebral disc degeneration are designed primarily to alleviate pain but do not restore disc structure or function. To treat end stage disc disease, we have developed an engineered disc for total disc replacement that replicates the hierarchical structure of the native tissue. This engineered disc consists of an aligned electrospun nanofibrous scaffold annulus fibrosus (AF) and a hydrogel-based nucleus pulposus (NP); combined they form a disc-like angle ply structure (DAPS). When seeded with cells, these composites increase in compositional and functional properties with time in in vitro culture. Based on this progress, the objectives of this study were two-fold; first, to evaluate the in vitro maturation of DAPS seeded with either native AF and NP cells or with mesenchymal stem cells (MSCs) to establish a growth trajectory and, second, to use our validated rat tail disc replacement model to determine if a cell-seeded DAPS can integrate into the rat caudal disc space.

Methods
AF Fabrication: Poly(e-caprolactone) (PCL) and poly(ethylene oxide) (PEO) nanofibers were electrospun onto a rotating mandrel as aligned fibrous sheets. Strips were cut 30° to the fiber direction and two strips with alternating ±30° alignment were wrapped concentrically to form the AF region of the DAPS, sized to fit the rat caudal disc space. One layer (th = 125µm) of PEO was included for every two layers of PCL (th = 125 µm) to provide routes for cell infiltration. AF constructs were seeded with either bovine AF cells or bovine MSCs (2M cells/construct).

NP Fabrication: Methacrylated hyaluronic acid (MeHA) was produced by reacting HA with methacrylic anhydride. A 1% w/v solution was formed by dissolving MeHA and 0.05% Irgacure 2959 in phosphate-buffered saline. Bovine NP cells or MSCs were suspended in the MeHA solution (20M cells/mL), followed by photo-polymerization with UV light in a mold to form the NP region. Growth Trajectory: AF and NP regions were cultured separately in serum-free media containing TGF-β3 for 2 weeks, and then combined to form the DAPS construct.

At 2.5, 5, 7.5, and 10 weeks, mechanical properties in unconfined compression (20 cycles, 0N to −3N, 0.5 Hz, data analyzed at 20th cycle), glycosaminoglycan (GAG) content, and picrosirius red (collagen) and alcian blue (GAG) stained histological sections were evaluated.

In vivo DAPS Implantation: Athymic rats were prepared for DAPS implantation by installing an external fixator designed to stabilize two adjacent rat caudal vertebrae. AF/NP cell-seeded DAPS precultured for 10 weeks were implanted into the native disc space and rats were euthanized 5 weeks post-operatively. Vertebral-DAPS-vertebra segments were excised and scanned by micro-CT and then sectioned and stained with alcian blue/picrosirius red.

Results
The AF and NP regions of both MSC- and disc cell-seeded DAPS increased in biochemical content with time in culture (Figure 1). Collagen and GAG staining increased with time, starting at the periphery of the AF at 2.5 weeks and gradually reaching deeper portions of the AF by 10 weeks. Collagen and GAG staining in the NP increased over time, with collagen staining strongest at the center of the NP, while GAG staining was evenly distributed throughout. Quantification of GAG content in each region showed a steady increase in deposition in both AF and NP regions for both cell types, with GAG production in MSC-seeded DAPS outpacing that of disc-cell seeded DAPS (Figure 2a). Mechanical properties of the DAPS decreased slightly over...
of immunocompromised rats, constructs remained in the disc space, retained their morphological features, and showed signs of integration with surrounding native tissue structures. However, loss of proteoglycan in the NP region was evident, suggesting that it may be necessary to deliver factors in vivo to sustain the phenotypic production of ECM in this region.

In this study we implanted DAPS at the point of highest maturation (i.e., at 10 weeks). Implantation at earlier times, when DAPS constructs are at their maximum growth rate (as opposed to maximum growth state) may be necessary to improve integration. This strategy has proven successful for the integration of engineered cartilage into native cartilage5, and a study by Bowles and co-workers reported strong vertebral integration of cell-seeded engineered discs after a shorter 2 week preculture period.4 Taken together, our data support the continued translation of a cell-based disc-like angle-ply structure for the replacement of severely degenerated intervertebral discs.

Acknowledgement
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References
Sprifermin (rhFGF18) Preserves Articular Cartilage Depth-Dependent Properties During in Vitro Culture

Introduction

The current clinical practice of osteochondral allograft transplantation requires a time delay between tissue harvest and transplantation to allow for testing of bacterial and viral contamination. During this time, allografts are stored in cold conditions in an attempt to preserve viability and tissue properties. Although not ideal, due to the very low chondrocyte survival, this procedure is preferred to in vitro culture methods, as the latter results in the rapid loss of mechanical properties and biochemical content. More generally, in vitro culture of explants is widely used experimentally to study chondrocyte response in their natural environment, however the rapid turnover of matrix makes results stemming from such long-term cultures difficult to interpret. Several studies have focused on developing in vitro culture systems to preserve allograft native properties including one recent report of a serum-free media formulation containing dexamethasone that preserved mechanical properties and biochemical content in juvenile bovine explants for up to 8 weeks. Sprifermin (recombinant human FGF18 [rhFGF18]) stimulates chondrocyte proliferation and matrix production in vitro, and reduces cartilage degeneration and increases de novo matrix formation by osteoarthritic cartilage in vivo. We recently showed that a one day per week exposure to Sprifermin preserved explant mechanical properties in a serum-containing media, and that this preservation was due to a decrease in matrix loss and MMP activity over the first 3 weeks. Here, we extend this analysis to query local mechanical properties to better gauge the dynamics of explant remodeling in response to Sprifermin. Our findings show that Sprifermin preserved or improve mechanical properties in a depth-dependent manner and attenuated matrix loss over six weeks of culture. These findings may provide a new method by which to preserve allografts during testing periods prior to transplantation.

Methods

Full thickness cartilage explants (4mm diameter) were harvested from the trochlear grooves of juvenile bovine knees. After overnight culture in Complete Medium (CM: DMEM with 10% FBS, 1X PSF, 1% Fungizone, 1% MEM Vitamins, 25 mM HEPES buffer, and 50 µg/ml Vitamin C), explants were trimmed to a similar thickness and cultured in CM with or without rhFGF18 (Sprifermin, 100 ng/ml) applied for 24 hours each week. Over six weeks, explant mechanical properties were evaluated using uniaxial unconfined compression. Explants were tested using a microscope mounted micrometer-driven platen and load cell assembly with a glass slide bottom for imaging (N = 3-5). Cell nuclei were stained with Hoechst 33342 and images and load readings were acquired at equilibrium (0, 4, 8, 12, 16, and 20% strain). Images were processed using two-dimensional digital image correlation software (VIC-2D, Correlated Solutions) to calculate strain throughout the depth of the tissue. A custom MATLAB program (MathWorks) was then used to calculate average strains in 10 equal bins throughout the depth of the sample. The first and last bins were excluded from the analysis to avoid edge effects and the remaining data was grouped further into 20-30%, 30-60%, and 60-90% of the depth to approximate the average strains in the superficial, middle, and deep zones, respectively. Equilibrium moduli in each bin were calculated from the average strain (at an average strain of 8%) and the measured boundary stress at this step. Error bars in all figures represent the standard deviation (SD). Statistical analysis consisted of a 2-way ANOVA with Bonferroni post-tests.

Results

In the superficial zone, ranging from 10-30% of the depth, the equilibrium modulus of control cultures steadily declined through Week 4 (Day 1 $E_v = 1108 \pm 343$ kPa, Week 4 $E_v = 316 \pm 150$ kPa) followed by a slight increase in weeks 5 and 6 (Week 5 $E_v = 646 \pm 150$ kPa, Week 6 $E_v = 451 \pm 153$ kPa). Treatment with rhFGF18 increased the equilibrium modulus from Day 1 through week 2 (Day 1 $E_v = 1108 \pm 343$ kPa, Week 2 $E_v = 2052 \pm 259$ kPa) and then was maintained Day 1 levels for weeks 3 through 6 (Week 3 $E_v = 1193 \pm 482$ kPa). In the middle zone, 30-60% of the depth, the equilibrium modulus of controls decreased from Day 1 through Week 6 (Day 1 $E_v$, etc.)
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the unique material properties of cartilage are heterogeneous and differ within discrete zones, bulk measurements only tell part of the story. Assessment of local mechanical properties enables specific analysis of depth-dependent characteristics of articular cartilage and in this study their changes over time in culture. Our findings show a distinct increase in modulus from the superficial to middle to deep zones at day 1, consistent with the reported literature. In control cultures, the mechanical properties decreased very quickly throughout the depth and stabilized between weeks 3 and 6. This resulted in preservation of depth-dependence, though at lower values than at harvest under these control conditions. Treatment with rhFGF18 increased the modulus in all three zones through week 2 of culture, before falling back to day 1 levels at week 3 followed by a rebound at week 4 and another decrease to day 1 levels at week 6.

Discussion

Previous studies have shown that the bulk mechanical properties of articular cartilage explants decrease rapidly in vitro and treatment with rhFGF18 has a preservative effect on cartilage mechanics and biochemical composition. Given the unique material properties of cartilage are heterogeneous and differ within discrete zones, bulk measurements only tell part of the story. Assessment of local mechanical properties enables specific analysis of depth-dependent characteristics of articular cartilage and in this study their changes over time in culture. Our findings show a distinct increase in modulus from the superficial to middle to deep zones at day 1, consistent with the reported literature. In control cultures, the mechanical properties decreased very quickly throughout the depth and stabilized between weeks 3 and 6. This resulted in preservation of depth-dependence, though at lower values than at harvest under these control conditions. Treatment with rhFGF18 increased the modulus in all three zones through week 2 of culture, before falling back to day 1 values through six weeks of culture. This indicates that rhFGF18 is able to maintain or improve the mechanical properties of cartilage in a depth-dependent manner when cultured under free swelling conditions in a serum containing media. This finding suggests that rhFGF18 is able to prevent or reverse the...

Figure 1. (A) Strain map of a day 1 juvenile bovine explant showing depth-dependent strain across the ten bins (B) and through three regions of interest (C, superficial, middle, and deep zones). Strains were highest in the superficial zone and lower in the middle and deep zones. Corresponding modulus values were calculated for each bin (D) and the three regions of interest (E) from these local strains along with the boundary stress during compression.

Figure 2. Equilibrium modulus in (A) the superficial zone, 10-30% of the depth, (B) the middle zone, 30-60% of the depth, and (C) the deep zone over six weeks of in vitro culture with and without rhFGF18 treatment (*p < 0.05, **p < 0.01, ***p < 0.001).

= 1756 ± 75 kPa, Week 6 E_y = 554 ± 247 kPa) while the 1+6 treatment resulted in a large increase at week 2 (Week 2 E_y = 2966 ± 766 kPa) before returning to day 1 levels for weeks 3 through 6 (Week 3 E_y = 1700 ± 308 kPa). The deep zone showed the most variability but still showed similar trends through the first two weeks of culture, with the equilibrium modulus decreasing in the control culture (Day 1 E_y = 2136 ± 483 kPa, Week 6 E_y = 1129 ± 683 kPa). Treated explants increased in mechanical properties in the deep zone through week 2 (E_y = 3455 ± 804 kPa) with a decrease back to day 1 levels at week 3 (E_y = 2259 ± 363 kPa) followed by a rebound at week 4 (E_y = 3609 ± 1360 kPa) and another decrease to day 1 levels at week 6 (E_y = 2195 ± 696 kPa).
loss of extracellular matrix of cartilage explants, and may be a useful additive in the preservation of cartilage properties for osteochondral allografting procedures.

Significance

Sprifermin has the potential to preserve the mechanical integrity of cartilage explants cultured in vitro and in a physiologically relevant depth-dependent manner. This finding suggests that the current practice of storing allografts in the cold could be replaced by the inclusion of rhFGF18 in standard culture conditions to stably maintain important cartilage biomechanical properties during the time period required for safety screening.

Acknowledgement

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References

Biphasic Finite Element Modeling Reconciles Mechanical Properties of Engineered Cartilage Constructs Derived from Different Testing Modalities

Introduction

Cartilage is a hydrated, load-bearing and specialized tissue with unique biomechanical properties. Given its poor healing capacity, a number of tissue engineering and regenerative medicine strategies have emerged to address the repair of large cartilage defects. There has been significant progress in this field, with a variety of scaffolds, pre-conditioning bioreactors, and cell types generating cartilage-like tissue in vitro whose bulk properties approach that of native cartilage. Attention has now turned towards fabrication of engineered cartilage with anatomic curvature to reconstitute complex joint geometries, as well as evaluation of biophysical properties of engineered constructs in vivo. While a number of standard mechanical assays (e.g., confined and unconfined compression) are used to assess mechanical function of native tissue and engineered constructs, these assays generally require samples of regular geometry and assume homogenous material properties across the test specimen. These are generally not compatible with complex anatomic constructs maturing in an in vivo setting. As a consequence, indentation testing, using either spherical or plane-ended indenters, is the standard analysis tool for in vivo analysis. Given the dissimilarity in testing profiles and boundary conditions across these testing configurations, however, reported ‘moduli’ can differ by as much as an order of magnitude. To address this disconnect, we developed a biphasic finite element model using the freeware FEBio representing two common testing configurations (indentation and unconfined compression). The goal of this study was to develop this methodology and evaluate the maturation of tissue engineered constructs using these testing configurations side-by-side, and to determine whether the FE models and curve fitting procedures could provide a reconciled set of mechanical properties across testing platforms.

Methods

To carry out this study, juvenile bovine mesenchymal stem cells (MSCs) were seeded at a density of 2 x 10^5 cells/ml in 1% weight/volume methacrylated hyaluronic acid hydrogels. Constructs were cultured in a chemically defined chondrogenic medium for 3, 6, and 9 weeks. At each time point, constructs were subjected to mechanical testing (in indentation and unconfined compression, n = 4 per time point). Indentation testing consisted of three consecutive stress-relaxation tests (compressive ramps spanning 0-5, 5-10, and 10-15% strain applied at a rate of 0.1%/second, with 600 second relaxation periods between each ramp). Unconfined compression testing consisted of creep, stress-relaxation, and dynamic tests as previously described. Quasi-axisymmetric finite element models of both mechanical tests were created in FEBio by modeling a 5° wedge and scaling loads accordingly (Figure 1A,D). The engineered cartilage constructs were modeled as a biphasic material consisting of an isotropic neo-Hookean solid phase with an isotropic fiber distribution. Both the indenter and loading platen were modeled as rigid bodies. The parameter optimization algorithm in FEBio was utilized to curve-fit the material parameters Young’s Modulus, kς (a measure of fiber modulus), and permeability for both the unconfined compression stress-relaxation tests and the second step of the indentation test. Calculations of traditional outcome measures were also performed; the equilibrium and dynamic moduli from unconfined compression tests were calculated along with an estimation of modulus using the Hertz model for indentation testing. Statistical analysis consisted of 1-way and 2-way ANOVA with Bonferroni post hoc test.

Results

Biphasic finite element models were successfully constructed in FEBio. Fitting of stress relaxation data from indentation and unconfined compression was readily accomplished at each time point (Figure 1C,F). Traditional mechanical property outcomes from unconfined compression showed an increase in equilibrium modulus (Figure 2A) from week 3 (39.6 ± 19.7 kPa) to week 6 (341.4 ± 86.7 kPa) and week 9 (325.9 ± 56.0 kPa), and increase in dynamic modulus (Figure 2B) from week 3 (576.3 ± 65.6 kPa) to week 6 (2248 ± 533 kPa) and week 9 (2301 ± 231 kPa). The indentation
BIPHASIC FINITE ELEMENT MODELING RECONCILES MECHANICAL PROPERTIES OF ENGINEERED CARTILAGE CONSTRUCTS DERIVED FROM DIFFERENT TESTING MODALITIES

these two different testing modalities, the FEBio extracted parameters were consistent across platforms, aside from one parameter at one time point (week 6 Young’s modulus).

Discussion

As the field of cartilage tissue engineering expands, and transitions into non-traditional shapes and in vivo settings, it is essential to develop testing modalities that can be employed across these more clinically relevant platforms. Moreover, given the large body of literature using traditional tests of uniform samples (e.g., unconfined compression), it was essential to develop analysis methods that enable comparison across
Reconciliation of this data in one material model allows for comparison of findings across groups, and tests of multiple samples or locations, which may speed the development of functional cartilage replacements.

Acknowledgement

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References


In Vitro Maturation and In Vivo Delivery of Cartilage Repair Composites Composed of Minced Cartilage in a Photopolymerizable Hyaluronic Acid Hydrogel

Introduction

Damage to the articulating cartilages of joints causes focal lesions that are recalcitrant to repair and provoke more widespread osteoarthritic changes over time. As such, a number of surgical repair strategies have been tested, including microfracture, osteochondral grafting, and autologous chondrocyte implantation. Fragments generated by rim preparation and/or loose bodies contain viable chondrocytes and well organized cartilage matrix. Indeed, in vitro studies have shown that chondrocytes can migrate out from such cartilage and the tissue can be maintained by mechanical loading. More recently, a novel treatment option has been described wherein allogeneic (juvenile) cartilage fragments are secured within defects using fibrin glue as a vehicle. Likewise, several studies in goats and rabbits have evaluated the possibility of using autologous cartilage fragments in a one step re-insertion repair of the lesion site. The purpose of this work was to determine whether a photo-crosslinkable hydrogel based on methacrylated hyaluronic acid (HA), which has been shown to enhance chondrogenic differentiation of MSCs and enhance cartilage like tissue formation, could be used as a vehicle for the delivery of cartilage fragments. Further, we developed novel composites including both HA hydrogel, cartilage fragments, mesenchymal stem cells, and delivery microspheres for the pro-chondrogenic factor TGF beta. These composites were evaluated in vitro and in vivo.

Methods

Fabrication of HA/Minced Cartilage/MSC Constructs: Cartilage was harvested from the trochlear groove of juvenile bovine knee joints, sliced to 0.3mm thickness and minced into cubes (average fragment size 0.3x1mm). Fragments were mixed with a 1% polymerizable HA solution with or without MSCs (at 60 million cells/mL) and cast between glass plates. The same process was repeated using a commercially available solution of fibrin glue. After setting, 4mm diameter constructs were punched and cultured in TGF-beta containing chemically defined medium. Constructs were harvested after 3 or 4 weeks and assessed for viability (Live/Dead staining) and histology (H&E, Alcian blue and Picrosirius Red staining of paraffin sections).

In Vivo Assessment: To test the capacity of HA/minced cartilage composites in vivo, two juvenile (6 months, male, 32.9-37.7kg) Yucatan minipigs were used. Four 4 mm diameter full thickness chondral defects were created in each trochlear groove and 25% of the harvested cartilage volume was minced and used for treatment of an adjacent defect (see Figure 2 a-d). Defects were treated by minced cartilage with HA (HAmC, n = 4), minced cartilage with HA and TGF-beta loaded microspheres (HAmC + MS, n = 4), HA only (HA, n = 4) or left as untreated chondral defects (CD, n = 4). Microspheres were produced as described. After 6 weeks pigs were euthanized. Gross view images were acquired and samples were mechanically evaluated by indentation testing at the center of the defect and at the visually ‘best’ location using a spherical indenter (2mm diameter) and a 3 step stress-relaxation protocol. Samples then underwent micro-CT analysis (55kVp and 145µA) in 4 distinct regions of interest adjacent to the bone/cartilage interface. Analyses for bone volume per total volume (BV/TV) were evaluated. After incubation with

Figure 1. H&E, Alcian blue and picrosirius red staining for (A) HA embedded and (B) fibrin embedded minced cartilage fragments after 3 weeks of culture in TGF-beta containing medium (black scale bar = 500µm, white scale bar = 100µm).
Lugol’s solution for 48 hours, a second scan followed to enable analysis of defect fill. Samples were decalcified, paraffin embedded, cut into 6µm sections and stained with Safranin-O/Fast-Green and H&E. One adjacent osteochondral plug per joint served as control. Statistical analysis was carried out by ANOVA with Bonferroni’s post-hoc tests, as all samples were normally distributed and had equal variances. A regression analysis was performed for BV/TV and results of indentation testing in the center of the defects.

Results

Minced cartilage fragments cast in HA retained high viability, comparable to the response seen in fibrin (data not shown). Likewise, cellular outgrowth from the fragments was observed to the same extent as in fibrin (Figure 1a,b), although staining intensity was lower in HA-based composites. MSC-seeded composites showed chondrogenic differentiation of co-delivered MSCs and therefore a more homogenous distribution of cartilage specific ECM (Figure 3). The surgical model showed that the defects could be refilled (25% of the initial volume) with autologous cartilage. Histology showed that these cartilage fragments were well maintained in the defect 6 weeks postoperatively (Figure 2 e-h). Biomechanical testing revealed no significant differences amongst treatment groups, and a lower moduli compared to adjacent cartilage controls (p < 0.001, data not shown). Indentation testing in the visually best looking regions resulted in better mechanical properties than in the defect centers, with a small trend towards higher biomechanical properties for samples treated with minced cartilage. Micro-CT evaluation showed no significant difference in bone loss between treatment groups. Regression analysis between BV/TV and indentation modulus did not show a strong correlation (R² = 0.014). Histological sections showed the minced cartilage fragments in place, with more intense staining in the group containing TGF-beta loaded microspheres. Higher resolution images showed outgrowth of chondrocytes from the minced cartilage fragments.

Figure 2. Intraoperative preparation of defects with (A) quartering of explants before explantation, (B) mincing of the explanted cartilage, (C) replantation of minced fragments (two bottom defects) filling 25% of the defect volume (before addition of HA) and (D) after six weeks in vivo (green scale bar = 4mm). 2e-h) Safranin O/Fast Green (left column) and H&E (middle column) staining for representative samples from each group: (E) CD (F) HA g| HAmC h) HAmC+MS (black scale bar = 2mm). 10× magnification of H&E stains (right column) showing chondrocytes exiting from the replanted cartilage fragments (∗) at 6 weeks postoperatively (white scale bar = 300µm).

Figure 3. Composites containing minced cartilage fragments and MSCs after 4 weeks of in vitro culture. a) Alcian blue and b) Fluorescence imaging of labeled MSCs. c) Live staining and d) Picrosirius red staining at this same time point (green scale bars = 500µm, white scale bar = 100µm).
Discussion

In this study we evaluated a novel cartilage repair composite based on minced cartilage embedded in a photopolymerizable hydrogel with co-delivered MSCs. Consistent with the literature,\textsuperscript{4,6} we found chondrocyte outgrowth from the minced cartilage fragments using both fibrin and HA as the delivery vehicle. In the case of HA, addition of MSCs to the composites led to the more rapid accumulation of extracellular matrix between minced fragments, and a higher cell density. When these composites were tested in vivo, the HA hydrogel was able to maintain the cartilage pieces in place over six weeks. However, at this early time point, functional restoration of cartilage properties had not yet been achieved, as was evidenced by our biomechanical and histological testing. Whether this was due to the relative low volume of minced fragments in the defect (only 25% of defect volume), the lack of bone marrow stimulation, or the result of the short term time points assayed here, remains to be determined. Ongoing studies are now assessing in vivo whether an increase in cell number by the addition of MSCs, the delivery of TGF-laden microspheres, and/or longer healing periods will culminate in a more functional repair.

Significance

This study demonstrates that photo-polymerizable HA is a viable delivery vehicle for situating cartilage fragments in chondral lesions. Ongoing work will establish novel composites of MSCs, cartilage fragments, and growth factor delivery and test their capacity to promote in vivo cartilage repair.

Acknowledgements

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References

Age Dependent Cartilage Repair and Subchondral Bone Remodeling in a Minipig Defect Model

Introduction

Given the prevalence of focal cartilage injuries, and the propensity for such defects to instigate the early onset of osteoarthritis, there exist a number of surgical treatments and options to enhance repair. While such treatments can positively impact regeneration of cartilage, they may have unwanted effects on adjacent structures. For example, after treatment by microfracture or autologous chondrocyte implantation (ACI), subchondral bone remodeling has been reported, ranging in severity from upward boney migration (due to changes in subchondral bone activity) to the formation of intrasional osteophytes or cysts. Similar to the human condition, large animal models also show changes in subchondral bone during repair of chondral defects. In studies involving microfracture, upward subchondral bone plate migration is commonly reported. Here, unloading of the underlying bone (due to the lack of load transmission through the cartilage in the defect) may contribute to this atypical remodeling. Given these findings, and because such remodeling could compromise outcomes of tissue engineered cartilages in repair approaches, the objective of this study was to evaluate subchondral bone remodeling as a function injury type and repair scenario in a Yucatan minipig. Further, since skeletal maturity likely impacts both bone remodeling (due to changes in subchondral bone activity) and inherent cartilage repair capacity (likely due to changes in endogenous stem cell populations and reduced cell number), both skeletally mature and immature groups were evaluated.

Methods

To carry out this study, three juvenile (6 months, male, 32.9-37.7kg) and three skeletally mature (18 months of age, male, 62.0-64.0kg) Yucatan minipigs were used with IACUC approval from the Philadelphia VA Medical Center and the University of Pennsylvania. In each animal, 4mm diameter defects were created bilaterally in the trochlear groove [10]. Treatment conditions included an untreated full thickness chondral defect (CD, n = 3adult/3juvenile), a partial thickness (~50%) chondral defect (PCD, n = 3/3), and a full thickness chondral defect treated with microfracture (MFX, n = 3/3). After 6 weeks post-operatively, animals were euthanized and joints harvested. Following imaging the gross appearance of each lesion, osteochondral samples containing the lesion site were removed from the trochlear groove and imaged by micro-CT (55kVp and 145µA). Bone volume per total volume (BV/TV), trabecular thickness, trabecular number and trabecular spacing were quantified as a function of distance from the cartilage interface (Fig. 2a). Samples then were scanned a second time after incubation with Lugol’s solution for 48 hours in order to visualize defect fill. Samples were next decalcified, cut to 6µm thin sections, stained with Safranin O/Fast-Green or H&E and scored by 6 blinded reviewers using the ICRS II scoring system. Similar to the human condition, large animal models also show changes in subchondral bone during repair of chondral defects. In studies involving microfracture, upward subchondral bone plate migration is commonly reported. Here, unloading of the underlying bone (due to the lack of load transmission through the cartilage in the defect) may contribute to this atypical remodeling. Given these findings, and because such remodeling could compromise outcomes of tissue engineered cartilages in repair approaches, the objective of this study was to evaluate subchondral bone remodeling as a function injury type and repair scenario in a Yucatan minipig. Further, since skeletal maturity likely impacts both bone remodeling (due to changes in subchondral bone activity) and inherent cartilage repair capacity (likely due to changes in endogenous stem cell populations and reduced cell number), both skeletally mature and immature groups were evaluated.

Results

Micro-CT analysis showed marked differences between adult and juvenile minipigs in terms of BV/TV in the subchondral regions of cartilage lesions. CD and MFX groups showed increased bone loss in juveniles compared to adults, while the PCD group showed a slight increase in BV/TV in juveniles (Figure 1 and Figure 2c). Results reached significance (p < 0.006) between defect groups in range 1 (see Figure 2c). Defect fill (Figure 2b) assessed from post-Lugols micro-CT was not significantly different between animals or groups, but tended to be higher in juveniles compared to adults. Histology showed qualitatively better fill in juveniles, with some evidence of Safranin O positive staining. Quantification of this histology using the ICRS II scoring system showed equal overall assessment for the CD groups, better overall assessment for the juvenile MFX groups compared to adult MFX, and values close to the control samples for the PCD groups (Figure 3b). Furthermore, for the CD
PCD groups showed some evidence of overgrowth. These findings are consistent with previous reports in the literature. We also found that, while defects of both ages filled to some extent with fibrous tissue, defects in juvenile animals filled to greater extent and were more likely to contain PG and type II collagen, indicative of better quality repair. Additional time points are required to fully elucidate the spatiotemporal pattern of boney remodeling and defect fill, and further studies are required to understand the causative mechanism of the bone remodeling in juveniles and the apparent decrease in cartilage formation in the adults. Based on these findings, it is recommended that both pre-clinical and clinical studies of cartilage repair carefully evaluate and monitor changes in subchondral bone, for instance using novel MRI imaging methods to avoid radiation exposure in patients. Regardless of the cause, the boney remodeling needs to be addressed if the minipig is to be used for the study of cartilage repair techniques. That is, it will be difficult to interpret findings of even the best engineered cartilage in a repair site if it is placed atop a subchondral bone plate undergoing marked remodeling. A remodeling suchondral plate may likewise increase the risk of treatment failure for cell based cartilage repair and so speed the onset of osteoarthritis as a consequence of altered biomechanical signals in the cartilaginous repair tissue.

**Significance**

This large animal study of cartilage repair shows the significant impact that skeletal maturity has on the propensity of subchondral bone to remodel as result of chondral injury. This is important finding to consider as a selection criteria for studying cartilage repair in animal models, and could likewise direct new analyses and understanding of human patient’s cartilage repair outcomes and be an important factor in the effectiveness of new therapeutic approaches.
Acknowledgements

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References


Critical Regulatory Role for Collagen V in Establishing the Unique Mechanical Properties of Joint Stabilizing Tendons

Introduction

Classic (type I) Ehlers-Danlos Syndrome (EDS) is a rare genetic disease associated with heterozygous mutations in collagen V.\(^1\) Patients with classic EDS exhibit connective tissue hyperelasticity, as well as joint laxity and dislocations, indicating a potential role for collagen V in structures that contribute to joint stability.\(^2,3\) Recent studies demonstrated that collagen V plays a crucial role in the anterior cruciate ligament (ACL)\(^4\) which is a primary knee stabilizer, when compared to its role in the flexor digitorum longus (FDL) tendon\(^5\) that does not have a major function in providing joint stability. However, due to the differences in anatomy and structure between these tissues, assessing the differential effects of collagen V in joint stabilizing tissues is difficult. Therefore, the purpose of this study was to determine if the contribution of collagen V to the establishment of mechanical properties in tendons and ligaments is primarily related to the role of the tissue in joint stability. Tendons that are similar in structure, exhibiting a tendon-to-bone insertion site graded in composition and organization, but different in their contributions to joint stability were analyzed. Accordingly, we examined the supraspinatus tendon (SST), which plays a crucial and direct role in joint stability of the shoulder, and the Achilles tendon (ACH), which does not contribute directly to joint stability. We hypothesized that the absence of collagen V would result in decreased mechanical properties in the supraspinatus tendon, but not in the Achilles tendon.

Methods

Sample Preparation Mice from two genotypes, \textit{Col5a1}^+/+ (Wild Type, \(n = 5-9\)) and a conditional knockout targeted to tendon/ligament, \textit{ScxCre+ Col5a1}^-/- (\textit{Col5a1} KO, \(n = 8-13\)) were sacrificed at P60 (IACUC approved).\(^6\) Achilles tendons were carefully dissected from the hind limb and the muscle was removed, leaving the Achilles tendon attached to the calcaneus. The supraspinatus tendon-bone complex was similarly dissected to remove muscle and other surrounding soft tissue. The cross-sectional areas of both tendons were measured using a custom measurement device and stain lines were applied to denote a 2.5mm (supraspinatus) or 5mm (Achilles) gauge length. The humerus was then potted in PMMA and the supraspinatus tendon was secured in custom grips with sandpaper. The Achilles tendon and calcaneus were both secured in custom grips for mechanical testing.

Mechanical Testing The tendons were then mechanically tested with the same loading protocol consisting of ten cycles of preconditioning from 0.02N to 0.04N, a stress relaxation at 5% strain and a constant ramp to failure at 0.1% strain per second. Local strain was measured optically and mechanical parameters were calculated.

Statistics Comparisons were made between wild type and collagen V null tendons using Student’s t-tests with significance set at \(p < 0.05\).

Results

\textbf{Achilles Tendon} Cross-sectional area and maximum load were reduced in the collagen V null group (Figure 1). In addition, stiffness at the midsubstance and insertion site was also reduced in the null group (Figure 2). However, there was no difference between groups in maximum stress or modulus at either location.

\textbf{Supraspinatus Tendon} Cross-sectional area, maximum load and maximum stress were all significantly reduced in the collagen V null group (Figure 1). In addition, the collagen V null group exhibited severely reduced stiffness and modulus at both the insertion site and midsubstance (Figure 2).

Discussion

Removal of collagen V resulted in severely decreased maximum load and stiffness in both tendons. However, in the Achilles tendons, neither the maximum stress nor modulus demonstrated changes, indicating that these results were due to tissue size rather than a change in tissue material quality. These results were consistent with our previous results in the FDL,\(^5\) which like the Achilles tendon does not contribute directly to joint stability. Conversely,
these four tissues (Figure 3) which span a variety of structural architectures, functional roles, and tissue type indicate that the functional role of joint stability may be a major determinant of the importance of collagen V in that tissue. While this is a significant and interesting finding, this study did not directly measure joint stability or mechanical changes in the other soft tissues that surround joints, which could further support the supraspinatus tendon did show significantly and severely reduced modulus and maximum stress. These material and structural mechanical results are consistent with previous work in the ACL. 4 Since both the ACL and the supraspinatus tendon act primarily as joint stabilizers, these results support that collagen V plays a critical role in joint stabilizing tendons and ligaments. Furthermore, the synthesis of results from

**Figure 1.** (A) Collagen V Null tendons were significantly smaller in both the Achilles and supraspinatus tendons, but there was no difference in (B) percent relaxation in either tendon. (C) Maximum load was also significantly reduced in the collagen V null group for both tendons. (D) Maximum stress was significantly decreased in the null group in the supraspinatus tendon, but no differences were found in the Achilles tendon.

**Figure 2.** (A) Stiffness was significantly decreased in the collagen V null group in both tendons at both the insertion and midsubstance of the tissue. (B) Modulus was decreased in the null group at both locations only in the supraspinatus tendon. There were no differences in modulus between groups in the Achilles tendons.
Significance

Collagen V plays a crucial role in establishing tendon-specific mechanical properties only in tendons and ligaments that contribute to joint stability, suggesting that EDS-related joint instability observed in the clinical population may be directly related to inferior soft tissue mechanical function.

Acknowledgement

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References


Figure 3. Collagen V plays a significant role in establishing the mechanical properties in joint-stabilizing tissues (ACL and SST), but not in tissues that do not have a direct role in joint stability (ACH and FDL).
Biceps Detachment Alters Rotator Cuff Tendon Properties and Joint Function in a Supraspinatus Tendon Tear Rat Model

INTRODUCTION

The glenohumeral joint of the shoulder is stabilized by the rotator cuff musculotendinous units with the supraspinatus superiorly, the subscapularis anteriorly and the infraspinatus and teres minor posteriorly. Tears of the rotator cuff are often related to overuse and are commonly concurrent with damage to the long head of the biceps (LHB). To alleviate pain which is frequently attributed to the LHB, surgeons regularly tenodese or tenotomize the LHB. Recent data in a rat model indicates that the LHB may play a role in anterior stabilization of the glenohumeral joint in the presence of multi-tendon cuff tears (involving the supraspinatus and infraspinatus). However, the mechanical effect of detachment of the LHB in the presence of an isolated supraspinatus tear is unknown. Therefore, the objective of this study was to use an established rat rotator cuff detachment model to investigate shoulder function and mechanical properties of the infraspinatus and subscapularis tendons 8 weeks following supraspinatus and LHB tendon detachment. We hypothesized that detachment of the LHB in the presence of a supraspinatus tear would decrease shoulder function and intact cuff tendon mechanical properties.

METHODS

Experimental design

Twenty-eight adult male Sprague-Dawley rats (IACUC approved) underwent 4 weeks of overuse treadmill activity (17 m/min, 1 hr/day, 5 days/wk, 10° decline) to create a tendinopathic condition in the supraspinatus tendon prior to surgical detachment to induce an “acute-on-chronic” condition. Animals were then randomized into two surgical groups: unilateral detachment of the 1) supraspinatus tendon only (SO) or 2) supraspinatus and LHB tendons (SB). Post-surgery, animals were allowed 1 week of cage activity before gradually returning to the overuse protocol over a 2 week period. All animals then completed 5 weeks of overuse activity prior to sacrifice (8 weeks post tendon detachment).

Ambulatory measurement

To assess shoulder joint function, forelimb ground reaction forces were recorded using an instrumented walkway one day prior to detachment surgery (baseline) and at 3, 7, 14, 28, 42, and 56 days after surgery.

Tendon mechanical testing

Tensile testing was performed on the upper and lower bands of the subscapularis tendon and the infraspinatus tendon. Tendons were dissected from the shoulder and cleaned of excess soft tissue. Stain lines were then placed along the length of the tendon for optical strain measurement. Cross sectional area was measured using a custom laser device. Tendons were then subjected to a mechanical testing protocol consisting of a preload to 0.08 N, ten cycles of preconditioning (0.1-0.5 N at 1% strain/s), a stress relaxation to 5% strain (5%/s) followed by a 600s hold, and a ramp to failure at 0.3%/s. Stress was calculated as force divided by cross sectional area and 2D Langrangian strain was determined optically using custom tracking software.

Statistical analysis

For the ambulatory assessment, significance was assessed using a 2-way ANOVA with repeated measures on time with follow-up t-tests between groups at each time point. Multiple imputations were conducted using the Markov chain Monte Carlo method for missing data points (~8%). Tissue mechanics were assessed using a one-tailed t-test. Significance was set at $p < 0.05$.

RESULTS

Ambulatory measurement

Significant alterations in ground reaction forces were noted in the SB group compared to SO (Figure 1). Specifically, the SB group had a significant change in medial/lateral force towards medial at 3, 7, and 14 days after surgery. Additionally, the SB group had significantly decreased propulsion force and braking force compared to the SO group at 3, 7, and 14 days after surgery. No differences existed between groups in vertical force.
**Tendon mechanics**

In the infraspinatus tendon, stiffness and elastic modulus at the insertion were significantly decreased in the SB group compared to the SO group (Figure 2). The midsubstance of the infraspinatus tendon had a significant increase in cross-sectional area in the SB group (Figure 2). No significant changes were noted at the insertion site of the upper-subscapularis tendon. Cross-sectional area and elastic modulus were significantly increased in the midsubstance of the upper-subscapularis tendon (Figure 2). No significant changes were found in the lower-subscapularis tendon at either the insertion or the midsubstance.

**DISCUSSION**

Detachment of the LHB in the presence of a supraspinatus tear alters shoulder function, is detrimental to the infraspinatus tendon, and improves mechanical properties of the upper-subscapularis tendon midsubstance. Alterations in ground reaction forces indicate a change in glenohumeral joint function between the SO and SB groups. Decreased braking and propulsion forces in the SB group compared to the SO group indicate inferior joint function, in contrast to the previous multi-tendon (supraspinatus and infraspinatus) study in which LHB tendon detachment restored propulsion force close to baseline. A change towards increased medial force suggests that the SB group compensated for a lack of medial stability due to LHB tendon detachment, which is similar to the previous multi-tendon study, suggesting that the LHB plays a role in medial stability both in the presence and absence of the infraspinatus. The absence of the LHB tendon may result in posterior translation of the humeral head and impingement of the infraspinatus under the posterior-lateral acromion. Previous findings of a multi-tendon tear showed decreased joint damage and improved mechanical properties of the subscapularis tendon upon the detachment of the LHB tendon by balancing the anterior forces of the glenohumeral joint. In the current study, detachment of the supraspinatus tendon alone did not disrupt the anterior-posterior force balance; however, the additional detachment of the LHB tendon did result in altered anterior-posterior forces and damage to the infraspinatus tendon. Slight, but significant improvement in the midsubstance mechanical properties of the upper-subscapularis tendon suggests that detachment of the LHB tendon may allow the subscapularis tendon to adapt to a supraspinatus tear in a positive manner, although the mechanism of action is unknown. Possible reasons include a reduction in bony adjacency with the coracoid process and functional differences in the glenohumeral joint after a
LHB tendon tear. In conclusion, detachment of the LHB in the presence of an isolated supraspinatus tear to alleviate pain might increase the probability of tear progression towards the infraspinatus. This data will help guide clinicians in treatment options for patients with supraspinatus tendon tears.

SIGNIFICANCE
This study provides evidence to dissuade LHB tendon tenotomy in the presence of a supraspinatus tendon tear based on mechanical force balance concepts.

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**Figure 2.** (A-C) (A) No changes in cross section area at the insertion of any tendon. The SB group had increased cross sectional area at the midsubstance of the infraspinatus and the upper subscapularis. (B) The SB group had decreased stiffness at the insertion of the infraspinatus. There were no changes in stiffness at the midsubstance of any tendon. (C) The SB group had decreased modulus at the insertion of the infraspinatus. The upper subscapularis had increased modulus at the midsubstance.
Effect of Ultrasound-Guided Dry Needling on the Healthy Rat Supraspinatus Tendon

Introduction

Chronic tendon injuries or overuse resulting in tendinopathy are common clinical problems. Conservative treatments, including rest, physical therapy and NSAID administration, are often ineffective. Recently, there has been an emergence of novel treatments for tendinopathy utilizing dry needling, or repeatedly introducing a needle into the abnormal tissue.\(^1,2\) It is believed that micro-trauma to the tendon leads to disruption of pathological tissues, induction of bleeding, and release of factors to stimulate healing. Dry needling, typically done using ultrasound guidance, has been described alone as well as in combination with the injection of platelet-rich plasma, autologous blood,\(^3\) glucose,\(^4\) among other substances, demonstrating promising results, though no randomized controlled studies have been performed. Moreover, a controlled laboratory model to study this potential, as well as basic evidence supporting this practice is lacking.\(^5\) Therefore, the objective of this study was to perform ultrasound-guided dry needling in healthy rat supraspinatus tendons to evaluate the acute vascular, biological, and mechanical response in the tendons, to understand the initial effects of dry needling. We hypothesized that there would be an early increase in blood flow, inflammation, cellularity, and matrix formation. Additionally, there would be a decrease in material properties, but no change in the structural properties of the needled tendon compared to healthy control tendon.

Methods

Study Design: 32 Sprague-Dawley rats were used (IACUC approved). 22 rats were subjected to bilateral ultrasound-guided dry needling and randomly assigned for sacrifice at days 1, 3 or 7 following the procedure to evaluate histology (n = 6 at days 1, 3, and 7) and mechanics (n = 10 at day 7). 10 healthy rats were sacrificed to serve as controls. 6 randomly assigned rats underwent color Doppler ultrasound imaging 24 hours prior to needling (as an internal control), 5 hours and 24 hours after needling.

Dry Needling: Using a 14 MHz ultrasound transducer, the rotator cuff was visualized in the transverse plane. A 27G needle was inserted posteriorly and guided between the humeral head and acromion to enter the supraspinatus tendon. The tendon was penetrated 10 times along its length. This technique was validated to consistently and accurately needle the rat supraspinatus tendon.

Color Doppler: Using a 14MHz transducer, B-mode and color Doppler images were acquired for each shoulder. A regional analysis of blood flow (between the humeral head and the skin) evaluated changes in the surrounding vasculature, and a local analysis (between the humeral head and the acromion) evaluated blood flow in the tendon region. The mean color level (MCL—average velocity of colored pixels), the fractional area (FA - percent of colored pixels in region of interest), and the color weighted fractional area (CWFA—average flow per total unit area of the tissue) were quantified. A one-way ANOVA with repeated measures and a Bonferroni post hoc test were performed (*p < 0.05).

Mechanics: The right supraspinatus tendon was dissected and prepared for tensile mechanical testing with preconditioning, stress-relaxation, and ramp to failure as described.\(^6\) Images were taken during testing to calculate 2D Lagrangian strain. T-tests were performed (*p < 0.05, #p < 0.1).

Histology and Immunohistochemistry: The left supraspinatus tendon was processed, embedded, sectioned at 7µm, and stained for safranin-o/fast green (Safo), hematoxylin and eosin (H&E), interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), and type III collagen. Images were graded by three blinded investigators for H&E cell shape (1-spindle to 3-round), H&E cellularity (1-low to 3-high), Safo staining intensity (1-low to 3-high), and DAB staining intensity (1-low to 4-high). A Kruskal-Wallis test and a Dunn’s post hoc test were performed (*p < 0.05, #p < 0.1).

Results

For Doppler imaging, the CWFA in both the local and regional areas were significantly increased 5 hours-post dry needling (Figure 1). There was a significant increase in cross sectional area, and mechanical testing revealed a significant decrease in maximum stress, insertion modulus, midsubstance modulus, and stiffness (Figure 2). For histology, there was a significant
increase in IL-1β, type III collagen, and rounded cell shape at day 1, a significant increase in cellularity at days 1 and 7, and a significant increase in glycosaminoglycans (GAG) content at days 3 and 7 (Figure 3).

**Discussion**

Dry needling the rat supraspinatus tendon caused an increase in blood flow, the initiation of an inflammatory response, and formation of granulation tissue. Doppler imaging showed increases in blood flow both regionally in the shoulder, as well as in the needled tendon area, supporting the induction of a systemic and local response to this micro-damage. Histology results support a cellular response to this micro-damage, with an early increase in cellularity with a more rounded cell shape. Granulation tissue was formed as indicated by the increases in type III collagen and GAGs. Additionally, the increase in inflammatory mediators is consistent with a previous study evaluating dry needling in injured rat tendons. Mechanical properties confirm that micro-damage was induced in the tendon, initiating...
the formation of granulation tissue in the damaged areas, which caused an increase in the cross sectional area and a subsequent decrease in material properties. Maximum load was not significantly different from the control, supporting that this injury may not dispose the tendon to early risk of failure. Further investigation is needed to more completely characterize the biologic response, as well as to evaluate later time points to determine the tendon healing potential to dry needling. This is the first study to demonstrate that the rat supraspinatus tendon can be dry needled consistently under ultrasound guidance, and that a controlled healing response can be elicited from this procedure. Further studies will apply this method in a tendinopathy model to evaluate the effect of dry needling on pathologic tissue.

Significance

Although dry needling is widely used in clinical practice for the treatment of tendinopathy, the lack of basic scientific studies examining the effects of this procedure is an important issue in preventing its recommendation for routine use. While further studies are necessary to examine the longer term effect on treated tendons, this study establishes a controlled model for evaluation of the mechanism and efficacy of dry needling in treating tendinopathy.

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References

P² Porous Titanium Implants Improve Early Tendon Healing in a Rat Supraspinatus Repair Model

INTRODUCTION

Rotator cuff tears are common musculoskeletal injuries which often require surgical repair. Unfortunately, repairs often fail and improved repair strength is essential. In an effort to increase repair strength, various materials and biologics have been incorporated into rotator cuff repairs. P² Porous titanium (DJO Surgical, Austin TX) has been shown to promote osseointegration and subdermal integration. However, the ability of P² Porous titanium to aid in a supraspinatus tendon-to-bone repair through tissue ingrowth has not been evaluated. Therefore, the purpose of this study was to investigate P² porous titanium implants used to augment supraspinatus tendon-to-bone repair in an established rat supraspinatus repair model. We hypothesized that supraspinatus tendon-to-bone repairs with the addition of P² implants would allow for ingrowth and increased repair strength when compared to shoulders receiving standard supraspinatus repair alone.

METHODS:

Experimental design: Thirty-two adult male Sprague-Dawley rats (400-450g) were used in this study (IACUC approved). All rats received bilateral supraspinatus detachment and repair, in which one limb was randomly assigned P² titanium implant with the contralateral limb receiving the standard repair. The implant procedure consisted of creating a ~3 mm deep, 3 mm wide recess in the greater tuberosity using a high speed burr. The 3 mm diameter hemispherical implant was tamped into the recess and the supraspinatus was repaired over the implant. Three animals were sacrificed immediately following surgical procedure (time zero) for histological analysis to confirm implant placement and for comparison to ingrowth at later time points. Remaining animals were allowed normal cage activity following surgery and were sacrificed after 2 weeks (n = 6), 4 weeks (n = 9) and 12 weeks (n = 14). Limbs from a subset of animals (n = 4 each at 4 and 12 weeks) were dissected immediately at sacrifice and fixed for histological analysis. The remaining shoulders were frozen for subsequent mechanical testing.

Tendon mechanical testing: Supraspinatus tendon-to-bone complexes (with or without implant) were dissected from the shoulder and cleaned of excessive soft tissue. Stain lines were then placed on the tendon for optical strain measurement. Cross sectional area was measured using a custom laser device. Tendon-to-bone complexes were then subjected to a mechanical testing protocol consisting of a preload to 0.08 N, ten cycles of preconditioning (0.1-0.5N at 1% strain/s), a stress relaxation to 5% strain (5%/s) followed by a 600s hold, and finally a ramp to failure at 0.3%/s. Stress was calculated as force divided by cross sectional area and 2D Langrangian strain was determined optically using custom tracking software.

Histology/SEM: Specimens for histology and SEM were embedded in PMMA for tissue-implant interface analysis. Specimens were first viewed in the SEM under BSE to detect incorporation between P² implant and bone. The specimens were then stained with Sanderson’s Rapid Bone Stain and viewed under transmitted and polarized light for tissue ingrowth into the P² implant.

Statistical analysis: Comparisons were made using Student’s t-tests with significance set a p ≤ 0.05.

RESULTS

Tendon mechanical testing: No differences in cross sectional area were detected at any time point (Figure 1A). Percent relaxation was significantly increased in the P² implant group at 2 weeks, but there was no difference at 4 and 12 weeks (Figure 1B). Maximum load was significantly increased in the P² implant group at 2 weeks, but not at 4 weeks (Figure 1C - note that maximum load was not reported at 12 weeks due to failure at the grip at this time point). Elastic modulus was significantly increased in the P² implant group at 4 weeks, but not at 2 or 12 weeks (Figure 1D). No differences were detected in stiffness at any time point (data not shown).

Histology/SEM: The BSE analysis demonstrated bone ingrowth and skeletal attachment of the implant to the host bone which was significantly greater at both time points analyzed, 4 and 12 weeks when...
Figure 1. (A-D) (A) No differences in area were noted at any time point. (B) P2 implant group had significantly increased percent relaxation at 2 weeks. No differences were noted at 4 and 12 weeks. (C) P2 implant group had significantly increased maximum load (76%) at 2 weeks. No differences were noted at 4 weeks; 12 weeks not reported due to failure at the grip at 12 weeks. (D) P2 implant group had significantly increased modulus at 4 weeks. No differences were noted at 2 and 12 weeks.

Figure 2. (A-C) Scanning Electron Microscope BSE images showing % bone attachment to the P2 at all time points. White = implant, Black = pore space and Grey = bone. (A) Time = 0 specimens showed 3.21 ± 0.52%, (B) 4 Week specimens showed 19.57 ± 5.81% and the (C) 12 Week specimens showed 27.18 ± 12.93% of bone present within the porous coating (growth was significantly greater at 4 and 12 weeks when compared to 0 weeks).
SIGNIFICANCE
This data supports the use of porous titanium implants to improve tendon-to-bone healing based on a rat supraspinatus repair model.

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compared to time zero (Figure 2). The histological analysis showed soft tissue integration with both the implant and bone (Figure 3).

DISCUSSION
Results indicate superior mechanical properties in the P2 implant group compared to standard supraspinatus repair at 2 and 4 weeks, and tissue ingrowth at all time points. Importantly, at 2 weeks, the P2 implant group had a 76% increase in maximum load compared to standard repair. As supraspinatus tendon re-tears are extremely common early1 and occur at the tendon to bone interface, this finding supports the reduction of re-tear risk with the P2 implant. Although no differences were detected in maximum load at 4 weeks, the increase at 2 weeks denotes that P2 implants improved early tendon-to-bone healing (through so-called “Velcro effect” and early tissue ingrowth). Additionally, at 4 weeks, the P2 implant group had significantly increased elastic modulus, further supporting increased mechanical properties due to the P2 implant. Clinically, improved early healing might allow a faster rehabilitation and associated recovery, with the ability to resume daily activities sooner. This study demonstrates that the P2 implant improves tendon-to-bone healing up to 4 weeks (with no detrimental effects at longer time points), suggesting that the P2 porous titanium may be of benefit for use in clinical rotator cuff repairs.
Novel Application of a µCT Perfusion Technique to Evaluate Achilles Tendon Vessel Microarchitecture in Three Dimensions

Introduction
Regional variation in Achilles tendon vascularity is believed to contribute to mechanical property deficits, tendinopathy, and rupture; however, this remains controversial.1 This disagreement likely arises since previous studies using laser Doppler flowmetry, angiography, or histology cannot quantify vessel architecture (i.e., orientation, anisotropy, and topology) with micron resolution in three dimensions. Therefore, the purpose of this study was to demonstrate the reliability of a new perfusion-based µCT laboratory technique, and to quantify Achilles tendon insertion and midsubstance vessel architecture. We hypothesized that the µCT perfusion method would be reliable between limbs, and that the Achilles tendon midsubstance would demonstrate decreased vessel volume, number, and thickness, but increased spacing, anisotropy, and connectivity relative to the insertion.

Methods
18 limbs from 9 female rats were used. A radiopaque perfusion medium (Microfil, Flow Tech) was used to generate vasculature corrosion casting. Following perfusion, the Achilles and plantaris tendons, surrounding soft tissue, and calcaneus were harvested en bloc. These tissues were placed in a 7mm diameter tube filled with 1xPBS within a µCT scanner (µCT 35, Scanco Medical AG, Switzerland) and two separate 1.6mm regions representing the insertion and midsubstance were scanned (isotropic voxel size: 3.5µm) (Figure 1A). Vessel volume, thickness, number, spacing, connectivity, and anisotropy were obtained using manufacturer-provided software. Paired T-tests were utilized to evaluate differences between limbs and between insertion and midsubstance vessel architecture (α = 0.05). For the latter statistical tests, the two limbs for each animal were averaged together.

Results
There were no differences between limbs for any of the parameters computed when compared within regional subgroups. Compared to the insertion, vessel volume decreased, and connectivity and anisotropy increased in the midsubstance (p < 0.01) (Figure 1 B-D). No differences were observed in vessel thickness, number, or spacing between regions.

Discussion
This study provides the first analysis of Achilles tendon microarchitecture in 3D. This work is consistent with previous 2D histological and angiographic studies, and adds to previous research by quantifying regional differences in vessel anisotropy and connectivity. Together, these parameters provide a mechanism that could help explain the specific changes that contribute to tendinopathy and rupture observed in the Achilles tendon midsubstance.

Acknowledgement
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References
Multidisciplinary Evaluation of Treatments for Achilles Tendon Ruptures During Early Healing in an Animal Model

Introduction
Achilles tendon ruptures are common and devastating injuries, resulting in significant pain, disability, and healthcare costs. Despite the higher risk for complications and increased costs, operative treatment is often assumed to provide superior outcomes compared to non-operative treatment. However, recent reviews have suggested that outcomes for Achilles ruptures are not necessarily superior with surgical treatment, depending on the rehabilitation protocol (e.g., duration of immobilization and exercise). To elucidate the basic mechanical, structural, and biological mechanisms governing these clinical outcomes, it is necessary to evaluate the role of surgical intervention and rehabilitation strategies throughout the healing process. Therefore, the objective of this study was to investigate the effects of surgical repair and hind limb immobilization on joint function and early Achilles tendon healing following complete transection. We hypothesized that repaired tendons with more aggressive rehabilitation would have superior mechanical, structural, histological, and functional properties compared to non-repaired tendons and compared to those with moderate rehabilitation.

Methods
Sprague Dawley rats (N = 100) received two weeks of treadmill training (up to 60 minutes at 10m/min) (IACUC approved). All animals then underwent surgery to remove the central plantaris longus tendon and received blunt misubstance transection to their right Achilles tendon. Animals were then randomized into repaired (R) (Modified Kessler approach) (n = 50) or non-repaired (NR) (n = 50) groups, and all hind limbs were immobilized in plantar flexion. These groups were further divided into aggressive (1 week immobilization (IM1), 1 week cage activity, 1 week exercise) or moderate (3 weeks immobilization (IM3)) rehabilitation (n = 25/group). Functional evaluation (n = 10-24/group) of passive ankle joint range of motion (ROM) and stiffness was completed prior to surgery and after 3 weeks of healing using a custom torque cell and accelerometer-based device on anesthetized animals. All ex vivo assays were performed after 3 weeks of healing.

After sacrifice, the Achilles tendon-foot complex was carefully removed en bloc, fine dissected, measured for cross sectional area (CSA), and gripped. Tendons were then loaded at 1N in a PBS bath while a series of sagittal B-mode high frequency ultrasound images (HFUS) were acquired using a 40MHz scanner (MS550D; VisualSonics, CA) (n = 10-11/group). Tendons were then mechanically tested (n = 10-11/group) with a protocol consisting of stress relaxation (6% strain), a low-load dynamic frequency sweep (ranging from 0.1 to 10 Hz), and fatigue testing (~10-75% of ultimate failure load) at 2Hz using a sinusoidal waveform until failure (Instron Electropuls 3000). For histological analysis, Achilles samples were processed using standard paraffin procedures (n = 8/group). Sagittal sections (7 µm) were collected and tendon samples were stained with hematoxylin and eosin (H&E).

Functional ankle joint properties (i.e., resting joint angle at zero torque, toe and linear ankle stiffness, and ankle ROM) for both dorsiflexion and plantar flexion were evaluated. Achilles tendon percent relaxation, dynamic modulus (E'), tanδ, hysteresis, and cycles to failure were computed from mechanical testing data. Echogenicity mean and standard deviation were evaluated from the HFUS images for the injury region. H&E stained sections were imaged at the injury site of each tendon at 200X and were graded by three blinded investigators for cellularity and cell shape. One-way ANOVAs were used to evaluate the effects of treatment on mechanical and structural properties. Significant relationships (α = 0.05) were analyzed with post hoc Student’s t-tests with Bonferroni corrections. For histological grading, non-parametric Kruskal-Wallis tests were performed.

Results
After three weeks of healing, the R,IM1 group achieved a resting joint angle position closest to pre-surgery values (Figure 1A). Decreased dorsiflexion ROM (Figure 1B) and increased ankle stiffness (Figure 1C,D) was observed in
moderate rehabilitation groups. Tendon CSA was increased in the R tendons compared to NR tendons, but IM3 decreased the CSA in these groups. Quasi-static tendon mechanical testing revealed a decreased percent relaxation in the R groups (Figure 2A). No differences in toe-region dynamic modulus or tan δ were observed. Interestingly, more than 70% of the IM3 tendons, though none of the IM1 tendons, failed while ramping to the fatigue loading protocol. NR tendons demonstrated increased cycles to failure, |E’|, and hysteresis during fatigue loading compared to R tendons (Figure 2B-D). Ultrasound tendon evaluation revealed that the IM3 groups had increased echogenicity mean compared to IM1 groups (Figure 3). Surprisingly, there were no significant differences found in cellularity and cell shape between groups.

Discussion

Early Achilles tendon healing following a variety of common clinical treatment methods was evaluated. Joint IM had a larger effect on ankle stiffness and ROM in dorsiflexion than repair strategy. Tissue echogenicity, a surrogate of tendon structure, indicated that longer IM duration resulted in more hyperechoic tendon. It is possible that IM promotes deposition of a stiffer matrix, but a return to exercise is necessary to allow full recovery of fatigue resistance. Superior fatigue mechanics in the IM1 group is in agreement with the suggested benefits of early rehabilitation for optimal Achilles tendon healing.6 Future work will relate organizational measures from HFUS to tendon fatigue mechanical properties. Additional studies will evaluate the optimal treatment combinations for moderate and late healing, and relate functional and structural measures acquired to ex vivo mechanical properties.

Significance

This study begins to define the scientific basis for treatment methods already used clinically, but not yet optimized for early Achilles tendon healing. Specifically, we evaluated the 1) role...
of repair and specific IM protocols and 2) use of functional measures for return to activity criteria following Achilles tendon rupture. Taken together, this study demonstrated that aggressive rehabilitation leads to improved ankle function and tendon mechanics after early healing. Interestingly, within this aggressive rehabilitation group, R tendons demonstrated improved functional outcomes, but tendon mechanical integrity was better in NR tendons. Ultrasonic evaluation showed promise to detect changes in healing capacity between groups with different rehabilitation strategies.

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References
Differential Effects of Growth Factors on Neonatal and Adult Achilles Tenocytes

**Introduction**

Tendon tears in adults are a common orthopaedic problem and often fail to heal even after surgical repair. Neonatal healing is superior to adult healing across multiple tissue types, and immunohistochemical studies in tendons have shown age-related differences in matrix composition and growth factor expression. However, it is not known whether adult cells have an innate inability to synthesize matrix and initiate a successful repair, or whether the adult wound environment lacks sufficient presentation of growth factor stimuli to affect repair. During the repair process, several growth factors act as cues to initiate and regulate cellular responses such as cell proliferation and extracellular matrix production. Therefore, we hypothesized that neonatal tendon cells would be more responsive than adult cells to two growth factors that are upregulated during tendon healing: transforming growth factor β3 (TGFβ3) and basic fibroblast growth factor (bFGF).

**Methods**

Achilles tendons were harvested from postnatal day 3 (P3, neonatal) and five month old (adult) male Sprague-Dawley rats. Tendons were finely diced and placed in culture dishes with Dulbecco’s modified Eagles medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and antibiotics. Cells migrated out of the tissue and were expanded to confluence. To evaluate age and growth factor effects on tenocyte migration, a transwell assay (8 micron, Millipore) was performed with 3 concentrations of TGFβ3 and bFGF. Cells were plated at 2 × 10^5 cells/ml and incubated for 6 hours with the specified factor in serum-free DMEM. Migration towards growth factor supplemented media was normalized to cell migration towards serum-free media. Collagen production was performed to evaluate proliferative effects of growth factors, cells were plated at 5000 cells per well in a 96 well plate and treated with either TGFβ3 or bFGF in phenol-free DMEM supplemented with 2.5% FBS. MTT assays (Life Technologies) were performed on days 3 and 6. To quantify the effect of growth factors on collagen production, a Sircol collagen assay (Biocolor) was performed. Cells were plated in 12 well dishes at 1 × 10^5 cells per well and treated with TGFβ3 or bFGF in DMEM supplemented with 2.5% FBS. After 6 days, aliquots of media were complexed with Sircol dye reagent and analyzed colorimetrically. Two-way ANOVA with repeated measures with follow-up t-tests between groups at each time point were performed with statistical significance set at p < 0.05 and trends at p < 0.1.

**Results**

**Tenocyte Proliferation:** After three days, all concentrations of growth factors induced a significant increase in proliferation in adult cells, whereas neonatal cells only trended towards greater proliferation (Figure 1). After six days, adult cells continued to respond to bFGF but not to TGFβ3 (Figure 1). Higher concentrations of both bFGF and TGFβ3 induced significantly more neonatal cell proliferation than control cultures.

**Tenocyte Migration:** At 6 hours, all concentrations of bFGF and TGFβ3 induced greater migration than serum-free media (Figure 2). Similar to the proliferative response, a greater number of neonatal cells migrated towards 10% FBS supplemented media than adult cells.

**Collagen production:** In adult cells, TGFβ3 increased collagen production compared to basal media (Figure 3). In contrast, neonatal cells were more responsive to bFGF. Most interestingly, neonatal cells produced greater than two-fold more collagen than adult cells at baseline conditions (2.5% FBS in DMEM). When treated with 10% FBS, both types of cells produced a quantity of collagen above the detectable range of the assay.

**Discussion**

During tendon healing, growth factor cues stimulate cell proliferation and migration to the site of injury, as well as collagen deposition and reorganization. Our data show that both neonatal and adult tenocytes respond to exogenous growth factors, though the pattern of response differs based on cell age. Adult cells proliferated and migrated similarly to neonatal cells in response to growth factors, suggesting that these cells are capable of responding to stimuli to initiate a healing response. Along with previously reported differences in growth factor...
Figure 1. MTT proliferation after 3 and 6 days of growth factor treatment. bFGF and TGFβ induce a mitogenic response early in adult cells, but the response is only sustained by bFGF treatment. Neonatal cells are slower to respond. Asterisks indicate significant differences from control treatments ($p < 0.05$). Crosses indicate significant differences between cell types ($p < 0.05$).

Figure 2. Transwell migration assay. bFGF and TGFβ act as chemotactic agents for every concentration of both factors, with no significant differences between cell types. Asterisks indicate significant differences from control treatments ($p < 0.05$).
expression during aging, the data support the concept that these cells may simply lack growth factor stimuli in their environment. Tissue engineered approaches to tendon healing often include the addition of a growth factor to enhance healing. This in vitro data supports the value of growth factor treatments in adult tendons.

While some commonalities in response were noted, major differences between neonatal and adult cells were also delineated. First, neonatal cells responded more robustly to FBS than adult cells. FBS contains a combination of factors including bFGF and TGFβ as well as other factors known to enhance tendon healing such as vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF). This combination of factors may be more representative of a biological healing response, where a combination of factors may yield an overall synergistic effect. The increased response in neonatal cells suggests that younger cells have a greater capacity to respond to such a combination of factors than adult cells. Indeed, results suggest that neonatal cells are capable of producing greater than five times more collagen than adult cells over the same period of time. Because the production and reorganization of collagen is vital to the regeneration of such a load-bearing tissue, this result may be the primary distinction between young and old tissue healing. However, the addition of the highest concentration of TGFβ did increase collagen production in adult cells by two-fold over control treatment, suggesting that stimulation of collagen production in older tissue is feasible. Future studies will establish the type and quality of collagen production after in vivo delivery of growth factors to injured tendons in order to determine the optimal dose and delivery timeline.

**Significance**

The poor intrinsic healing capacity of adults predisposes surgical repair of tendons to potential failure, while fetal and neonatal tissues provide a more robust healing response and can achieve mechanical properties closer to that of uninjured tissue. This study demonstrated that adult tenocytes respond similarly to neonatal cells in some aspects of the healing response, particularly in the response to pro-mitotic and promigratory factors, though neonatal cells showed an overall higher level of collagen biosynthesis. More broadly, this study supports the targeted use of exogenous growth factors in tissue-engineered tendon repair approaches in adults.
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References

Achilles Tendons from Decorin and Biglycan Deficient Mice Demonstrate Inferior Mechanical and Structural Properties Predicted by an Image-based Empirical Damage Model

**Introduction**

The Achilles tendon is among the most commonly injured musculoskeletal structures affecting as many as 2.5 million people per year in North America. Major class I small leucine rich proteoglycans (SLRPs), specifically decorin and biglycan, play an important regulatory role during collagen fibrillogenesis, ultimately affecting tendon mechanical integrity, yet the impact of these SLRPs on the Achilles tendon has not been described. Therefore, the objective of this study was to define the relationship between Class I SLRPs and Achilles structure and function, while also exploring the use of an empirical damage model to predict how these altered structural and regulatory molecules impact the dynamic mechanical behavior of the Achilles tendon. We hypothesized that the absence of decorin and biglycan would lead to altered mechanical and structural properties, and that these altered parameters used in an adapted empirical damage model could be used to successfully predict dynamic mechanical behavior.

**Methods**

**Experimental Design:** Achilles tendons (N = 102) from WT (C57Bl/6), decorin-null (Dcn−/−) and biglycan-null (Bgn−/−) female mice were harvested at maturity (P = 150 days), middle (P = 300 days), and old (P = 570 days) age (n = 9-11 for each group) (IACUC approved). All tendons were harvested and then randomized to blind a single dissector at the time of fine dissection and subsequent testing and analysis.

**Tendon Mechanical Testing:** Tendons were secured proximally using a sandpaper grip while maintaining the calcaneal insertion distally. This construct was loaded into custom fixtures on an Instron 5848 Testing system. Samples, with a 5mm gauge length, underwent a dynamic mechanical testing protocol consisting of: 1) preloading to 0.05N, 2) preconditioning, 3) stress relaxations to equilibrium stress at 4%, 6% and 8% strain, each followed by a sinusoidal frequency sweep progressing from 0.1 Hz through 1, 5 and 10 Hz, and 4) a ramp to failure at 0.1%/sec.

**Tendon Imaging:** Alignment maps of tendons were collected using a polarized light image capture system. Briefly, this system consisted of two rotating polarizing plates and software-synchronized image capture during mechanical testing. Alignment maps were used to quantify collagen organization based on the birefringence signal phase and magnitude. From these measures, the apparent birefringence and circular standard deviation were determined throughout loading.

**Damage modeling:** A previously described empirical damage model was adapted to evaluate differences in parameters altered through genetic variation. Predictions of dynamic modulus were made using evaluation based on equilibrium stress at 6% strain and the calculated birefringence, again at 6% strain. For these calculations, model fit parameters were taken at moderate strain and middle age.

**Statistics:** Power analysis was conducted prior to experimentation and based on data variance in previous studies to ensure sufficient power. One-way ANOVAs were used to evaluate significant differences in mechanical properties between genotypes. Significant relationships were subsequently evaluated using post-hoc Student’s t-tests with Bonferroni corrections (α=0.05; with significance set at p < 0.0167). Damage model fits between predicted and measured dynamic modulus were calculated and reported as Pearson’s coefficients of determination ($R^2$ values).

**Results**

When compared to Achilles tendons from WT mice, mechanical properties were significantly inferior in the Dcn−/− and Bgn−/− mice. Ultimate load was significantly higher for WT tendons compared to SLRP null tendons for middle (P = 300) and old (P = 570) age. WT tendons at maturity (P = 150) had significantly higher ultimate loads when compared to Bgn−/− tendons, but not when compared to Dcn−/− tendons (Figure 1a). The dynamic modulus was similarly reduced for the mature and middle aged
tendons; however this difference diminished with age (Figure 1b). Age-dependent differences in collagen birefringence were also detected (Figure 2a). When incorporated into an empirical damage model, both image-based and mechanical-based inputs resulted in predicted values of dynamic modulus that were moderately correlated to the experimental values observed (Figure 2b,c).

Discussion
Decorin and biglycan have a varied effect on tendons throughout the body. In the Achilles tendon, their absence results in inferior mechanical properties. This is consistent with studies exploring the effect of SLRPs in the flexor carpi ulnaris and the flexor digitorum longus. However, similar studies of the patellar tendon demonstrated that the absence of decorin caused an increase in modulus, and neither the absence of decorin or biglycan had any effect on tail tendon fascicles. The age dependent decrease in collagen fiber organization is consistent with previous work that found increased fiber heterogeneity resulting from knockout of SLRPs. The ultimate load was reduced in the SLRP null tendons, suggesting direct implications for risk of Achilles tendon rupture. In light of the prevalence of Achilles pathology, exploring such structure-function relationships is a critical step in understanding how the Achilles tendon might fail, how to prevent failure, and how to better treat Achilles injuries. Additionally, this work extends the use of damage models as applied to predicting tendon dynamic mechanical properties in two ways; extending their use to circumstances involving genetic variance, and demonstrating that they can be used with image-based inputs. Importantly, meaningful differences were detectable using image-based evaluation of collagen organization, a parameter that has previously been measured with high frequency ultrasound, thereby providing a potential opportunity for clinical translation of our basic research findings.

Clinical Significance
By developing a deeper insight into how SLRPs impact tendon and how understanding differences may help predict altered tendon function, we can better monitor, prevent and rehabilitate tendon injuries. This may be particularly clinically relevant in the context of image-based evaluation of structure as it can be used as a predictive tool for function.

Acknowledgements
The authors acknowledge Mark R. Buckley and Andrew A. Dunkman for assistance and the NIH/NIAMS and NSF GRFP for funding.

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Introduction

Muscle and tendon beneficially adapt to non-injurious exercise. Previous studies suggest that inflammation plays an important role in the regeneration of muscle and tendon following acute injury; e.g., however, the mechanisms governing the roles of inflammation in the adaptation of muscle and tendon to beneficial loading have not been identified. The objective of this study was to screen for acute and chronic inflammatory, as well as ECM genes involved in the beneficial adaptation of rat supraspinatus (supra) tendon and muscle to non-injurious loading. Our global hypothesis was that a mild inflammatory response is a normal, physiologic requirement for muscle and tendon to adapt to load. Specifically, 1) a mild inflammatory response (changes in arachidonic acid cascade) would present in the tendon and muscle after a single bout of loading, and 2) the tissue will show adaptive matrix changes (increased collagen expression and MMP/TIMP changes indicating turnover) with chronic loading.

Methods

20 male, Sprague-Dawley rats (400-450g) were divided into cage activity (CA) or acute or chronic exercise (EX) groups (IACUC approved). Acute groups were divided into 12 or 24 hour euthanasia time points following a single exercise bout, and chronic groups were divided into 1 or 8 weeks of repeated exercise (n = 4 each group). EX animals walked on a flat treadmill using a previously validated protocol. Control CA animals maintained cage activity for 5 weeks. Supra tendon and muscle were harvested, RNA was extracted, and a custom Panomics QuantiGene 2.0 Multiplex array was used to detect 48 target genes for inflammation, ECM components, matrix turnover, and factors associated with tissue adaptation or degeneration. Target gene signal was normalized by the geometric mean of 3 housekeeping genes and log2 transformed. Principal components analysis (PCA) was used to visualize global similarities among the 40 samples and for the 4 separate categories of interest: chronic tendon, chronic muscle, acute tendon, and acute muscle. For each category, a 1-way ANOVA (3 levels) with pairwise contrasts was used to compare CA and EX genes. Because this was a screening experiment, an inclusive analysis was conducted. Significance was set at p ≤ 0.05 and genes with a positive or negative fold change ≥ 1.25 were included.

Results

PCA confirmed distinctions between tissues and time points supporting the study design (not shown). Supporting our hypotheses, acute exercise caused an altered inflammatory response in muscle and tendon, indicated by changes in arachidonic acid cascade components and MMP/TIMPs (Table 1). As expected, inflammatory genes were more changed acutely than chronically. Chronic tissue had more matrix-related gene changes, suggesting tissue adaptation (Table 2). Several growth factors also significantly changed with acute and chronic exercise (not shown).

Discussion

Tendon and muscle showed time-dependent responses to exercise. More chronic gene changes were found at 1 than 8 weeks, indicating that this adaptive process begins soon upon

<table>
<thead>
<tr>
<th>Table 1. Inflammatory and matrix genes changed with acute exercise.</th>
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<tr>
<td>Chronic Tendon</td>
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<tr>
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</tr>
<tr>
<td>Arachidonic Acid Cascade</td>
</tr>
<tr>
<td>CA-EX12</td>
</tr>
<tr>
<td>CA-EX24</td>
</tr>
<tr>
<td>EX12-EX24</td>
</tr>
<tr>
<td>Matrix Turnover</td>
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<tr>
<td>CA-EX01</td>
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<tr>
<td>CA-EX08</td>
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<td>EX01-EX08</td>
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initiation of an exercise routine. Results suggest that tendon response to chronic, beneficial exercise is distinct from overuse. Unlike overuse, we did not find increased expression of cartilage markers (Sox9, Acan, Col2a1), heat shock proteins (Hspa2, Hspb1), or nitric oxide synthases (Nos2, Nos3) in tendon. In conclusion, this study suggests a role of physiologic inflammatory processes and matrix turnover in the response of supra muscle and tendon to acute and chronic beneficial load. Future studies can use these results to distinguish beneficial and detrimental loading effects, identify tissue recovery, and develop new treatments.

Table 2. Inflammatory and matrix genes changed with chronic exercise.

<table>
<thead>
<tr>
<th>Arachidonic Acid Cascade</th>
<th>Acute Tendon</th>
<th>Acute Muscle</th>
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<tbody>
<tr>
<td>CA-EX12</td>
<td>Ptger4</td>
<td>Ptges</td>
</tr>
<tr>
<td>CA-EX24</td>
<td>Ptges, Ptger4</td>
<td>Ptges, Ptgf1</td>
</tr>
<tr>
<td>EX12-EX24</td>
<td>Ptges, Ptger4</td>
<td>Ptges, Ptgf1</td>
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<tr>
<td>CA-EX12</td>
<td>—</td>
<td>Timp4, Col1a1</td>
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<tr>
<td>Matrix Turnover</td>
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<tr>
<td>CA-EX24</td>
<td>Mmp14, Timp3</td>
<td>Timp3, Col1a1</td>
</tr>
<tr>
<td>EX12-EX24</td>
<td>Mmp14, Timp3</td>
<td>Timp3, Timp4</td>
</tr>
</tbody>
</table>

References
Tendon Healing in a Supraspinatus Tear and Repair Rat Model is not Altered by Overuse-Induced Tendinopathy

Introduction
Rotator cuff tears are prevalent musculoskeletal disorders which most commonly occur clinically following a period of overuse-induced or chronic tendinopathy. The typical laboratory model of rotator cuff repair, however, is based on an acute surgical detachment of an otherwise normal tendon. To best mimic the clinical scenario of an “acute-on-chronic” supraspinatus tendon tear, we have recently utilized a rat model of supraspinatus tendon overuse which induces a tendinopathic condition to precede surgical creation of a tendon tear. However, it is unclear whether this added model complexity is advantageous or even necessary when evaluating the healing response of a repaired tendon. Therefore, the objective of this study was to evaluate the mechanical and histological properties of supraspinatus tendon healing following tendon detachment and repair in a normal tendon or in a tendon subjected to overuse to induce a tendinopathic state prior to surgical injury. We hypothesized that overuse activity prior to surgical detachment and repair would not alter the healing supraspinatus tendon mechanical or histological properties.

Methods
Experimental design: Twenty-three adult male Sprague-Dawley rats (400-450g) were used in this IACUC approved study. Rats in the overuse group (n = 9) were subjected to a two week training period followed by four weeks of downhill overuse treadmill activity (17m/min, 1hr/day, 5days/wk, 10° decline) to induce a tendinopathic condition, while control rats (n = 14) were allowed normal cage activity. All animals were then subjected to bilateral supraspinatus detachment and repair surgery. Following surgery, animals from both groups were allowed cage activity until sacrifice 4 weeks later. The left limbs of each animal were used for mechanical testing while the right limbs were used for histological analysis.

Mechanical testing: Supraspinatus tendons were dissected from the shoulder and cleaned of excess soft tissue. Stain lines were placed along the length of the tendon for optical strain measurement. Cross sectional area was measured using a custom laser device. Tendons were then subjected to a mechanical testing protocol consisting of a preload to 0.08 N, ten cycles of preconditioning (0.1-0.5 N at 1% strain/s), a stress relaxation to 5% strain (5%/s) followed by a 600s hold, and a ramp to failure at 0.3%/s. Stress was calculated as force divided by cross sectional area and 2D Langrangian strain was determined optically using custom tracking software.

Histology: A subset of muscle-tendon-bone units (n = 4 per group) were dissected, processed, paraffin embedded, and sectioned at 7µm using standard histological techniques. Sections were stained with hematoxylin and eosin (H&E) to assess cell shape and cellularity and alcian blue and picrosirius red (ABPR) to assess collagen fiber organization. The insertion site and midsubstance of the tendon were each evaluated separately. Cell shape and cellularity were graded by three blinded investigators using a semi-quantitative method. Fiber organization was quantified by measuring the circular standard deviation of collagen fibers from images taken with a polarizing microscope and analysis with custom software, as described previously.

Statistical Analysis: Mechanical testing comparisons were made between the two groups using student’s t-tests with significance set at p ≤ 0.05. Histological comparisons were made using Mann-Whitney U tests with significance set at p ≤ 0.05.

Results
No statistical differences were found between groups in cross sectional area (Figure 1A), modulus (not shown), maximum stress (not shown), stiffness (Figure 1B, or maximum load (Figure 1C). The overuse group had significantly greater percent relaxation (though only by 5%) compared to the control group (p = 0.04, Figure 1D). In addition, no statistical differences were observed in cell shape and cellularity (Figure 2) and circular standard deviation (Figure 3).

Discussion
Overall, there were no differences in any of the elastic mechanical properties between the healing tendinopathic and normal tendons.
following injury and repair surgery. Percent relaxation, a measure of viscoelasticity, was slightly increased following repair of a tendinopathic tendon. This slight but statistically significant increase is consistent with previous findings in response to overuse, suggesting that these changes were not masked by the repair. However, no differences were observed between overuse and control groups in the primary study parameters which would directly affect clinical outcomes in this setting, specifically, maximum load and stiffness. We hypothesize that the biological effects of the surgical injury overshadow the relatively milder changes typically evoked by overuse. Because the clinically relevant parameters were not altered in the overuse group, we conclude that when examining healing tendons 4 weeks after a repair, the acute injury model 

Figure 1. (A-D) Mechanical testing results: (A) No difference was found in cross sectional area. (B) No difference was found in stiffness. (C) No difference was found in max load. (D) Percent relaxation was significantly greater (though only 5%) in the overuse group.

Figure 2. No differences were observed in cellularity and cell shape.
to assess potential biologic differences during the early stages of rotator cuff healing.

Significance
This study helps to define an appropriate rat model for assessing healing of the supraspinatus tendon after injury.

Acknowledgments
This study was supported by the PVAMC and the NIH/NIAMS supported Penn Center for Musculoskeletal Disorders (P30 AR050950). The authors acknowledge Sarah Yannascoli, Adam Caro and Joshua Gordon for their contributions.

References

Figure 3. No differences were observed in collagen fiber organization.

is satisfactory and the more complex tendinopathic model is unnecessary in this rat supraspinatus repair model. Future studies could evaluate early differences in these two models.
Effect of Scapular Dyskinesis on Supraspinatus Tendon Healing in a Rat Model

Introduction

Rotator cuff tears are common conditions that often require surgical repair to improve function and relieve pain. Unfortunately, despite pain relief, the success associated with repair integrity is mixed, with 5-95% of patients having recurrent tears\(^1\text{,}^3\), resulting in decreased strength and function. Several factors may contribute to repair failure including age, tear size, and time from injury. However, the mechanical mechanisms resulting in repair failure are not well-established making clinical management difficult. Specifically, altered scapular motion (termed scapular dyskinesis) may be one important and modifiable factor which can place the healing tendon at risk for re-injury\(^4\).

Therefore, the objective of this study was to determine the effect of scapular dyskinesis on supraspinatus tendon healing following repair. We hypothesized that scapular dyskinesis will result in H1) diminished joint function and passive joint mechanics and H2) decreased supraspinatus tendon healing following repair due to the compromised mechanical environment present.

Methods

Experimental Design: A rat model of scapular dyskinesis was used. This condition was created by denervating the trapezius and serratus anterior muscles through surgical transection of the spinal accessory and long thoracic nerve, respectively. 70 adult male Sprague-Dawley rats (400-450 grams) were randomized into two groups: nerve transection (SD) or sham nerve transection (Control). Following this procedure, all rats underwent unilateral detachment and repair of the supraspinatus tendon. All rats were sacrificed at 2, 4, or 8 weeks after transection and frozen (for mechanical testing at 4 and 8 weeks, \(N = 10\)) or fixed in formalin (for histology at each time point, \(N = 5\)).

Ambulatory Assessment: Forelimb gait and ground reaction forces were quantified over time in all animals using an instrumented walkway. Data was collected one day prior to nerve transection to obtain baseline ambulatory values and then collected at days 3, 7, 14, 28, 42, and 56 post-injury. Parameters were normalized to body weight.

Passive Joint Mechanics: Passive shoulder joint range of motion and stiffness were measured over time using a custom instrument and methodology\(^5\). Measurements were taken one day prior to nerve transection, and at days 14, 28, and 56 days post-surgery. Briefly, under anesthesia, the forearm was secured into a rotating clamp at 90\(^\circ\) of elbow flexion and 90\(^\circ\) of glenohumeral forward flexion. The scapula was manually stabilized to isolate glenohumeral motion. The arm was then rotated through internal and external rotation three times. A bilinear fit utilizing least-squares optimization was applied to calculate joint stiffness in the toe and linear regions for both internal and external rotation. Parameters were normalized to baseline values.

Tendon Mechanical Testing: At the time of testing, the animals were thawed and the humerus was dissected with the supraspinatus intact. Stain lines, for local optical strain measurement, were placed on the tendon. Cross sectional area was measured using a custom laser device. To determine biomechanical properties, tensile testing was performed as follows: preload, preconditioning, stress relaxation, and ramp to failure. Stress was calculated as force divided by initial area, and 2D Lagrangian optical strain was determined.

Histology: Tendons were harvested immediately after sacrifice and processed using standard paraffin procedures. Sagittal sections (7 um) were collected, and stained with Hematoxylin–Eosin (H&E). Cell density and cell shape were graded by three blinded investigators, using a scale of 1-3 (1 = low, 2 = moderate, 3 = high) for cellularity and 1-3 (1 = spindle shaped, 2 = mixed, 3 = rounded) for cell shape. Polarized light images were analyzed using custom software to evaluate tendon organization, as previously described\(^7\).

Statistics: For the ambulatory assessment, multiple imputations were conducted using the Markov chain Monte Carlo method for missing data points. For both ambulatory assessment and passive joint mechanics, significance was assessed using a 2-way ANOVA with repeated measures on time with follow-up t-tests between groups at each time point. Tissue mechanics between groups were assessed using a t-test.
at each time point. Histology scores were evaluated using a Mann-Whitney test. Significance was set at $p < 0.05$, trends at $p < 0.1$.

**Results**

Joint function was significantly altered in the SD group compared to control (Figure 1). Specifically, braking force was significantly decreased at later time points (6 and 8 weeks post-injury) and propulsion force was significantly increased at all time points (except 3 days post-injury). No differences were observed in passive joint mechanics (not shown).

Elastic and viscoelastic parameters were altered in the presence of scapular dyskinesis (Figure 2). Specifically, mid-substance modulus was significantly diminished at 4 weeks in the SD group compared to control, while no differences were observed at 8 weeks. However, a trend toward increased percent relaxation, a measure of inferior viscoelastic properties, was observed in the SD group compared to control at 8 weeks. Interestingly, tendon cross-sectional area was significantly decreased at the insertion at 4 weeks post-injury, with a similar trend at the mid-substance (not shown). Tendon organization and cell shape were also altered (not shown). Specifically, a trend toward greater disorganization was observed at the mid-substance in the SD group compared to control at 2 weeks post-injury. Additionally, a trend toward a more rounded cell shape was observed at the insertion in the SD group compared to control at 4 weeks post-injury. No differences were observed in cell density (not shown).

**Discussion**

While the prevalence of rotator cuff repair failures is well-documented, the mechanical mechanisms by which failure occurs are not well-established, making clinical management difficult. Previous studies have demonstrated a strong association between scapular dyskinesis and shoulder injury. Using this animal model, we prescribed scapular dyskinesis and rigorously evaluated the effect on supraspinatus tendon healing following cuff repair in a controlled manner. Results demonstrated that scapular dyskinesis alters joint function and leads to compromised supraspinatus tendon properties. Loading environment is particularly important in healing tissues and in this study, scapular dyskinesis likely placed abnormal and excessive loads on the healing tendon, thus compromising its mechanical integrity. Specifically, tendon mechanical, organizational, and histological properties were diminished in the presence of SD, indicative of diminished tissue healing. Identification of scapular dyskinesis as a potential mechanical mechanism of failed rotator cuff healing will help guide clinicians in prescribing treatment strategies for patients with cuff tears. Specifically, successful pre-operative scapular rehabilitation may be necessary to achieve successful outcomes post-operatively.

![Figure 1](image.png)

*Figure 1.* (A) No differences were observed in medial-lateral forces between groups. (B) The SD group had a significantly decreased braking force compared to control at 6 and 8 weeks. (C) The SD group had a significantly increased propulsion force compared to control at all time-points (except 3 days post-injury). (D) No differences were observed in vertical force between groups. Data is shown as mean and SD ($^*p < 0.05$).
Clinical Significance
This study identifies scapular dyskinesis as a mechanical mechanism for compromised supraspinatus healing following repair. Identifying modifiable factors that lead to compromised tendon healing will help improve outcomes following repair.

Acknowledgements
The authors acknowledge Adam Pardes and Bob Zanes for assistance and the NIH/NIAMS for funding.

References
Mechano-activatable Microcapsules for Tunable Drug Delivery

Introduction

A particularly desirable feature of controlled drug delivery is self-regulation, wherein physiological feedback actively regulates release kinetics. Extant systems in this domain commonly employ stimuli-responsive vehicles that rely on internal triggers to precipitate release, such as temperature, pH, or chemical reactions. The sensitivity of these triggers can be tuned by biomaterial composition or structure to regulate release in a given physiologic or pathophysiologic state. However, to date, such delivery vehicles have not been specifically tuned for mechanically activated release.

Tissues within the body experience mechanical perturbations across multiple force magnitudes and length scales, from mechanotransduction at the cell level to the dynamics of load-bearing joints. These forces not only maintain tissue homeostasis, but can also initiate degenerative processes when applied at supra-physiologic levels. Given the centrality of mechanical loading in normal tissue function, our objective was to develop a mechanically activated drug delivery system to stimulate regeneration and repair in mechanically loaded musculoskeletal tissues (e.g., cartilage, muscle, bone). Towards this goal, we developed a novel class of mechano-activatable microcapsules (MAMCs, Ø~50-100 µm), and illustrate here the tuning of design parameters to enable differential responses to varying applied mechanical stimuli.

Methods

**MAMC Fabrication:** Mechanically activated microcapsules (MAMCs) were produced with a poly(lactic-co-glycolic) acid (PLGA) copolymer shell (doped with Nile Red) and an aqueous core containing FITC-dextran, 2 MDa, (Figure 1C). Microcapsules were fabricated using a glass-capillary microfluidic system to produce a highly monodisperse water-in-oil-in-water (W/O/W) emulsion with ~100% encapsulation efficiency (Figure 1A, B). Using osmotic annealing, the wall thickness to radius ratio (t/D) was tuned by modulating the concentration of PLGA (50:50) in the middle phase, as well as the solute (NaCl) concentration in the inner and outer phases. Three batches of microcapsules were fabricated, with a t/D ratio of (1) 0.008 (t~400nm, D~50µm), (2) 0.012 (t~600nm, D~50µm), and (3) 0.015 (t~1500nm, D~100µm). All capsules were maintained in 0.15M NaCl at 23°C.

**MAMC Compression:** To demonstrate mechano-activation, a single layer of MAMCs was subjected to increasing levels of load between two glass coverslips (Figure 2). Microcapsules were loaded to ~50g, 200g, and 500g; intact, unloaded MAMCs served as a negative control while MAMCs sheared between two glass slides served as a positive control. After overnight incubation at 23°C in phosphate-buffered saline (PBS), z-stack images were collected at 20X magnification using a Nikon confocal microscope. The mid-slice was used to determine whether a single MAMC was “full” or “empty” (devoid of FITC-dextran). Fluorescence intensity of the supernatant was also assayed to measure bulk MAMC release (Ex/Em: 490/520).

**MAMC Mechano-activation in 3D Hydrogels:** To validate mechano-activation in a three-dimensional construct, MAMCs were embedded in a three-dimensional construct, MAMCs were embedded in a photo-crosslinked poly(ethylene glycol) diacyrylate (PEGDA) hydrogel. Using a custom micromechanical compression device mounted atop a confocal microscope (Figure 3A), MAMC-laden hydrogels were compressed in unconfined compression, from 0-20% strain at steps of 4%, followed by compression until hydrogel failure. Individual MAMCs (n = 2/hydrogel) were...
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Results

To assess mechano-activation, isolated MAMCs (t/D=0.015) were subjected to increasing load (Figure 2). MAMC deformation increased with applied load, resulting in a graded pattern of microcapsule rupture and release of encapsulated FITC-dextran. Sheared MAMCs served as a positive control, with ~100% of MAMCs devoid of a fluorescent signal. The fluorescence intensity of the buffer solution also correlated with applied load, confirming MAMC mechano-sensitivity (not shown).

To demonstrate mechano-activation within a 3D context, MAMCs were embedded in a 30% (v/v) PEGDA hydrogel and evaluated using a confocal-mounted compression device (Figure 3A). 30% PEGDA was chosen as an encapsulating matrix as it has a stiffness comparable to both native and mature engineered cartilage.14,15 With compression of the hydrogel, MAMCs deformed in a dose-dependent fashion, becoming ellipsoid at 20% strain and rupturing upon hydrogel fracture (observed at ~57% strain). At t/D ratios of ~0.012 and 0.015, MAMCs underwent folding and/or sharp bending of the capsule wall, while at a t/D ratio of ~0.008, MAMCs maintained a rounded appearance with compression.

Discussion

In this study, we developed a method to generate microcapsules that are mechano-sensitive and characterized the behavior of their mechano-activatable properties towards the development of a novel platform for controlled and self-regulated drug delivery. Within this MAMC population, the amount of rupture and release was readily controlled by the magnitude of the applied load. While low loads resulted in rupture of only a small fraction of MAMCs, higher loads resulted in > 50% release. Within the context of a 3D environment, the deformation behavior and mechanism of MAMC rupture was in part dependent on the wall thickness-to-radius ratio (t/D).8

Previously, drug delivery mediated by mechanical rupture has primarily focused on mechano-chemical or thermal mechanisms to initiate release, wherein pH or temperature induced phase changes result in structural defects in the capsule shell.2,9 Our MAMCs are designed in a manner analogous to that of self-healing polymers used in material science applications, where microcapsules containing a ‘healing agent’ are embedded in a matrix and, upon fracture, initiate polymerization and ‘repair’. Building from this self-healing concept, mechano-activation of MAMCs can be designed to stimulate repair or regeneration through biologic mechanisms spurred by the release of factors from the MAMCs. Future studies will focus on tuning MAMC mechanical behavior via alteration of fabrication parameters, with the goal of designing...
a cohort of microcapsules with different failure thresholds in order to program sequential therapeutic delivery. Techniques such as atomic force microscopy and finite element modelling will be used to characterize MAMC strain and rate-dependent deformation, rupture, and release profiles. In addition, initial efficacy studies will measure the chondrogenic effects of growth factors (e.g. TGF- β) released from MAMCs in a dynamically loaded engineered cartilage model. This work provides an initial characterization of MAMCs, and sets the stage for the widespread application of this drug delivery system for musculoskeletal repair and regeneration.

**Acknowledgements**

This work was supported by the National Science Foundation, the Department of Veterans' Affairs, and the Penn Center for Musculoskeletal Disorders.

**References**

TGF-beta and BMP Signaling Pathways Regulate Chromatin Condensation in Mesenchymal Stem Cells in Response to Dynamic Loading

Introduction
Mesenchymal stem cells (MSCs) are a promising cell source for regenerative therapies given their multipotent nature. Along with soluble cues, exogenous mechanical perturbations play important roles in modulating MSC lineage-specification. MSC differentiation is accompanied by chromatin remodeling and changes in gene expression. In previous work, we showed that dynamic tensile loading (DL) evoked chromatin remodeling and ultimately condensation. Further, we demonstrated that ATP release and subsequent calcium signaling played a role in early signaling events mediating this DL-induced chromatin condensation. In addition to these pathways, it is well established that transforming growth factor beta (TGF-β) and bone morphogenetic protein (BMP), members of the TGF-β superfamily, regulate cellular processes including growth and differentiation. Binding of TGF-β and/or BMP to cell surface receptors initiates phosphorylation of Smad proteins and transcriptional activation of target genes. Recent work has shown that Smad2/5 (pSmad2/5) signaling is activated by cyclic strain. However, the role of signaling through this pathway in mechanically induced chromatin condensation in MSCs has not yet been explored. In this study, we queried whether different loading conditions (i.e., frequency and duration of applied load) regulated chromatin condensation, and ascertained whether these changes were in part mediated through the TGF-β/BMP signaling pathways.

Methods
Aligned poly(e-caprolactone) (PCL) nanofibrous scaffolds were fabricated via electrospinning and incubated in 20 µg/mL fibronectin in PBS overnight to enhance cell attachment. MSCs isolated from juvenile bone marrow were seeded at 200,000 cells per scaffold. Constructs were cultured in a chemically defined media (CM) without exogenous growth factors. Dynamic tensile loading (DL, 3%) for varying durations (30, 150, or 600 sec) and frequencies (0.2 ~ 2 Hz) was applied after 2 days of pre-culture, using a custom bioreactor. To assess chromatin condensation, nuclei were stained with DAPI and scanned across their mid-sections using a confocal microscope (Zeiss, LSM 510). The chromatin condensation parameter (CCP) was quantified using a gradient-based sobel edge detection algorithm implemented in MATLAB to measure edge density in nuclei. To determine the role of TGF-β superfamily signaling on DL induced condensation, pharmacologic inhibitors SB431542 (SB, 10µM, Sigma) to inhibit Smad 1/5/8 (BMP signaling) or LDN193189 (LDN, 100nM, Reagents Direct) to inhibit Smad 1/5/8 (BMP signaling) were applied for 2 hours and washed off prior to application of DL (3%, 1Hz, 600 sec). After DL, constructs were fixed and CCP quantified.

Given that our previous studies had shown that soluble ATP released to the media was a key mediator of condensation, we also collected conditioned media after each episode of DL, with and without TGF-β/BMP inhibition. This supernatant was then added to naive (unloaded) MSC-seeded constructs. After 30 min, these constructs were fixed and CCP was determined (Figure 2 A). To measure the concentration of ATP in the media, a luciferin/luciferase assay was performed (ATP Assay Kit, KA1661, Abnova). To determine intracellular Ca2+ levels with static stretch, MSCs on scaffolds were loaded with the fluorescent calcium indicator, Cal-520 (3 mM, AAT Bioquest) for 1 h at 37 °C. Constructs were placed into a micro-tensile device mounted on a confocal microscope. Time-series images of basal [Ca2+]i signal were recorded (every 4s for 10 min). Grip-to-grip strain of 3% was then applied (at 0.05%/s), and [Ca2+]i response was measured for an additional 10 min. A custom MATLAB program was used to analyze [Ca2+]i oscillations (Figure 3A and B).

Figure 1. A) DAPI stained nuclei (Top Row) and corresponding edge detection (Bottom Row) (DL: 3%, 1hz, 600s, Bar = 3 µm), B) heat map of CCP values with changes in duration and frequency of DL (n = 20, *, p < 0.05 vs. CM control, +: p < 0.05 vs. 0.2 Hz, ‡: p < 0.05 vs. 0.5 hz).
Results
Dynamic loading led to chromatin condensation in MSC nuclei, increasing the number of visible edges (Figure 1A). No change in CCP was observed with 30 sec of DL, except in the case of DL at 2 Hz (Figure 1B). DL at 1 and 2 Hz for 150 sec increased CCP, but not at 0.2 or 0.5 Hz (Figure 1B). Interestingly, with 600 sec of DL, CCP increased in all conditions, independent of loading frequency (Figure 1B).

When DL (600 sec, 3%, 1 Hz) was applied in the context of blockade of either TGF-β or BMP signaling (SB or LDN), DL induced increases in CCP were blocked (Figure 2B). Addition of media conditioned by DL (3%, 1 Hz, 600s) increased CCP values in unloaded MSC-seeded constructs (Figure 2C). Conversely, pretreatment of DL-constructs with SB or LDN blocked this condensation (Figure 2C). Consistent with our previous findings, DL (3%, 1 Hz, 600s) triggered ATP release into the media (Figure 2D); both SB and LDN pretreatment blocked this ATP accumulation (Figure 2C). This finding suggests that blockade of Smad signaling attenuates release of ATP upon DL, short-circuiting the load induced chromatin condensation events. To probe additional downstream responses, we also monitored [Ca^{2+}] oscillations in MSCs (Figure 3A and B). With treatment with SB or LDN, there were no changes in average signal intensity, peak duration (not shown), or time to peak in any group (Figure 3C) when constructs were exposed to grip-to-grip strain of 3%. However, changes in the number of peaks in a 10 min observation window (Figure 3D), the time between peaks (not shown), and % of responding cells (not shown) with static stretch were all altered by inhibition of TGF or BMP signaling.

Discussion
In this study, we showed that dynamic loading leads to rapid chromatin condensation in MSCs, and that the degree of condensation depends on both the frequency and the duration of loading. In addition, we found that blockade of either Smad 2/3 or Smad 1/5/8 signaling attenuated ATP release and subsequent alterations in Ca^{2+} signaling, and thereby limited chromatin condensation. Consistent with this finding, a recent study showed that fluid shear stress results in rapid increases in cellular contractility and ATP release. Likewise, addition of either BMP or TGF-β can increase contractility, and is dependent on Smad signaling. It may be that inhibition of these pathways via pre-treatment with SB or LDN decreases cellular contractility to the point where insufficient stress is generated in the cytoskeleton and so mechanically induced ATP release with applied stretch is no longer possible. Ongoing studies are now exploring changes in cell contractility with inhibition of Smad pathways, and further delineating the manner by which these pathways interact with ATP/calcium signaling. Overall, these new data suggest that dynamic tensile loading triggers ATP release by MSCs, and that this release is modulated by both TGFβ and BMP signaling pathways.

Acknowledgements
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References
Mechanically Induced Purinergic and Calcium Signaling Directs Chromatin Condensation in Mesenchymal Stem Cells

Introduction

Mechanical cues play important roles in directing lineage-specification of mesenchymal stem cells (MSCs). However, the mechanisms by which physical cues regulate chromatin condensation and gene expression remain unclear. Within the nucleus, histone methylation, mediated by the histone methyltransferase EZH2, leads to chromatin condensation, silencing transcriptional events, while preserving lineage-specific gene expression. Previous work has shown that mechanical forces applied through magnetic beads induce rapid chromatin condensation in HeLa cells\(^1\). More recently, we have shown that dynamic tensile loading (DL) evokes heterochromatin formation in MSCs, which is dependent on acto-myosin contractility. Indeed, this mechanically induced condensation occurs more rapidly than with the addition of soluble differentiation factors. We further showed that ATP/calcium signaling played a role in early signaling events mediating this DL-induced chromatin condensation; exposure to Apyrase (an ATP diphosphohydrolase) abrogated DL-induced chromatin condensation. To further delineate the role of ATP/calcium signaling in this process, the current study interrogated key nodes in this signaling pathway via pharmacologic inhibition. Furthermore, given that mechanical inputs have been shown to imprint a ‘mechanical memory’ on MSCs, we queried whether multiple loading events would regulate the persistence of these changes in chromatin condensation and gene expression over the long term.

Methods

Bovine bone marrow derived MSCs (2×10^5) were seeded onto aligned poly(ε-caprolactone) nanofibrous scaffolds, and constructs were cyclically stretched (3%, 1Hz) using a custom bioreactor (short term: 600s sec, long term: 3 hour) in a chemically defined media [CM]. At each time point, an image-based edge detection algorithm was used to determine a chromatin condensation parameter (CCP) by quantifying chromatin density and organization in individual DAPI stained nuclei. To probe key signaling nodes involved in chromatin condensation, we applied selected pharmacologic inhibitors prior to loading. To investigate the role of the histone H3K27 methyltransferase EZH2, constructs were pretreated with 2.5µM of GSK343 (GSK, Sigma). Likewise, to interrupt ATP/calcium signaling, constructs were exposed to Flufenamic acid (FFA, 500 mM, a hemichannel blocker), BAPTA (50uM, an extracellular Ca^{2+} chelator), NK-62 (10uM, a Calmodulin kinase II inhibitor), and Cyclosporine A (CYP, 5uM, a Calcineurin inhibitor). ATP in the media was also measured using an ATP assay Kit (Abnova). To monitor changes in [Ca^{2+}]\(_i\) within cells, constructs were placed into a micromechanical test device mounted onto confocal microscope and cells were labeled with Cal-520™ (AAT Bioquest). Constructs were treated with ATP (0.1mM or 1mM, Thermo Sci.) or were dynamically stretched (3%, 1Hz, 30sec), and [Ca^{2+}]\(_i\) in individual cells was recorded every 4s for 10 mins. YAP (a transcriptional regulator) nuclear localization was evaluated with FFA abrogated the CCP response with 600s loading also triggered YAP staining intensity and localization was visualized by immunofluorescence (Santa Cruz Biotech.), and quantified using ImageJ (where nuclear staining was normalized cytoplasmic staining). To determine whether repeated mechanical loading introduced a mechanical memory in these cells, constructs were dynamically loaded (3%, 1Hz, 6 hour/day) for 1 day (DL×1), 3 days (DL×3) or 7 days (DL×7), after which they were returned to free swelling culture for an additional 5 days. At set time points after cessation of loading, CCP was measured and expression levels were determined by real time RT-PCR. Statistical analysis was performed by ANOVA with Fisher’s post-hoc tests.

Results

Consistent with our previous findings, 600s of DL led to chromatin condensation in the nuclei of MSCs, increasing the number of visible edges (Figure 1A) and the measured CCP (Figure 1B). This increase in CCP peaked at 600s, and was reduced at 3 hours of DL. Loading also triggered ATP release (not shown). Blocking hemichannels with FFA abrogated the CCP response with 600s of DL, but did not abolish the response with 3
hours of DL (Figure 1C). Conversely, when calcium/calmodulin/calcineurin signaling was interrupted via the inclusion of BAPTA, NK-62 and CYP2A, both the short term and the longer term response was blocked (Figure 1D, 1E). Similarly, addition of a methyltransferase inhibitor (GSK), which blocks the action of EZH2, eliminated DL-induced CCP changes at both time points (Figure 1F). Monitoring internal [Ca\textsuperscript{2+}] showed a decrease in the time between peaks and an increase in the number of peaks when constructs were treated with ATP or exposed to 30 sec of DL (Figure 2A, 2B). With both ATP addition and DL, the transcription regulator YAP was mobilized to the nucleus (Figure 2C, 2D). In longer term studies, the number of loading cycles influenced the magnitude of chromatin condensation and the permanency of the condensation state. Increasing the number of loading events resulted in a larger increase in CCP (Figure 3A), and condensation persisted for a longer period of time after cessation of loading (Figure 3A). Additionally, aggrecan expression (AGG) increased to a greater extent with increasing number of loading events, and this expression remained elevated for prolonged periods after loading (Figure 3B).

Discussion
In this study we showed that dynamic tensile loading of MSCs seeded on aligned nanofibrous scaffolds resulted in marked chromatin condensation. Building from past findings related to ATP release with loading, we further showed that blockade of hemichannels by FFA was involved in the early signaling response, but not in the response to sustained (3 hours) dynamic loading. Conversely, when calcium in the extracellular media (BAPTA) and calcium-responsive

Figure 1. (A) Representative DAPI stained nuclei (top row) and corresponding edge detection (bottom row) (DL: DL for 600s, bar = 3 µm), (B) Chromatin condensation parameter (CCP) with either 600s or 3 hours of DL (n = ~20, *: p < 0.05 vs. CM, +: p < 0.05 vs. 600s, mean ± SEM), (C-F) CCP values with short and long term loading under pharmacologic inhibition of ATP/Ca\textsuperscript{2+} signaling (n = ~20 per group per time point; red line: DL for 600s, blue line: DL for 3hr, green line: unloaded control, mean ± SEM).

Figure 2. Time between calcium peaks (sec) and number of peaks over 10 mins following exposure to ATP (A) or application of DL (B) (*: p < 0.05 vs. control condition). (C) Images of nuclear localization of YAP and quantification (D) with the addition of ATP or application of DL (n = ~20, *: p < 0.05 vs. control (red line), mean ± SD).

Figure 3. Changes in chromatin condensation and gene expression with multiple loading events (×1, ×3, or ×7) and with time after cessation of loading (up to five days). (A) CCP (green line: control condition, n = ~20, *: p < 0.05 vs. CM condition, +: p < 0.05 vs. DL ×1, t: vs. DL ×3, mean ± SEM). (B) AGG gene expression (green line: CM condition, n = 3, *: p < 0.05 vs. CM condition, +: p < 0.05 vs. DL ×1, t: vs. DL ×3, mean ± SD).
signaling elements (such as calmodulin and calcineurin) in the cell were blocked (using KN-62 and CYP A), both the short term and long term loading response was eliminated. This suggests that both the early and late response depend on calcium mediators, but only the early signaling events utilize hemichannels. Furthermore, when we blocked the activity of the H3K27 methyltransferase EZH2, no chromatin condensation was observed at any time point. This suggests that EZH2 serves as a common downstream integrator of the response to mechanical loading. Ongoing studies are probing the relationship between EZH2 activation and calcium signaling. When mechanical perturbation was applied multiple times, the magnitude of chromatin condensation (and ECM gene expression) increased. This suggests that there exists an extended capacity for condensation and remodeling of nuclear architecture, where repeated loading events may refine and expand locations of condensed chromatin within the genome. This advanced state of chromatin condensation also imparted a degree of permanency to the load conditioned state, where increasing the number of loading cycles sustained the condensed state for a longer period of time after cessation of loading. This implies that a mechanical memory is established in the chromatin architecture with dynamic loading. Ongoing work is now focused on identifying structural features and pathways that regulate chromatin architecture to establish this mechanical memory within the nucleus.

Significance

Mechanical cues play critical roles in directing MSC lineage specification, though the mechanisms by which they do so remain poorly understood. Here, we show that dynamic tensile loading induces chromatin remodeling through both purinergic and calcium signaling pathways, culminating in activation of an enzyme that provides epigenetic modification to histones within the nucleus. Further, we show that repeated loading imparts a mechanical memory to the MSC nucleus, suggesting that these mechanical perturbations can persistently change the trajectory of differentiation through structural remodeling of the chromatin.

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References

Preconditioning Stem Cells to Maximize Regenerative Potential in the Challenging Microenvironment of the Intervertebral Disc

Introduction

Nearly 85% of adults will experience low back pain in their lifetime. Disc degeneration, an inflammatory cascade resulting in structural and mechanical failure, is strongly implicated as a cause. Current therapies, both palliative and surgical, do not restore disc structure and mechanical function. Current research is focused on the use of stem cell-based therapies for disc regeneration. Previous studies have demonstrated that mesenchymal stem cells (MSCs) are capable of undergoing differentiation to a nucleus pulposus (NP)-like phenotype following implantation into prototype hydrogels. However, it is likely that the specialized environment of low oxygen and nutrient supply in the NP will profoundly affect MSC survival and growth. To address this challenge, we sought to develop a method by which MSCs could be “primed” prior to implantation to maximize survival and extracellular matrix biosynthesis in vivo. Specifically, we evaluated MSC matrix production and proliferation in high-density, low oxygen pellet cultures following monolayer preconditioning in atmospheric (21%) and physiological low (2%) oxygen environments, and with or without TGF-β3 supplementation.

Methods

Cell Isolation and Preconditioning: MSCs from juvenile bovine hind legs were isolated and expanded to confluence in basal media (high glucose DMEM, 10% FBS, and 1% PSF) at atmospheric oxygen. Cells were then trypsinized and expanded through one additional passage in each of the six conditions: 21% O₂ ± TGF-β3 (10 ng/ml), 2% O₂ ± TGF-β3 and Late Addition (LA) of TGF-β3 (added 1 day prior to pelleting) in both 21% and 2% O₂. Further, to investigate effects of preconditioning on proliferation during expansion, 5,000 cells/well were also plated into 6-well plates using four of the previously described conditions (excluding LA 21% and 2% O₂), and the number of live cells were quantified using the MTT assay at time points up to 7 days.

Pellet Culture: At 80% confluency, cells from each preconditioning group were pelleted at a density of 200,000 cells/well in 96-well plates and cultured in chemically defined media with (CM+) or without (CM-) TGF-β3 (10 ng/ml) under three different conditions: High Glucose CM+, High Glucose CM-, and Low Glucose CM-. All groups were cultured for 14 days in 2% O₂. GAG content (DMMB assay) and DNA content (PicoGreen assay) per pellet were determined following Proteinase K digestion (n = 3 per condition). Statistical significance between preconditioning methods was established by one-way ANOVA with Bonferroni post hoc tests (p < 0.05).

Results

Effects of Preconditioning on Proliferation during Expansion: Cells expanded in 2% O₂ without TGF-β3 exhibited significantly, though only moderately higher rates of proliferation 1 and 3 days after plating compared to both 21% O₂ groups (Figure 1). Cells expanded in 2% O₂ with TGF-β3 exhibited significantly higher rates of proliferation 3 and 5 days after plating compared to both 21% O₂ groups. By 7 days, cells approached confluence for all groups and differences were no longer apparent.

Effects of Preconditioning on Pellet Composition: GAG content of pellets cultured in Low Glucose CM- (representative of the challenging in vivo conditions of the NP) was significantly greater for cells preconditioned in 2% O₂ with continuous TGF-β3 compared to all other conditions except 2% O₂, LA (Fig. 2). For pellets cultured in High Glucose CM-, cells preconditioned in 2% O₂ (with or without TGF-β3) resulted in GAG content that was significantly greater than all 21% preconditioning groups. For pellets cultured in High Glucose CM+, cells that were preconditioned in 2% O₂ with LA TGF-β3 had significantly greater GAG content than cells preconditioned in 21% O₂ with continuous TGF-β3, but there were no other differences. While there was lower GAG content in all 21% O₂ preconditioning groups in High Glucose CM-pellet media compared to CM+ as expected, interestingly those preconditioned in 2% O₂ had similar GAG content as found in the High Glucose CM+ pellet groups. DNA content in the Low Glucose CM- condition was significantly higher in cells preconditioned in 2% O₂, LA TGF-β3 compared to all other expansion conditions.

conditions except 21\% \text{O}_2 \text{ without TGF-\beta3} (Figure 3). Pellets cultured in High Glucose CM\textsuperscript{−} had significantly higher DNA for cells preconditioned in 2\% \text{O}_2 \text{ without TGF-\beta3} compared to those preconditioned in 21\% \text{O}_2 \text{ (all variations)} and those preconditioned in 2\% \text{O}_2 with continuous TGF-\beta3. For pellets cultured in High Glucose CM\textsuperscript{+}, cells preconditioned in 21\% \text{O}_2 \text{ without TGF-\beta3} had higher DNA content compared to cells preconditioned in 21\% or 2\% \text{O}_2 with continuous TGF-\beta3.

**Discussion**

In this study, we investigated the efficacy of monolayer preconditioning using low oxygen and TGF-\beta3 in order to improve the biosynthetic performance of MSCs in the challenging in vivo biochemical environment of the NP. Low glucose media and 2\% \text{O}_2 were used to simulate a nutrient- and oxygen-deficient environment. Increased proliferation during monolayer expansion in 2\% \text{O}_2 is consistent with recent work [3]. Cells preconditioned in 2\% \text{O}_2 with continuous TGF-\beta3 supplementation resulted in the greatest GAG content in the Low Glucose CM\textsuperscript{−} environment, which is consistent with previous findings involving MSCs cultured on 3-D scaffolds. By contrast, DNA production for pellets in the Low Glucose CM\textsuperscript{−} media was greater in cells preconditioned in 2\% \text{O}_2 with late addition of TGF-\beta3. Since DNA content is indicative of cell proliferation, 2\% \text{O}_2 \text{ LA TGF-\beta3} may be the best preconditioning environment to promote cell growth after implantation in the disc. While increased cell proliferation may enhance regeneration potential, this must be balanced against the limited nutritional supply in the in vivo space. Interestingly, preconditioning in 2\% \text{O}_2 resulted in significantly improved GAG synthesis for pellets cultured in High Glucose CM\textsuperscript{−}, almost equivalent to TGF-\beta3 supplementation. This suggests that glucose supplementation combined with stem cell delivery may be an alternative to growth factor therapy. In conclusion, this study suggests that monolayer preconditioning in 2\% \text{O}_2 with TGF-\beta3 may lead to enhanced proliferation rates during monolayer expansion and enhanced GAG production following delivery to the in vivo space.
Significance

Stem cells represent a novel therapeutic approach for disc degeneration and associated low back pain. This study investigates the conditions required to optimize these cells for successful growth and survival in the challenging in vivo environment, and is a critical step toward pre-clinical studies.

Acknowledgements

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References

This past September, the University of Pennsylvania Department of Orthopaedics unveiled the Penn Musculoskeletal Center with a highly anticipated symposium on Excellence in Orthopaedics. Hosted by Dr. L. Scott Levin and the Penn faculty and residents, the event was a greatly heralded summit inviting physicians, health care leaders and professionals from across the region and country to share their experiences and thoughts on delivering high quality health-care. Numerous faculty, staff and residents from surrounding training and private Orthopaedic programs in the region attended the symposium for the unique opportunity it afforded.

With the opening of Penn’s Musculoskeletal Center in the heart of University City, the department hosted over a dozen visiting professionals with decades of experience in Orthopaedics and health-care. The recent changes in the department and Penn health system were highlighted in Dr. Levin’s opening remarks, with an emphasis on the support from the university.

J. Larry Jameson, MD, PhD, as the current Dean of the University of Pennsylvania School of Medicine, was highlighted as an instrumental supporter of the department’s effort to improve clinical care and education. In addition, special emphasis was placed on the efforts of Ralph Muller, the CEO of the University of Pennsylvania health system and a stalwart proponent of the Penn Musculoskeletal and Rheumatology Service Line.

The morning proceeded with talks by the distinguished invited lecturers, as pictured. Topics included changes in subspecialty care, improving health care in an evolving medical landscape, surgical quality initiatives, bundling care packages and the evolution of clinical education and research, among other topics. As director of the McKay Orthopaedic Research Laboratory, Lou Soslowsky, PhD, gave a special presentation on the state of research and basic science ventures at the University of Pennsylvania. Additionally, Marvin Steinberg, MD, Emeritus Professor of Orthopaedic Surgery drew on his six decades of experience to describe the evolution of the field of Orthopaedic Surgery and his experiences in clinical education and patient care.

The day concluded with a tour of the brand new Penn Musculoskeletal Center and plans for the future. The symposium was successful in celebrating the growth of the department and our chairman’s vision for the future of Penn Orthopaedics to, “Aim for perfection; settle for excellence.”
Now in its fourth year of use, the Human Tissue Lab (HTL) has become an integral part of the University of Pennsylvania Orthopaedics department. Founded by Dr. L. Scott Levin in 2011 and under the continued direction of Lorianne Kish-Burdsall, the HTL has been integrated into the resident educational core curriculum, with monthly sawbones and dissections led by the various subspecialty attendings in the department. In addition, the divisions of arthroplasty, sports medicine, upper extremity, shoulder and elbow and sports medicine all hold regular team-based sessions in the HTL, with the goal of improving resident education through small group review of anatomic approaches and basic surgical skills.

Multiple regional and national groups have been invited to use the lab for their sessions, including the International Congress for Joint Reconstruction (ICJR), the Foundation for Orthopaedic Trauma Lower Extremity course, the International Hand and Composite Tissue Allotransplantation Society as well as the Philadelphia Spine Summit Inaugural meeting. The Penn Orthopaedic community is grateful for the opportunity to participate in these frequent courses, and takes great pride in the institution’s world-class capabilities and the leadership’s insatiable commitment to continuing education.

Finally, the Human Tissue Lab has been a highlight of Visiting Professor Grand Rounds, which are featured in the upcoming section. Following didactic lectures in Agnew-Grice auditorium, visiting professors were invited to lead prosections in the HTL. Residents, fellows and attendings from the departments and divisions of Orthopaedics, Neurosurgery, and Plastics were frequently in attendance and were able to collaborate and share their perspectives through these hands-on sessions, led by world-renowned experts from a variety of backgrounds and subspecialties. With advanced AV capabilities, more than 50 physicians were regularly able to gather in the HTL and participate in the prosection, while gaining insight into the professors’ personal experiences as well as their leading vision of basic anatomy, pathophysiology and surgical technique.
The next morning Dr. Nunley began with an educational resident lecture, “Athletic Stress Fractures of the Foot and Ankle,” where he drew on his vast experience in dealing with athletes at the collegiate, professional and Olympic levels.

After a brief break, Dr. Keith L. Wapner gave a formal introduction to the lectureship, dedicated to the memory of his late wife. Giving a stirring and emotional speech, Dr. Wapner explained how the June C. Wapner Memorial lecture was established to honor his wife’s lasting legacy to their two sons and her indomitable spirit. Echoing his words, Dr. L. Scott Levin paid homage to June’s lasting legacy through the lectureship, and he expressed his gratefulness for the opportunity to welcome a visiting professor who had personally known June.

Dr. Levin also conveyed profound gratitude for Dr. Nunley’s mentorship at Duke across 3 decades, referring to him as a renaissance man for his varied interests and areas of expertise, as well as being a personal friend and mentor.

Dr. Nunley then gave a captivating lecture showcasing his experience with total ankle arthroplasty over the course of his career and his philosophy on implants and patient outcomes. Touching on several cases with radiographic and clinical photos, he was able to illustrate to complexity of the total ankle arthroplasty and the inherent difficulty in these clinical cases and outcomes.

The University of Pennsylvania Department of Orthopaedics was truly fortunate to have Dr. James A. Nunley as the June C. Wapner Memorial Lectureship Visiting Professor, and look forward to continued collaboration in the future.
The University of Pennsylvania Department of Orthopaedics was honored to welcome Dr. Christopher I. Shaffrey for an informative visit this past October. Born and raised in Milwaukee, Wisconsin, Dr. Shaffrey earned his undergraduate degree from The Citadel, graduating magna cum laude, and earned his medical degree from the University of Virginia. He completed his surgical internship at the Naval Hospital San Diego before returning to The University of Virginia to complete both orthopaedic and neurosurgical residencies, followed by a fellowship in pediatric and adult reconstructive spine surgery at The University of Virginia in 1995. Following his postgraduate training, Dr. Shaffrey completed a scholarship obligation to the United States Navy at Portsmouth Navy Medical Center and was then appointed to the senior staff in neurosurgery and orthopaedic surgery at Henry Ford Hospital, followed by associate professorship in neurosurgery and orthopaedic surgery at the University of Washington, and ultimately returned to the University of Virginia as a Professor of Neurologic surgery. His busy clinical practice is complemented by his research and academic interests in spinal surgery, including research in pediatric and adult scoliosis, spinal trauma and tumors involving the spinal column, and clinical outcomes. He has been a funded principal investigator in numerous grants and clinical trials, has served on the boards of numerous journals, is an active reviewer for premier journals, and is the author of more than 100 publications, 500 national and international presentations, and has served as an editor for several textbooks on spinal surgery.

The morning began with a formal introduction of Dr. Shaffrey by Dr. Sean Grady who detailed Dr. Shaffrey’s many accolades and shared personal anecdotes of Dr. Shaffrey’s mentorship during his early years of training at UVA. Dr. Shaffrey then began with an educational resident lecture on when lumbar disease becomes spinal deformity, where he showcased several clinical cases including radiographs that illustrated the spectrum of disease and surgical correction that he has performed throughout his career. He expressed his inspiring philosophy that it behooves all surgeons to critically evaluate their surgeries in order to continually improve not only in surgical technique, but also in patient selection and procedure choice. Dr. Shaffrey’s talk prompted many insightful questions from the assembled faculty and residents, resulting in an enlightening discussion. Dr. Scott Levin closed the conversation by expressing his thanks for Dr. Shaffrey’s visit, and commended him for the unique insight afforded by his dual neurosurgical and orthopaedic training, his pioneering academic and clinical efforts, and his obvious dedication to patient care.

Dr. Shaffrey then gave a scintillating lecture focusing on the evaluation and management of cervical spine deformity. His talk highlighted several cases of severe kyphosis, and provided a detailed discussion on his approach to these cases beginning with patient evaluation, discussion of patient expectations, and the technical aspects of surgically correcting severe deformities. He emphasized the importance of using surgical intervention as a last resort for clinical symptoms, and that while surgery is a powerful tool, it should always be seriously considered in the context of the overall clinical picture and as part of shared decision making with the patient.

Following the lecture, Dr. Shaffrey hosted the neurosurgical and orthopaedic residents, fellows and faculty in a prosection in the Penn Human Tissue Laboratory. Employing his expertise in orthopaedic- and neurosurgical-based spinal surgery, he approached the cadaveric spine using a lumbar midline exposure and elegantly demonstrated the technique of Smith-Peterson osteotomy followed by pedicle subtraction osteotomy. Throughout the masterful dissection, Dr. Shaffrey commented on proper surgical technique and beautifully exposed the most relevant anatomic structures for spinal surgery. He engaged the questions of the residents, fellows and faculty present, and drew connections between the pathophysiology and treatment options for the adult spine. With greater than sixty orthopaedic and neurosurgical residents in attendance, Dr. Shaffrey spent the remainder of the morning involving the residents in the dissection and he expressed his pleasure with seeing the strong relationship between the two departments, particularly in a setting so conducive to surgical training and collaboration like the Human Tissue Lab.

The University of Pennsylvania Department of Orthopaedics was truly fortunate to have Dr. Christopher I. Shaffrey as a Visiting Professor for a combined lectureship, and the Department looks forward to continued collaboration in the future.
The University of Pennsylvania Department of Orthopaedic Surgery was privileged to host Dr. Sigurd Berven as part of the visiting professor lecture series this past October. Dr. Berven has an impressive resume and wide array of talents and interests. While studying human biology as an undergrad at Stanford University, Dr. Berven was (and remains) a talented athlete, including the privilege to serve as an alternate for the Olympic rowing team. Following his undergraduate degree, Dr. Berven spent time at Oxford University studying philosophy, politics and economics before obtaining his medical degree from Harvard Medical School. Staying in Boston, Dr. Berven completed his residency training at Harvard before moving west to pursue fellowship training in spine surgery at the University of California—San Francisco (UCSF). Today, he is a Professor of Orthopaedic and Neurosurgery, in addition to directing the resident education program and the spine fellowship at UCSF. In addition to this clearly demonstrated interest in education, Dr. Berven is very active clinically as the director of the combined spine service line, which integrates comprehensive care of the spine, implementing both Orthopaedic and Neurosurgical care. Dr. Berven has clinical interests including pediatric and adult deformity, degenerative conditions of the spine, spinal tumors, and spinal trauma. His research interests include assessing clinical outcomes of surgery and minimally invasive spine surgical techniques.

To kick off the educational morning, Dr. Vincent Arlet began with a formal introduction of Dr. Berven, highlighting his many accomplishments inside and out of academia. Dr. Berven gave two excellent presentations, the first of which was entitled, “Measuring Quality and Value in Orthopaedics and Spine Surgery.” This was a fascinating look into the pitfalls, challenges, and successes of evaluating how we care for the orthopaedic and spine patient. Dr. Berven wisely reminded the audience to maintain “patient centeredness” in our quality based metrics and ultimately concluded that we should measure patient-centered reports of outcomes accounting for risks, costs, and benefits. The second talk of the morning was equally interesting and titled, “Evaluating New Technologies in Orthopaedics.” In this talk, Dr. Berven stressed the importance of practitioners demanding that new technologies demonstrate benefits and added value. He cautioned us against simply adopting new technology without first evaluating this technology in a systematic and critical way so that new technology is not merely cost generating, but value adding. Both talks were filled with insight, wisdom, and sage advice and provided a wealth of material to contemplate for everyone in the audience.

Following these excellent lectures, Dr. Berven took his expertise to the state of the art Penn Human Tissue Lab for a hands-on demonstration of the direct lateral approach to the spine. First, he gave a brief presentation discussing the appropriate indications, important anatomy, technical challenges, and potential benefits to this approach. The ensuing demonstration of the direct lateral approach to the spine using a fresh frozen cadaver demonstrated not only Dr. Berven’s impressive surgical skill, but his immense knowledge of anatomy and expertise of instruction that comes from a career dedicated to leading and educating in the field of spine care. To take advantage of this tremendous learning opportunity, following the direct lateral approach, we flipped the cadaver and made the incision extensile to an anterior approach to better appreciate the exacting requirements of the surrounding anatomy.

The University of Pennsylvania Department of Orthopaedic Surgery was honored to host Dr. Sigurd Berven as a Visiting Professor. Dr. Berven is truly dedicated to resident education and helping residents find and pursue their passions. His visit highlighted his clinical and education expertise and the Penn Orthopaedic Surgery Department hopes his experience this past October is only the beginning of a fruitful and mutually beneficial collaboration.
He showcased many interesting and difficult cases, while providing historical perspectives on how the management of the same tumor has evolved over the course of his career. Interestingly, his slides also chronicled important development in tumor surgery, complete with pictures of mentors, protégés, and peers who have all contributed to the subspecialty. He painted a rich tapestry for residents and faculty about the progress and future outlook of orthopedic oncology.

Immediately thereafter, Dr. Sim hosted the orthopaedic residents in the human tissue lab to perform prosections. His masterful dissection was matched only by his insightful commentary. He discussed the most salient approaches to access various structures in the pelvis and how to avoid “alligators,” a moniker that he uses to refer to problems that may arise intraoperatively from technical errors. With the majority of the residency present, Dr. Sim spent the rest of the time engaging questions from residents, and drew many connections between anatomy, pathophysiology, and clinical symptoms for the benefit of resident education.

Penn Orthopedics was truly honored to have Dr. Franklin Sim as a visiting professor on November 6th of 2014, fostering a closer relationship between Penn and the Mayo Clinic.
Dr. Ben Kibler was the honored guest lecturer at the University of Pennsylvania Department of Orthopaedics Grand Rounds this past December. Dr. Kibler is a specialist in scapular motion and AC joint pathology at the Shoulder Center of Kentucky. He obtained his medical degree at Vanderbilt University in Nashville, TN, completed his internship at Parkland Hospital of Dallas, TX, and finished his Orthopaedic Surgery residency at the Vanderbilt Medical Center in 1977. Thereafter, he began his affiliation with the Lexington clinic.

Dr. Kibler is internationally renowned for his research in scapular motion and dyskinesis. He has over 87 publications listed in PubMed on this topic. Although he had many career options, he has dedicated his career to the scientific understanding of shoulder pathology. For his work on aiding athletes return to play, he served as former vice president of the American College of Sport Medicine and United States Tennis Association (USTA) National Sports Science Committee.

Dr. Kibler focused his attention on debunking myths about the scapula in his lecture. He emphasized that the scapula plays a key role in nearly every aspect of normal shoulder motion, and should be included as a crucial aspect of the shoulder examination. He stated that scapular dyskinesis and AC joint separation are three dimensional problems that often is misconstrued as a 2D problem on plain film. He encouraged residents to recognize that scapular dyskinesis is often associated with rotator cuff disease, shoulder impingement, labral injury, clavicle fracture, and shoulder instability. As such, failure to recognize scapular dysfunction and treating it accordingly will lead to poor outcome.

Dr. Kibler focused the second half of his lecture on AC joint separation and clavicle fractures. Specifically, he discussed the limitation of 2D plain film and its inability to assess displacement in the AP dimension. Furthermore, rotational deformity of the clavicle may be complicated by or compensated by scapular motion. As such, treatment of clavicle pathology traditionally dictated by the Neer Classification may be inadequate. The best outcome can only be achieved by a comprehensive evaluation of the shoulder girdle and a thorough understanding of underlying causes.

In the human tissue lab, Dr. Kibler discussed the importance of ligament reconstruction in the proper surgical treatment of AC dislocation. He states that popular approaches such as using “dog bone” fixation devices are inadequate because it fails to address instability from torn AC ligaments, conoid ligaments, and trapezoid ligaments. This opinion was echoed by our Dr. David Glaser. The reconstruction technique’s critical nature was demonstrated on the cadaveric sample, where residents appreciated the difference in AC joint stability based on the before and after results.

Penn Orthopaedics was truly honored to have Dr. Ben Kibler at Grand Rounds on December 4th, 2014.
Guest Lecturer: Dr. Marco Innocenti

January 22nd, 2015

Alexander L. Neuworth, MD

The University of Pennsylvania Department of Orthopaedic Surgery was honored to welcome Dr. Marco Innocenti for a unique visit in January. Born and raised in Florence, Italy, Dr. Innocenti graduated cum Laude from the University of Florence in 1981. Subsequently, he completed his Orthopaedic training in 1984 followed by a Hand surgery fellowship in 1987, both at the University of Florence. In 2004, Dr. Innocenti completed a Plastic Surgery residency at the University of Florence.

Dr. Innocenti currently holds the position of Director of the Plastic and Reconstructive Microsurgery Department at the Careggi University Hospital in Florence. He also serves as an Associate Professor and the Program Director of the Plastic Surgery residency at the University of Florence. Dr. Innocenti’s dedication to cutting edge research and medical education is illustrated by his very prolific contribution to the field with over 100 papers in international journals, as well as 12 book chapters. Furthermore, he currently serves as an Associate Editor for the American edition “Journal of Hand Surgery,” as well as a reviewer for the “Journal of Plastic Reconstructive and Aesthetic Surgery,” and for the European edition of the “Journal of Hand Surgery.”

As the former president of the Italian Society for Microsurgery, Dr. Innocenti currently serves as a European Delegate to the ISM, in addition to his multiple memberships in the American Society for Reconstructive Microsurgery, the American Society for Surgery of the Hand and the World Society for Reconstructive Microsurgery.

On Thursday morning, Agnew Grice was filled with faculty and residents from both the Orthopaedic Department and the Division of Plastic Surgery to welcome Dr. Marco Innocenti. Following a warm, heart-felt introduction by Dr. Levin, Dr. Innocenti gave two fantastic lectures on vascularized bone grafts and propeller flaps, demonstrating his world renowned expertise through complex case discussions. Drs. L. Scott Levin, Kristy Weber, Benjamin Chang and Neil Sheth actively participated in the discussion, sharing their respective areas of expertise while addressing the subtleties of the unique cases being presented.

Thereafter, Dr. Innocenti took the residents through a masterful surgical dissection in order to demonstrate his propeller flap technique while engaging his audience and answering many questions on anatomy, surgical indications, and his own unique experiences.

The Department of Orthopaedic Surgery at the University of Pennsylvania was honored to have Dr. Innocenti as a visiting professor on January 22nd, 2015. Dr. Innocenti’s visit demonstrated, once again, the spectacular collaboration at Penn between the Department of Orthopaedic Surgery and the Division of Plastic Surgery.
The University of Pennsylvania Department of Orthopaedics was honored to welcome Dr. Tamara Rozental for its 9th annual Leo Leung endowed lectureship this past January. Dr. Rozental serves as Associate Clinical Professor in the Department of Hand and Upper Extremity Surgery at Beth Israel Deaconess Medical Center in Boston. She graduated from the University of Pennsylvania Orthopaedic Surgery residency program in 2007. Following residency she completed a hand and upper extremity fellowship at the Brigham and Women’s Hospital in Boston. A rising star in the field, she is the recipient of the prestigious 2014 Sterling-Bunnell Traveling Fellowship for her early academic contribution to hand surgery through NIH-funded research in osteoporosis and distal radius fragility fractures. In addition, she serves as an Associate Editor for the Journal of Hand Surgery.

Dr. Rozental’s first lecture focused on fragility fractures of the distal radius. Much of her research efforts have tackled osteoporosis as a major public health problem, and the morbidity associated with distal radius fractures in the osteoporotic patient. Her publications have affected the practice of hand surgeons nationally in her promotion of early screening for osteoporosis after a distal radius fracture and prevention of subsequent fractures in both the female and male osteoporotic patient. Her talk was followed by an engaging question and answer discussion on osteoporosis screening practices and role of the orthopaedic surgeon in pursuing them.

In her second lecture, “The Boston Marathon Bombing: a Hand Surgeon’s Perspective,” Dr. Rozental gave a stirring account of her experience at Beth Israel following the 2013 terrorist attack. She reflected on the immense coordination, man-power and teamwork that it took to run 10 ORs emergently on a holiday in order to triage the severe orthopaedic injuries that day. In particular she spoke of the outflow of support from across the country and the unique relationship that she developed with her patients injured by the bombings, who supported her as she crossed the finish line at the 2014 Boston Marathon.

The University of Pennsylvania Department of Orthopaedics was truly fortunate to have Dr. Tamara Rozental MD as the Leo Leung Endowed Lectureship Visiting Professor, and we look forward to continued collaboration in the future.
The University of Pennsylvania Department of Orthopaedic Surgery was honored to welcome Dr. Stuart Weinstein, the Ignacio V. Ponseti Chair and Professor of Orthopaedic Surgery and Pediatrics at the University of Iowa, as a visiting professor this past February. Dr. Weinstein is one of the true giants of the field, having served as president of the AOA, ABOS, AAOS, and POSNA. After graduating from University of Washington School of Medicine, Dr. Weinstein spent the entirety of his orthopaedic career at the University of Iowa, a career that spans five decades. As one of the leaders in the field of Pediatric Orthopaedic Surgery, Dr. Weinstein has an overwhelming resume and wide array of talents and interests. He has published numerous articles, chapters, and books with a focus on pediatric spinal deformity, children's hip and foot problems, and the natural history and long-term outcome of pediatric musculoskeletal conditions. He has remained involved in the national organizations that govern orthopaedic surgeons and is the current Chairman of the Orthopaedic Political Action Committee.

To begin his enlightening visit, Dr. L. Scott Levin began with a formal introduction of our speaker, highlighting his many accomplishments inside and out of academia. Dr. Kristy Weber, a former resident of Dr. Weinstein’s, then introduced him with several anecdotes of his effect on her life and career. Dr. Weinstein then proceeded to give two fantastic presentations, the first of which was entitled, "DDH: What I Have Learned over the Last 39 Years." Drawing on his wealth of personal experience, Dr. Weinstein detailed the pitfalls, challenges, and successes of how we care for the patient with Developmental Dysplasia of the Hip, and how it has changed over the years.

The second talk of the morning was as unique as it was enlightening, “Advocacy: Why is it Important?” As the current Chairman of the Orthopaedic Political Action Committee, Dr. Weinstein was able to give us an inside view of the workings of the Orthopaedic PAC and its role in advocating for orthopaedic surgeons with the government. With a thorough history of the Orthopaedic PAC’s contributions to the field and its members, he illustrated the importance of being involved in health care policy and the coming changes that would be affecting all orthopaedic surgeons. His personal expertise and role in the national spotlight were on display, affording the audience an exclusive inside look at the national debate that is shaping health care policy.

Following these lectures, Dr. Weinstein met with the residents to go over cases and provide his unique expertise on pediatric surgical cases. In this personal setting, Dr. Weinstein walked the audience through his approach to several complicated pediatric cases. His experience was on display as he took residents through the appropriate workup, treatment and follow up of both common and rare conditions, showcasing a surfeit of expertise that comes from a long and illustrious career in the field of spine care.

The University of Pennsylvania Department of Orthopaedic Surgery was honored to host Dr. Stuart Weinstein as a Visiting Professor this year. His visit was both an honor and a privilege for the department, and we hope his presence is only the start of a successful and mutually beneficial relationship.
It is with pride and honor that the University of Pennsylvania Department of Orthopaedic Surgery welcomed Dr. John Callaghan, the Lawrence and Marilyn Dorr Chair of the Department of Orthopaedics and Bioengineering at the University of Iowa to celebrate the Tronzo lectureship.

The Tronzo lectureship was founded in 2003 by Dr. Raymond Tronzo and his wife Diana with the goal of establishing a forum for faculty and resident education on novel arthroplasty concepts. Dr. Tronzo, a native of Punxsutawney, PA graduated with a BS and an MA from Penn State University. After graduating from Jefferson Medical College, he completed his orthopaedic residency at the Philadelphia General Hospital under the mentorship of Dr. Anthony DePalma and Dr. John Royal Moore. Dr. Tronzo joined the staff at the University of Pennsylvania Department of Orthopaedic Surgery in 1968. Dr. Tronzo’s accomplishments include the first surgical textbook dedicated to the hip titled “Surgery of the Hip Joint,” as well as the Tronzo prosthesis, which pioneered press fitting and the concept of cementless biologic fixation. Dr. Tronzo was known at Penn for his surgical talent as well as his insatiable desire to teach, which is still illustrated today by the lectureship he developed.

Dr. Callaghan was an obvious choice for the 10th Annual Raymond G. Tronzo Lectureship. A graduate of the University of Notre Dame in South Bend (IN) and Loyola Medical School in Chicago (IL), Dr. Callaghan completed his orthopaedic residency at the University of Iowa. He subsequently went on to pursue a fellowship in hip and knee arthroplasty at the Hospital for Special Surgery. A world-renowned researcher, Dr. Callaghan has authored or co-authored nearly 300 peer-reviewed publications in addition to numerous honors. A respected and admired surgeon, he has been elected to many leadership roles including President of the American Academy of Orthopaedic Surgeons, the American Association of Hip and Knee Surgeon and the Hip Society as well as chair of the OREF amongst many other leadership roles. His dedication to advancing his field and teaching his colleagues has been evident throughout his career, and it was once again illustrated during his talks.

On Thursday morning, Dr. Callaghan began with a captivating lecture on the debated topic of mobile bearing use in total knee arthroplasty. Dr. Callaghan presented an immense body of data as well as his esteemed opinion on the topic leading to a highly educational faculty discussion at the conclusion of his first talk. Dr. L. Scott Levin then proceeded to deliver a heartfelt introduction, highlighting the tremendous contributions of Dr. Callaghan, while also sharing the Department’s gratitude for his military service. Dr. Callaghan’s second lecture gave an amazing historical perspective on total hip arthroplasty. Following a remarkable homage to Sir John Charnley, Dr. Callaghan focused on the evolution in implant designs and associated outcomes since the original Charnley implant.

Doctors Paul Lotke, Charles Nelson, Craig Israelite, Gwo-Chin Lee and Neil Sheth led the discussion that followed with many insightful questions.

Following the lectures, Dr. Callaghan hosted the faculty and residents at the Human Tissue Lab to demonstrate his approach for the Extended Trochanteric Osteotomy via a posterior exposure. His passion for teaching was evident throughout the prosection, as he exposed tips and tricks with the residents for every aspect of the surgical dissection from careful skin handling to management of the short external rotators and his technique for the osteotomy and its repair. The prosection concluded with several questions from residents and faculty during which Dr. Callaghan shared his wealth of knowledge and experience to the captivated audience.

The University of Pennsylvania Department of Orthopaedic Surgery was honored to invite Dr. John Callaghan, as the tremendous academic discussions sparked by his thought-provoking lectures and prosection were the ideal way to honor Dr. Raymond G. Tronzo’s vision for his lectureship.
The University of Pennsylvania Department of Orthopaedics was honored to welcome Dr. William Levine for the 15th annual Dr. Ernest J. Gentchos Lectureship this past April. Dr. Levine performed his Orthopaedic residency at New England Medical Center, and completed fellowships at Columbia-Presbyterian Medical Center (Shoulder and Elbow Surgery) and the University of Maryland (Sports Medicine), as well as serving as an ASES traveling fellow in 2003. As one of the leaders in the field, Dr. Levine has published numerous articles, chapters, and books on sports and shoulder & elbow surgery, and is currently involved in numerous clinical projects. Dr. Levine’s commitment through education and leadership roles has led to countless contributions in advancing the field of orthopaedic surgery. He is on the Board of Directors of the American Board of Orthopedic Surgery and serves as Deputy Editor for the Journal of the American Academy of Orthopedic Surgeons. He is also the head team physician at Columbia University. At Columbia University College of Physicians and Surgeons, Dr. Levine served as Program Director from 2002 to 2014, at which point he was appointed as the Frank E. Stinchfield Professor and Chairman of Clinical Orthopaedic Surgery.

The Ernest J. Gentchos Lectureship is a proud tradition at Penn Orthopaedics established in 2001 to honor the innumerable contributions of our own Dr. Ernest Gentchos. Born and raised in a village of Northern Greece, Dr. Gentchos attended medical school at the St. Louis University School of Medicine. Upon graduation, he served in the medical battalion with the US Army Air Cavalry Division during the Vietnam War, and then completed his residency training in orthopaedic surgery at the University of Pennsylvania. He elected to stay on as faculty, advocating that superior patient care relies on studying one’s patient, keeping an open mind, and challenging every idea. In addition to his countless academic achievements and clinical contributions, Dr. Gentchos carried his humanitarian passions outside the realm of medicine, through his establishment of several endowed scholarship. Dr. Gentchos sponsors several medical school, college, and high school students, and maintains that the greatest gift you can give anyone is that of education. With an ever-present thirst for knowledge, Dr. Gentchos’ mantra of “What did you learn today?” serves as a reminder that we are forever students in both Orthopaedics and life. In dedication to his unyielding enthusiasm for learning, teaching, and serving the orthopaedic community, the Penn Orthopaedic family was proud to host Dr. Levine as our 15th annual Gentchos Visiting Professor.

The morning began with introductions by Drs. David Glaser and L. Scott Levin. With Dr. Gentchos in the front row, the legacy of the lectureship was detailed and Dr. Levine was formally welcomed to the podium. Dr. Levine began the morning with a lecture entitled “How to be a Successful Resident.” With input from his own institution, our faculty and countless leaders and residents around the country, he elucidated what it takes to succeed as a young Orthopaedic trainee. Having prepared a talk tailored not only to Orthopaedics but the University of Pennsylvania community, Dr. Levine hosted an interactive forum with the faculty and residents detailing the path to personal and professional success. He focused on personal qualities that must be fostered in the workplace, including integrity, hard work and superior communication skills. With input from the majority of the faculty present, he was able to showcase what he’s learned in the course of his career, as a resident, faculty member, Program Director and Department Chairman.

Dr. Levine then took the opportunity to detail his thoughts of the field of Orthopaedics itself with a lecture entitled “Orthopaedic Education 2020: Challenges and Opportunities.” With the majority of the faculty and residents present, Dr. Levine detailed the changes in our field in the past 15 years and the breakneck speed at which changes are occurring, expected to only increase in the next five years. With emphases on resident training milestones, physician reimbursement and duty hour restrictions, he advocated for validated training models and the improvements needed to prepare the next generation of Orthopaedic Surgeons.
Following the lectures, Dr. Levine hosted the residents, fellows and faculty in a prosection in the Penn Human Tissue Laboratory. Beginning with an arthroscopic approach to the shoulder, he demonstrated common techniques and lectured on the myriad approaches and procedures possible from the lateral decubitus position. He then took the group through his preferred method of an open Latarjet procedure, employing the latest surgical techniques in the field and debating the merits of open vs arthroscopic approaches. After the commencement of clinical duties, Dr. Levine then met with several faculty members, including Dr. Lou Soslowsky, Director of the Mckay Orthopaedic Research Laboratory, and Dr. L. Scott Levin, Chairman of the University of Pennsylvania Department of Orthopaedics, culminating in a tour of the Penn Musculoskeletal Center.

The University of Pennsylvania Department of Orthopaedics was truly fortunate to have Columbia University’s Chairman Dr. William Levine as a Visiting Professor for the 15th annual Ernest J. Gentchos lectureship, and we greatly anticipate future collaboration between our departments.
Full List of Visiting Professors

4/24/14
Dr. Andrew Burgess (University of Texas Houston, Trauma)
Lectureship: 2014 Dr. Clifford Turen Memorial Lectureship
Topics: Crash Research and its Effects on Orthopaedics;
Pelvic Fractures: Acute Management
Dissection: Fasciotomies: Fine Points

6/12/14
Dr. Alison Toth (Duke, Sports)
Lectureship: 2014 Dr. Gentchos Lectureship
Topics: Biologic Targeted Treatment in Orthopaedic Surgery;
Tendon Reconstruction Using Grafts
Dissection: Shoulder Arthroscopy: Rotator Cuff Reconstruction Using Grafts

6/26/14
Dr. Howard An (Rush, Spine)
Lectureship: 2014-2015 Visiting Professor Lecture Series, AOSpine
Topics: Surgical Management of Cervical Radiculopathy & Myelopathy; Lumbar Spine Disorders: Current Treatment and Basic Science Research
Dissection: Posterior Cervical Laminectomy, Fusion, Laminoplasty

7/24/14
Dr. James Nunley (Duke, F&A)
Lectureship: 2014 June C. Wapner Memorial Lectureship
Topics: Athletic Stress Fractures of the Foot & Ankle; With So Many Total Ankles, How Do I Decide What to Use?
Dissection: Anatomy of the Hindfoot

10/2/14
Dr. Christopher Shaffrey (University of Virginia, Spine)
Lectureship: 2014-2015 Visiting Professor Lecture Series, AOSpine
Topics: When Does Lumbar Disease Become Spinal Deformity?: Evaluation and Management of Cervical Spine Deformity
Dissection: Principles of Spine Osteotomies: Simple to Complex

10/30/14
Dr. Sigurd Berven (University of California San Francisco, Spine)
Lectureship: 2014-2015 Visiting Professor Lecture Series, AOSpine
Topics: Measuring Quality and Value in Orthopaedics and Spine Surgery; Evaluating New Technologies in Orthopaedics
Dissection: Direct Lateral Approach to the Spine

11/6/14
Dr. Franklin Sim (Mayo Clinic, Tumor)
Lectureship: 2014-2015 Visiting Professor Lecture Series
Topics: Advances and Challenges in Musculoskeletal Oncology; New Concepts in the Treatment of Sacropelvic Tumors
Dissection: Anatomic Dissection of the Pelvis and Sacrum

12/4/14
Dr. Benjamin Kibler (Kentucky, Sports)
Lectureship: 2014-2015 Visiting Professor Lecture Series
Topics: Acromioclavicular and Clavicle Injuries; The Role of the Scapula in Shoulder Injuries
Dissection: Anatomic Acromioclavicular and Coracocalvicular Ligament Reconstruction

1/22/14
Dr. Marco Innocenti (Italy, Hand & Microsurgery)
Lectureship: 2014-2015 Visiting Professor Lecture Series
Topics: Vascularized Bone Grafts for Reconstruction; Propeller Flaps
Dissection: Open Demonstration of Lower Extremity Gastrocnemius and Propeller Flaps

1/29/15
Dr. Tamara Rozental (Harvard, Hand)
Lectureship: 2014 Dr. Leo Leung Memorial Lectureship
Topics: Distal Radius Fractures; The Boston Marathon Bombing: A Hand Surgeon’s Perspective
Dissection: Open Demonstration of Distal Radius and Radial Head Fixation

2/5/15
Dr. Stuart Weinstein (University of Iowa, Pediatrics)
Lectureship: 2014-2015 Visiting Professor Lecture Series
Topics: DDH: What I Have Learned Over the Last 39 Years; Advocacy: Why is It Important?
Case Presentations: Pediatric Hip and Spine Disorders

3/5/15
Dr. John Callaghan (University of Iowa, Joints)
Lectureship: 2015 Tronzo Lectureship
Topics: Mobile Bearing TKA; Why Did We Leave the Charnley THA?
Dissection: Extended Trochanteric Osteotomy

4/2/15
Dr. William Levine (Columbia University, S&E)
Lectureship: 2015 Dr. Gentchos Lectureship
Topics: How to be a Successful Resident; Orthopaedic Education 2020: Challenges and Opportunities
Dissection: Arthroscopic Shoulder Instability Repair with Open Latarjet
Under the direction of Dr. Lou Soslowsky, PhD, the Penn Center for Musculoskeletal Disorders (PCMD) held their annual Scientific Symposium this past November in the BRB Auditorium of the University of Pennsylvania. Designed to showcase and support the academic pursuits of PCMD members, the Symposium drew hundreds of participants and visitors from across the country to celebrate the work being done by the researchers at Penn.

The morning began with a session headed by new members, moderated by Rob Mauck, PhD. Speakers included Carla R. Scanzello, MD, PhD (A Role for CC-Chemokine Receptor 7 (CCR7) in Knee Osteoarthritis: Impact on Joint Structure and Function); D. Kacy Cullen, PhD (Tissue Engineering Strategies for Sensorimotor Regeneration and Functional Recovery following Neurotrauma); and Harvey E. Smith, MD (Tissue Engineered Constructs in the Treatment of Intervertebral Disc Degeneration).

The morning continued with lectures by affiliate PCMD members, moderated by Lou Soslowsky, PhD. Talks included "Regulation of Water Transport by Cells of Intervertebral Disc," by Irving M. Shapiro, BDS, PhD; "Contributions of ACTN-3 Genotype in Musculoskeletal Development of Malocclusion and Temporomandibular Joint Disorders," by James Scioté, DDS, PhD, MS; and "Chronic PTHrP Treatment Switches PTH Receptor Signaling in Chondrocytes," by Bin Wang PhD.

The lunch session coincided with poster presentations by all PCMD members, showcasing their work over the past year, which then led directly into the afternoon lecture session, moderated by Felix Wehrli, PhD. Sessions included "Intra-Articular Injection of a Nonsteroidal Anti-Inflammatory Drug has no Detrimental Effects on Joint Mechanics in a Rat Model," by Andrew F. Kuntz, MD; "Anabolic Treatment for Radiotherapy-Induced Osteoporosis," by Ling Qin, PhD; and "The Development of an In Vivo and In Vitro Derived Tissue Engineered Cartilage for Pediatric Airway Reconstruction in a Rabbit Model," by Ian N. Jacobs, MD.

The afternoon session concluded with an address by the keynote speaker, Dr. Henry M. Kronenberg, MD, moderated by Eileen Shore, PhD. As Chief of the Endocrine division at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School, as well as the current Vice President of the International Bone and Mineral Society (IBMS), Dr. Kronenberg has extensive experience in the field of bone and mineral metabolism and signaling. His keynote speech,
“How PTHrP regulates chondrocyte differentiation,” was a detailed look into what he and his team have accomplished at the forefront of bone research. After an enthusiastic question and answer session, Dr. Kronenberg then presided over the award announcements for posters and presentations given. The symposium was roundly judged an enormous success, and promises to be a highly regarded function and point of pride for the Penn Center for Musculoskeletal Disorders in years to come.
The University of Pennsylvania was honored to host the 2014 ASES European Traveling Fellows, Lionel Neyton, MD and Stefano Carbone, MD. The ASES European Traveling Fellow program is a unique opportunity for European surgeons with a clinical emphasis on shoulder and elbow surgery to share their research and clinical experiences with several major American training centers biannually over a 4 week period in autumn. Drs. Neyton and Carbone, despite a rigorous travel schedule and being away from home for several weeks before their final stop in Philadelphia, were enthusiastic to spend time with the Penn Shoulder and Elbow faculty this past October.

Beginning with a joint discourse among faculty, fellows, and residents from Penn and other Philadelphia-area orthopaedic programs, the two visiting fellows shared their experiences and training histories with their American brethren. Differences in training requirements and practice models were discussed, as well as emerging evidence between the international communities. Despite their pressing travel arrangements, Drs. Neyton and Carbone were able to spend time with clinicians in the shoulder and elbow group and discuss evolving paradigms in surgical care and several complicated cases. The two fellows were able to finish their visit with a tour and research meeting with Lou Soslowsky, PhD, Director of the McKay Orthopaedic Research Laboratory and Fairhill Professor of Orthopaedic Surgery. With a research emphasis on biomechanics of tendons, ligaments and the rotator cuff, Dr. Soslowsky was able to share his experience in research with the visiting fellows and gain insight into their experience with academic medicine.

The few days that Drs. Neyton and Carbone were able to spend with the Department of Orthopaedic Surgery were invaluable for all parties involved, and we hope to have continued collaboration with them and the ASES European Traveling Fellow program in the years to come.
This past January the University of Pennsylvania Department of Orthopaedics and Sports Medicine division were honored to host the Penn Orthopaedics 2015 Throwing Symposium. Advances in Throwing: Latest on Injury Prevention and Performance Optimization was developed with the goal of inviting athletic trainers, coaches, physical therapists and physicians from across the country to discuss innovative techniques in caring for the throwing athlete. This one day conference, held in the heart of University City on Penn’s campus, featured specialists from Penn and across the region discussing the key issues facing those involved in the musculoskeletal care of throwing athletes.

The event began with remarks highlighting the unique collegial environment of the Penn Throwing Center and its goal of combining specialists to effectively treat patients with musculoskeletal disorders resulting from throwing injuries. Discussions were held highlighting the normal and abnormal anatomy of throwing athletes, as well as common injury patterns and the options of surgical and non-surgical treatment pathways. The Penn Orthopaedics department, with Sports Medicine Chief Brian Sennett, MD and partners John Kelly, MD, Jim Carey, MD, Miltiadis Zgonis, MD, and Russell Huffman, MD, were joined by several speakers involved in the care of throwing disorders, including athletic trainers, physical therapists, and coaches.

Highlights of the day included lectures given by the two invited keynote speakers, as pictured. First was a speech by James P. Bradley, MD, entitled “Superior Labral Anterior-Posterior (SLAP) and Posterior Instability in Thrown.’” As a founding partner of Burke and Bradley Orthopaedics in Pittsburgh, Pennsylvania, Dr. Bradley is the Head Team Orthopaedic Surgeon for the Pittsburgh Steelers, and has a wealth of experience in the treatment of throwing athletes and the issues involved in surgical management.

As a conclusion to the day, the second keynote speaker, Craig D. Morgan, MD, gave a lecture entitled “The Disabled Throwing Shoulder- What I’ve learned in 30 years.” As a founding partner of the Morgan Kalman Clinic in Wilmington, Delaware, Dr. Morgan showcased the evolving pathways in the care of throwing disorders and his personal experience the management of musculoskeletal disorders involving throwers.

Penn Orthopaedics was delighted to welcome Drs. Bradley and Morgan as the keynote speakers of the Penn Orthopaedics 2015 Throwing Symposium. The event was uniformly judged a resounding success and a testament to Penn Orthopaedic’s commitment to improving patient care and clinical education.
On February 20 & 21, 2015 the University of Pennsylvania Department of Orthopaedic Surgery hosted the Perry Initiative to include both a Medical Student Outreach Program and High School Student Outreach Program. The Perry Initiative mission is to inspire young women to pursue careers in engineering and orthopaedics, as they are fields in which women are under-represented. It is named after Dr. Jacqueline Perry (1919-2013). She was one of the first women in orthopedics, but more importantly, she dedicated her life to research, education and providing excellent orthopaedic care to children and adults with neuromuscular disorders such as cerebral palsy or deficits following traumatic brain injury or stroke. Leaders like Dr. Perry are few and far between and she is deeply missed, but her legacy continues. The Perry Initiative was founded in 2009 by Dr. Jenni Buckley, a mechanical engineer currently at the University of Delaware, and Dr Lisa Lattanza, an orthopaedic upper extremity surgeon at University of California, San Francisco. Since its inception, their program has grown exponentially and is currently run by a staff of engineers based out of the University of Delaware.

This is the second time Penn has hosted the Perry Initiative, and the events were well attended. Medical students from multiple schools in the Philadelphia area were in attendance on Friday evening. The students were introduced to the lives of women orthopaedic surgeons, both in training and in practice. They participated in hands on workshops focused on intramedullary and external fixation of femur fractures, and the evening commenced with an interactive panel discussion. High school students from central and southeastern Pennsylvania, New Jersey, and Delaware were in attendance on Saturday. The program included workshops on suturing and knot tying, external fixation, intramedullary nailing, scoliosis correction, pelvic fracture fixation and knee arthroscopy. The engineers shared with the group the pathway to become an engineer and the many opportunities that exist within this diverse field. The orthopaedic surgeons shared the pathway to becoming a physician and then an orthopedic surgeon. Volunteers for the event included women orthopaedic residents and students from U. Pennsylvania (5), Drexel (1) and faculty from U. Pennsylvania (4), Thomas Jefferson (1), and Drexel (1). A great time was had by all in attendance. The Perry Initiative is a 501c3 non-profit funded primarily via donation. More information can be found at: http://perryinitiative.org/ and donations are accepted via the website.
The opening of the Penn Musculoskeletal Center at 3737 Market Street this year was marked by the dedication of the “Tony Searles Casting Room.” As highlighted in UPOJ Volume 24, the Penn Department of Orthopaedics lost a dear friend and role model with the passing of Anthony Searles on February 28th, 2014. Over the course of a four decade career at the Hospital of the University of Pennsylvania, “Dr. Tony” mentored countless residents, students and patients in the art of casting and fracture management. With a deft hand and gregarious attitude, Tony presided over the HUP casting room with an easygoing manner that put patients and trainees alike at ease. His skill with immobilization techniques and patients was readily apparent, and it was with great satisfaction the department unanimously decided to dedicate the new casting room in his memory. As Penn Orthopaedics continues to move forward in its mission to provide exemplary clinical care, we look back in appreciation for the life and service of Tony Searles.
Penn Orthopaedics is a proud participant and supporter of the Philadelphia Orthopaedic Society (POS), which celebrated its 100th anniversary this past year. In a city with as proud a tradition of advancing orthopaedic care as Philadelphia, the Philadelphia Orthopaedic Society is committed to advancing the field of Orthopaedic Surgery. As detailed in the mission statement, POS exists to “devote its resources to promote, encourage, foster and advance the art and science of orthopaedic Surgery… [and] to establish a forum for free discussion and teaching of orthopaedic methods and principles among the members.”

POS meets approximately once a month over the course of the year, hosting experts in the field of orthopaedic surgery from across the country in a forum dedicated to residents, fellows and attendings from the Philadelphia area. These lecturers bring a wealth of experience and wisdom from the forefront of medicine, and allow for a free discussion of ideas and techniques on a particular area of expertise. Speakers from this past year include Mark W. Pagnano, MD, from the Mayo Clinic in Rochester, Minnesota; Carlos Lavernia, MD, from Larkin Hospital in Miami, Florida; John C. Richmond, MD, from New England Baptist Hospital in Boston, Massachusetts; Mininder S. Kocher, MD, MPH, from Harvard Medical School/Boston Children’s Hospital in Boston, Massachusetts; and Lawrence Lenke, MD, from Washington University School of Medicine in St. Louis, Missouri.

Additionally, the society hosts an annual “Resident Bowl” at the end of each academic year, pitting a chief resident from each of the Philadelphia area training centers (Penn, Albert Einstein, Drexel, PCOM, Temple, and Jefferson) against each other in a congenial battle of orthopaedic knowledge. Penn’s own Adam Griska, MD, battled valiantly this year in an attempt to secure the Silver Bowl (pictured), only to be topped by Chukwu Emeka Nwodim, MD, from Temple University.

With a strong showing every month by Penn residents and faculty, POS meetings are an excellent opportunity to network, gather and gain insight into advances in the field of orthopaedic surgery. Penn Orthopaedics is proud to support and participate in activities hosted by the Philadelphia Orthopaedic Society, and hope to continue the tradition of partnership in the future.
This past April, coinciding with the Penn Relays, the University of Pennsylvania Department of Orthopaedic Surgery was thrilled to host the Penn Orthopaedics 2015 Cartilage Repair Symposium, which recorded its highest attendance ever at nearly one hundred and seventy participants from all over the United States and the World. New Directions in Osteochondral Repair and Regeneration was a multidisciplinary event geared toward medical professionals, engineers, and scientists with an interest in the latest techniques in cartilage biology and repair. With a focus on translational basic science, topics included various areas of investigation such as cartilage and fibrocartilage biology, biomaterials, stem cell use in tissue engineering, novel imaging modalities, and animal models, as well as the latest developments in clinical care and rehabilitation paradigms.

Invited keynote speakers included Elizaveta Kon, MD, from the Laboratory for Biomechanics and Technological Innovation, Rizzoli Orthopaedic Institute, Bologna, Italy; C. Wayne McIlwraith, PhD, DSC, from Colorado State University; Scott A. Rodeo, MD, from the Hospital for Special Surgery, New York, NY; and Rocky S. Tuan, PhD, from the University of Pittsburgh. The day began with remarks by the course directors, James L. Carey, MD, MPH, and Robert L. Mauck, PhD, welcoming the audience to Philadelphia and the symposium. Both alluded to the past three year’s symposiums and the continued success of the event, in addition to the advances made in the field in recent years. The day then continued with sessions of lectures and discussions, including “Cells and Materials for Osteochondral Repair,” moderated by Robert L. Mauck, PhD; “New Ideas in Cartilage Repair,” with moderator Suzanne Maher, PhD; and “Animal Models for Osteochondral Repair,” moderated by Thomas P. Schaer, VMD. A keynote speech was then given by Elizaveta Kon, MD, entitled “Historical
Perspective and Surgical Technique: Biometric Scaffolds for Osteochondral Repair,” moderated by James L. Carey, MD, MPH. The day concluded with a trip to the Human Tissue Lab, organized by Dr. Miltiadis Zgonis, where a group of surgeons and scientists participated in cadaver-based skill sessions. Participants were able to view these lectures in person and practice in small group sessions on the cadavers.

The next day, the symposium began with further lecture sessions, including “Translating Basic Science to Clinical Science,” moderated by Robert L. Mauck, PhD; “Surgical Techniques: Treatment of Large Osteochondral Lesions,” moderated by Brian J. Sennett, MD; and “Rehabilitations and Outcomes,” with moderator Lawrence Wells, MD. Following closing remarks by Drs. Mauck and Carey, the group then walked to Franklin Field for an afternoon at the Penn Relays. With world-class leadership, stimulating lectures and robust discussion sessions, the symposium was a boon for all those in attendance and promises to be a continued success for years to come.
Chief Residents

Nicole S. Belkin, MD*
Hometown: Port St. Lucie, FL
*Undergraduate: University of Florida
Medical School: University of Florida College of Medicine
Future directions: Academic sports medicine with special interest in caring for rugby athletes
Highlights: Personal and Professional mentorship and support received from sports and shoulder faculty.

John “Gabe” Horneff, MD
Hometown: Westmont, NJ
Undergraduate: Rutgers University
Medical School: University of Pennsylvania
Fellowship: Shoulder and Elbow, Rothman Institute at Thomas Jefferson University
Future directions: Up?
Highlights: Great magazine. Love it.

Kevin J. McHale, MD
Hometown: Sea Isle City, NJ
Undergraduate: La Salle University
Medical School: Jefferson Medical College
Fellowship: Harvard/Massachusetts General Hospital Sports Medicine Fellowship
Future directions: Career in orthopaedic sports medicine
Highlights: The countless hours spent with my co-residents in and out of the hospital, our attendings' dedication to resident education, yearly sports rotations, HUP trauma rotations, and time at home with my wife Kristen and son Luke

Christos D. Photopoulos, MD
Hometown: Sharon, MA
Undergraduate: McGill University
Medical School: Dartmouth Medical School
Fellowship: Kerlan-Jobe Orthopaedic Clinic
Future directions: Sports Medicine
Matthew P. Sullivan, MD
Hometown: Medfield, MA
Undergraduate: Tufts University
Medical School: Boston University School of Medicine
Fellowship: Orthopaedic Trauma - Harborview Medical Center
Future directions: Orthopaedic Trauma Surgery
Highlights: Starting a family with my beautiful wife and baby boy in Philadelphia. Being a part of this organization dedicated to helping sick patients and learning how to be a surgeon from the best and most talented physicians. Thank you Drs. Levin, Israelite, Mehta, Ahn, Donegan, Esterhai, and all of the other faculty members that have helped me get where I am today.

Ryan M. Taylor, MD
Hometown: San Antonio
Undergraduate: Dartmouth College
Medical School: UT Southwestern
Fellowship: UT Houston
Future directions: After completing my orthopaedic traumatology fellowship in Houston I hope to stay in Texas and go into practice where I can be close to my family and still work with residents and play a role in the education of future orthopaedic surgeons.
Highlights: Marrying my beautiful wife Adriana during my 4th year was by the far the pinnacle of my time in Philadelphia. I also will never forget the lifelong colleagues, friends, and family I have encountered during my time in Philadelphia.

Stephen J. Torres, MD
Hometown: Ocala, Florida
Undergraduate: University of Florida
Medical School: Albert Einstein College of Medicine
Future directions: General Orthopaedics at Andrews Air Force Base in Washington, D.C.
Highlights: Everyday brought something new. I enjoyed my time in Philadelphia and outside of the hospital.

Pramod B. Voleti, MD*
Hometown: Niskayuna, New York
Undergraduate: Princeton University, A.B. in Molecular Biology
Medical School: SUNY Downstate College of Medicine
Fellowship: Sports Medicine and Shoulder, Hospital for Special Surgery
Future directions: Academic sports medicine
Highlights: Married my wife Smitha; worked with outstanding attendings, fellows, and residents; completed research fellowship in Dr. Soslowsky’s lab
Current Residents

**Clinical Year 4**

- **Paul Max Courtney, MD**
  Undergraduate: Washington & Lee University
  Medical School: Georgetown School of Medicine

- **Stephen Y. Liu, MD**
  Undergraduate: Tufts University
  Medical School: Tufts University School of Medicine

- **Michael H. McGraw, MD**
  Undergraduate: Howard University
  Medical School: Howard University College of Medicine

- **Christopher M. Melnic, MD**
  Undergraduate: Boston College
  Medical School: Tufts University School of Medicine

- **Andrew H. Milby, MD**
  Undergraduate: Washington University
  Medical School: University of Pennsylvania School of Medicine

- **Nicholas Pulos, MD**
  Undergraduate: University of Pennsylvania
  Medical School: University of Pennsylvania School of Medicine

- **Jonathan B. Slaughter, MD**
  Undergraduate: University of Pennsylvania
  Medical School: Boonshoft School of Medicine at Wright State University

- **Sarah M. Yannascoli, MD**
  Undergraduate: Cornell University
  Medical School: Albert Einstein College of Medicine

*Six-Year Research Track*
CURRENT RESIDENTS

VOLUME 25, JUNE 2015

Clinical Year 3

Jason B. Anari, MD

Undergraduate:
The College of New Jersey

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

Joshua Gordon, MD*

Undergraduate:
Pitzer College

Medical School:
David Geffen
School of Medicine
at UCLA

Philip A. Saville, MD

Undergraduate:
University of Leicester

Medical School:
University of Leicester
(England, UK)

Vishal Saxena, MD*

Undergraduate:
Northwestern University

Medical School:
Pritzker
School of Medicine at the
University of Chicago

Russell N. Stitzlein, MD

Undergraduate:
Miami University

Medical School:
Cleveland Clinic
Lerner College of Medicine

Michael T. Talerico, MD

Undergraduate:
University of Notre Dame

Medical School:
Saint Louis University
School of Medicine

Nathan A. Wigner, MD, PhD

Undergraduate:
North Carolina State University

Medical School:
Boston University
School of Medicine

Chase Woodward, MD, MPH

Undergraduate:
Northwestern University

Medical School:
Feinberg School of Medicine
at Northwestern University

Research Year

Tyler R. Morris, MD*

Undergraduate:
The University of Pennsylvania

Medical School:
Drexel University
College of Medicine

Alexander L. Neuwirth, MD*

Undergraduate:
Rutgers University

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

* Six-Year Research Track
Clinical Year 2

Keith P. Connolly, MD

Undergraduate: Michigan State University

Medical School: University of Central Florida College 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

Daniel P. Lim, MD

Undergraduate: University of Southern California

Medical School: Keck School of Medicine at USC

Joshua C. Rozell, MD

Undergraduate: Emory University

Medical School: Drexel University College of Medicine

Joshua T. Steere, MD

Undergraduate: Creighton University

Medical School: Stritch School of Medicine at Loyola University Chicago

Chia H. Wu, MD, MBA

Undergraduate: University of Pennsylvania

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

Zachary R. Zimmer, MD

Undergraduate: Colgate University

Medical School: Stony Brook University School of Medicine

* Six-Year Research Track
Clinical Year 1

Blair S. Ashley, MD*
Undergraduate: The College of William and Mary
Medical School: University of Pittsburgh School of Medicine

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: Massachusetts Institute of Technology
Medical School: Harvard Medical School

Jonathan R. Dattilo, MD
Undergraduate: Northwestern University
Medical School: Johns Hopkins University School of Medicine

Daniel Gittings, MD*
Undergraduate: Providence College
Medical School: Boston University School 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

* Six-Year Research Track
With the opening of the Penn Musculoskeletal Center and the John Pryor Trauma Center, the Department of Orthopaedics has undergone many changes in the past year, and the residency program is no exception. With input from the faculty and program directors, our Administrative Chief Residents (Gabe Horneff, MD, Christos Photopoulos, MD, and Ryan Taylor, MD), have been proponents in the move to a four hour protected education Grand Rounds format every Thursday morning. A rigorous, two year curriculum has been implemented with the goal of consolidating resident education in a protected format in order to highlight important concepts and emerging literature in Orthopaedics. The new curriculum includes twice-monthly sessions in the human tissue lab with cadaveric and sawbones materials to practice hands-on surgical techniques, as well as twelve annual Visiting Professors from national and internationally renowned institutions. With frequent lectures from residents and attendings in every specialty, the new curriculum has been a resounding success in the first year of its application and will be carried forward as Penn Orthopaedics transitions to its new flagship location in Penn Medicine University City.

In addition, residents this past year were awarded a personalized thyroid shield for protection and safety during fluoroscopic imaging. With increasing case numbers and an emphasis on trauma fixation, the thyroid shields enable residents to become more involved in cases in and out of the operating room.

With the goal of keeping Penn Orthopaedics technologically advanced and competitive, all residents are now provided with a new iPhone and iPad mini. These devices come updated with hundreds of journal articles, reviews, previous lectures, and presentations, in a continuing effort to provide centralized education resources to all residents. They have quickly become vital to resident education and are a frequent fixture in grand rounds and morning conferences.
“What did you learn today?” - Dr. Ernest Gentchos

That is the question we should be asking ourselves before we close our eyes every night. Did we make the most of our time? Did we get everything out of the day that we possibly could?

The days can be long, but the years go by fast. It’s an old adage that never really quite hits home until you are on the other end, looking back at where it all started. For the three of us and the rest of our graduating class, the last five years of residency have absolutely flown by and seem to be gaining speed with each passing week.

As chief residents we have had a unique perspective on the program as it has developed and grown over the last year. There have been quite a few changes since we arrived in June of 2010. We came to Penn Orthopaedics just as Dr. Levin was getting his feet underneath him as the new Chairman, and to say he has hit the ground running is an understatement. His vision combined with the input and leadership of our triumvirate of Program Directors has witnessed significant faculty expansion, the creation of a new Musculoskeletal Center, and the recent transition of an entire Level I Trauma Center. Through all of these changes, we have continued to develop a residency program that offers a strong foundation in the vocation that we have chosen for ourselves.

As chief residents, we feel that one of the biggest contributions we have made this year is in our commitment to the residents and their education. The institution of weekly Thursday morning academic core curriculum sessions has given the residents protected academic time without having to worry about the daily grind of clinical duties. It has not been smooth sailing by any stretch, but we feel it has been an overall success. In addition to the involvement of our own faculty and residents, we have managed to have world-class visiting professors from all over the globe. The Human Tissue Lab has been seamlessly integrated into these visits with visiting professor prosections, dedicated regional anatomy sessions, and frequent sawbones exercises.

As Penn Orthopaedics continues to expand with the new trauma center, a surgicenter, a growing presence at Pennsylvania Hospital, CHOP, the VAMC, and Bayhealth, it is tough to meet the demands of much needed man power. To the residents—your cooperation and willingness to help out this year did not go unnoticed. We thank you for being so compliant with changing schedules, assuming new roles during this transition, and stepping up to fill in vacancies when needed. As you all continue through this journey in residency, understand that some days will be more challenging than others. But always remember—to touch so many lives, to help so many people, and to spend the rest of your lives doing something you’re all so passionate about is an absolute privilege. Our advice is to live by the words of Dr. Gentchos and all the mentors that helped shape us during our short time here. Help each other out. Take pride in your work. Treat patients like family. Never stop learning.

This dedication simply would not be complete without also thanking our significant others for their immense patience. They have tolerated our fatigue, listened to our complaints, and have soothed our concerns. Their lives have been impacted by what we do day to day just as much as our own. Adriana, Alexandra, and Mary Kate: we apologize for all the texts/emails/calls during dinner, the late nights hammering out emails on our laptops, the cancelled plans, and the inevitable conversation about all things Penn Orthopaedics when we get together. We will never be able to thank you enough for your understanding and being by our side through it all.

Looking back at the sacrifices we have made and the hardships we have endured, it is bittersweet to realize that it is all coming to an end. It is certainly sad to be leaving the friends, mentors, and colleagues we have worked so closely with over the last five years. At the same time, it is exhilarating to move on to the next part of our lives armed with the phenomenal training we have received here at Penn. As we near the end we have come to realize that all that we have done was well worth it. And in the words of one of our great mentors and one of the most humble and empathetic human beings anyone might have the pleasure of meeting, Dr. John Esterhai:

"I'm at peace with that."
Under the leadership and vision of Dr. L. Scott Levin, the Department of Orthopaedic Surgery at the University of Pennsylvania is a proud proponent of the Penn Musculoskeletal and Rheumatology Service Line. The MSKR Service Line aims to address the multidisciplinary needs of patients with musculoskeletal and rheumatologic disorders. By enhancing collaboration between the departments of Orthopaedics, Anesthesia/Pain Management, Musculoskeletal Imaging, Physical Medicine & Rehabilitation, and Rheumatology and streamlining the allocation of care resources, Penn Medicine is able to provide more efficient services to patients in diagnosis, treatment and continuing care. This increased efficiency translates to improved outcomes while achieving cost containment, resulting in advanced improvement in patient care, clinical education, and academic research endeavors.

Anesthesia/Pain Management

Under the direction of Dr. Nabil Elkassabany, the Department of Anesthesiology has been instrumental in improving care and maximizing value while establishing a regional anesthesia practice. Increased use of regional anesthesia techniques is anticipated to improve pain control while simultaneously decreasing operative turn-over time, post-operative narcotic requirements, and post-operative PACU stays for patients undergoing musculoskeletal extremity surgery.

The expanded capacity of six new operating rooms at Penn Medicine University City provides state-of-the-art anesthesia and pain care to Orthopaedic Surgery Patients. The PPMC Regional Anesthesia and Pain Service provide inpatient consultation for pain and palliative care services at PPMC in addition to outpatient pain services by faculty from the Pain Medicine Division.

Patient outcome data is collected throughout the clinical process, regardless of location, in an effort to accurately evaluate the effect of musculoskeletal care and develop innovative solutions. This allows for improved care across disciplines and locations, and the implementation of evidence-based practices to provide high quality services to patients. On the pain medicine service, areas of focus include non-operative spine pain, osteoarthritis, and rheumatoid arthritis. Active efforts are underway to explore best practices with regard to perioperative care, including rapid implementation of novel methods of pain care, to facilitate patient recovery. Annual combined Grand Rounds, as well as research projects investigating the impact of surgical positioning on cerebral oxygenation, illustrate the collaboration between the Departments of Anesthesiology and Orthopaedic Surgery, as future generations of Musculoskeletal Anesthesiologists and Orthopaedic Surgeons train side by side under the umbrella of the MSKR Service line.

Musculoskeletal Imaging

With the opening of the Penn Center for Specialty Care at 3737 Market Street, the MSK radiology department is now housed in one location with close proximity to a myriad of clinical specialties. The culmination of multiple years of work toward a unified musculoskeletal system, the service line allows clinicians and image specialists to hone in on diagnoses and treatment options, which streamlines the process of patient care referrals in both directions.

Departmental meetings between Orthopaedics and Radiology are now held every 6 weeks, to facilitate and coordinate improved clinical education between specialties, as well as enhance collaborative research endeavors. Future plans include combined upper extremity, sports medicine, and foot and ankle conferences, as well as inter-departmental research illustrated by new projects involving rotator cuff tear imaging and the role of tomosynthesis in fracture diagnosis and treatment.

Chief of MSK radiology Bruce Kneeland, M.D., states, “We’ve had great relationships with orthopaedic staff in the past; the collaboration between departments is heading in the right direction and we want to keep expanding. Incoming residents come into the program knowing research is an expectation. Dr. Levin is the single biggest reason I came back to work here…and he has been instrumental in building the relationship between Orthopaedics and Radiology.”
Physical Medicine and Rehabilitation

The long-time partnership between the Departments of Orthopaedics and Physical Medicine and Rehabilitation has been further enhanced with the opening of the new Musculoskeletal Institute.

With a center of operations at 3737 Market Street, the Penn Center for Human Performance is a state of the art facility that opened in the spring of 2015 with the goal of simplifying access to care of patients with musculoskeletal disorders. This innovative, cutting edge center is designed to facilitate the evaluation of patients pre-operatively and post-operatively to objectively quantify the impact of surgical or non-surgical intervention. The brand new biofeedback laboratory is designed to help promote rehabilitation protocols and provide immediate feedback on patient recovery, biomechanical joint properties, and post-operative guidelines. Along with the in-house human performance lab, clinicians are able to gauge healing metrics through the elaborate combination of motion analysis, neuromuscular testing, on-site electromyography and metabolic measurement systems, contributing to the existing world class care provided by PM&R for amputees in both biofeedback and prosthetic selection and fitting.

In addition, the facility boasts innovative rehabilitation equipment and a large, centralized space to care for patients in all walks of life. An indoor pool allows for low impact training and rehabilitation, while in house imaging capabilities, including X-ray, CT-scan and MRI, translate to easier access to resources for patients. With a centralized location housing clinicians and health care professionals from multiple departments, this center will enhance the common efforts of the PM&R and Orthopaedic teams to deliver the highest value of care.

Rheumatology

Led by Division Chief and Professor of Medicine and Epidemiology, Peter A. Merkel, MD, MPH, the Division of Rheumatology at the University of Pennsylvania is the leading center for care and research for rheumatic diseases in the greater Philadelphia area.

Penn Rheumatology is proud of the hard work undertaken with our clinical partners in forming the Penn Musculoskeletal and Rheumatology Service Line and the Penn Musculoskeletal Center at 3737 Market Street. The MSK Center will be the premier location for multidisciplinary management of patients with bone and joint diseases as well as a site for introducing groundbreaking new approaches in the pursuit of advanced clinical and translational research endeavors.

The MSKR Service Line provides additional opportunities to develop ever-more outstanding care and services for patients at all Penn Medicine sites.

Drs. Merkel and Levin share a common commitment to excellence and a ceaseless drive to accomplish all of Penn Medicine’s missions in healthcare: excellence in clinical medicine, cutting edge research, and world-class-education.
In 2011, the Center for Medicare and Medicaid Innovation announced the use of “bundled payments” for a care improvement initiative, where a price is determined and charged for a set of services to a patient. The goal is to reward successful clinical performance rather than the use of health care resources in fee-for-service models.

There are four bundle models, based on the encounter type and the hospital implementing the program. In the first model payments are bundled for hospital and physician services during each individual hospitalization. In the second model payments are bundled for an initial hospitalization and all post-acute care services for up to 90 days after discharge. In the third model payments are bundled for post-acute care services after hospitalization, excluding the hospital stay. The fourth model sets fixed prospective payment for all services during hospitalization plus readmissions within 30 days.1

For the first three models there is no fixed price; a discounted target price is set for the episode of care based on historical spending. Providers charge fee-for-service, and the Center for Medicare and Medicaid Services assesses whether actual spending is above or below target.1 The hospital is rewarded if they are under the target spending price, but penalized if they are over. For the fourth model, the fixed price is determined based on prior average cost at a particular institution, with a discount.

The goal of bundled payments is to mitigate unnecessary spending while encouraging quality care, thereby improving value. The principle is based on variation of cost of treatment of certain conditions. An analysis showed regional variation in medical costs without improved outcomes.1 Cost-analysis simulations for costs above the 25th percentile, when reduced to the 25th percentile, yielded a savings for the top 17 conditions of $10 billion annually. Thus, a bundle with a fixed cost at the 25th percentile would result in significant healthcare savings. Because cost and quality do not correlate, this saving may well occur without a quality penalty.

However, there are difficulties with implementing a bundled system of care. Institutions often do not have a fundamental understanding of the costs associated with the course of care. They cannot control cost at out-of-network care providers. Smaller institutions are at high risk when high year-to-year variation translates to large variations in the profits of the hospital.1 Charging a set price, regardless of the complexity, encourages facilities to refer complex care patients. Less complex patients require fewer services, resulting in increased profit. “Cherry picking” of such patients is a risk. Outliers can break a well-run bundle. Features such as stop-loss protection for high-cost cases and an ability to exclude cases with high-cost diagnosis may protect hospital systems, but the concern over “pricier” patients still remains because the protection is incomplete.

Post-acute costs, including readmission rates and the discharge of patients to rehabilitation facilities, are included in model two. Our initial focus will be identifying risk factors that can be mitigated to avoid readmissions in the 90-day period after surgery, and lowering the rate of admission post-discharge to skilled nursing facilities, inpatient rehabilitation facilities, and the other acute-care inpatient facilities.

Bundled care management has helped us understand and develop processes aimed at both lowering cost and improving patient safety. At present, our most active bundle is the CMS Bundled Payments for Care Improvement (BPCI) for patients having revision hip and knee surgery since January 1, 2014. Figure 1 shows the most recent CMS data from 2010 and 2011 for Presbyterian Medical Center, which uses a type 2 bundle. In a type 2 bundle, the major part of the pie diagram cannot be impacted directly; however, the post-acute costs do have the potential for mitigation. Approximately two-thirds of the post-acute costs are related to skilled nursing facilities (SNFs) and inpatient rehabilitation facility costs, and the other third of the post-acute cost is for readmissions. This finding gives us two areas of focus to lower cost.

**Readmission Management Program**

Readmission management aims to identify and mitigate risks that predict readmission, both patient factors and process factors. Mitigation can occur prior to admission, during the inpatient stay, and in the post-acute period. Preadmission hospital prevention aims to manage modifiable disease. Our Risk Stratification Program has been effective in identifying patient risk factors that may lead to ICU admission and rapid response in care issues; we have also learned that it predicts readmission rates. We have been able to develop programs that improve the hospital safety record, with an ongoing goal to expand the Pre-Hospital Risk Program to address readmission risk issues.

The second time period is inpatient hospital care, during which communication with the outpatient provider is established and medical co-morbidities are managed prior to discharge to reduce readmission rates. The third time period involves management during the post-acute 90 days with clinical guidelines designed to manage common clinical presentations. The “Hot Joint Protocol” illustrates a successful algorithm for addressing painful TKAs.
A. Preadmission Management of Modifiable Diseases

Modifiable diseases include common, well-defined conditions of varying complexity and prevalence. As a pilot in the PPMC population, we propose to mitigate the effects of these diseases and have identified several potential targets for preoperative disease modification including malnutrition, obesity, diabetes, and anemia.

Low albumin has long been shown in surgical literature to be associated with wound complications. Poor nutrition is thought to impair fibroblast proliferation resulting in impaired collagen synthesis, leading to higher rates of wound complications and surgical site infections. Interestingly, high levels of preoperative albumin are thought to prevent complications with higher levels being independently associated with lower risk of readmission. Hypoalbuminemia also appears to prevent subsequent healing after infection. In a retrospective review of almost 12,000 cases of lower extremity arthroplasty, of those who became infected, initial irrigation and debridement were less successful in the malnourished population. Research at this institution corroborates this data, as recent work shows that the overall hypoalbuminemia correlates with higher rates of unplanned ICU admissions.

At present, our effort is focused on understanding the etiology of low albumin in our patients, as malnutrition represents only one factor causing serum albumin less than or equal to 3.5g/dL. We found that 16% of all our patients have an albumin level less than or equal to this cutoff. Chronic liver disease is also an important contributor to many patients’ hypoalbuminemia. Paradoxically, obese patients often suffer from low albumin. Approximately 25% of our patients who have a BMI greater than 38 have a level of albumin less than or equal to 3.5g/dL. Courtney et al found malnutrition (with an albumin < 3.5g/dL), but not obesity, to be an independent risk factor for complications. We are developing a pilot to identify and evaluate patients with low albumin and to identify resources available for nutritional support.

Similar data exist for patients with diabetes mellitus. It is important to note that hyperglycemia has also been shown to be an independent predictor of morbidity and mortality in surgical patients. Kremers found that there was an increased risk of developing prosthetic joint infections in patients with perioperative hyperglycemia >180 within one week of surgery. Iorio found the rate of overall infections, including superficial and deep surgical site infections, to be higher in diabetics: 3.4% compared with 0.84% in non-diabetics. Particularly germane to the discussion of evaluating diabetes control in the setting of bundled payments is that there is a significant difference in the length of hospital stay and overall hospital cost between non-diabetic, controlled diabetic, and uncontrolled diabetic patients. Marchant et al showed that the mean length of stay in uncontrolled diabetics was 6.2 days, compared with 4.6 days in controlled diabetics. The median cost of admission is also statistically significant, with the difference between normoglycemia and uncontrolled diabetics in excess of $2,000. Perioperative complications including cerebrovascular accidents, urinary tract infections, ileus, pneumonia, postoperative hemorrhage/shock, and need for blood transfusion were significantly increased in uncontrolled diabetics compared with non-diabetic and controlled diabetic patients. These data suggest that good preoperative control of blood sugar may be a modifiable risk factor for total joint infection.

A further modifiable risk factor to be taken into consideration for implementation of bundled payments is preoperative anemia. Risk factors for requiring transfusion during total joint arthroplasty include age, preoperative hematocrit, BMI of < 30 kg/m², female sex, and ASA class of > 2. A review by Monsef et al showed there was a significantly significant increase in mean length of stay with a preoperative Hb < 12: 4.2 compared with 3.7 days. Overall, patient hemoglobin levels preoperatively until two days after the procedure were found to be inversely related to length of stay and also a barrier to discharge in fast-track hospital stays.

B. Hospital Management and Discharge Preparation for Patients

The co-management process with the PPMC hospitalists has been an effective part of lowering morbidity and mortality of our patient population. Involvement of the hospitalists with inpatient care and with pharmacy reconciliation has resulted in better prepared patients. Additionally, the hospitalist providers are involved in communication with outpatient care providers, thereby optimizing transition of care.

Penn Chart Acute Transfer Tool (PCATT) is an electronic document we have developed to enhance communication with post-acute providers. This EMR-based program facilitates transition of care by providing inpatient data, physical therapy goals, and discharge plans to outpatient teams.

C. Post-Acute Care Interventions

Two major efforts are being pursued. The first is the nurse navigator who can support the transition of care, and to enhance compliance with the care plan. We expect to lower unnecessary emergency room (ER) visits, to decrease...
readmission rates, and to decrease leakage rate of readmissions to non-UPHS hospitals. By reaching out to the patient and providing appropriate recommendations, nurse navigators can effectively guide patient care after discharge.

The post-acute management through the patient office has also been bolstered, by providing office access to post-surgical care within a half-day of any acute occurrences. Improved phone access and same-day/next day office visits support this effort. Additionally, patients with medical emergencies are encouraged to come to one of the UPHS ER’s, where there are pathways to evaluate and care for our patients.

Our first care pathway effort was aimed at the patient who presents to the emergency department or office with the concern that a total knee arthroplasty may be infected. In the six months from July to December of 2013 we had 16 readmissions to Presbyterian Medical Center with a diagnosis of wound infection; of those 16, only one had a proven wound infection. This finding suggested that the evaluation of the “hot joint” as an outpatient would likely result in lowering unnecessary readmissions rates. The Hot Joint Pathway was developed based on the AAOS/AAHKS guidelines for periprosthetic infection. The pathway starts with the CRP, a highly sensitive test in identifying prosthetic joint infections. If the CRP is normal, the patient is safely discharged home with office follow-up. This protocol has been successful as illustrated by the decreased readmission rate in the six months following implementation (Figure 2).

D. Post-Acute Care and Location of Care

Our rate of SNF and inpatient rehabilitation transfers exceed the state and national averages, resulting in increased costs. Identification of patients who need SNF placement is an important modifiable factor of care. We are in the process of examining preoperative and inpatient indicators suggestive of discharge to SNF and correlating these findings with readmission risk. The four preoperative components of this assessment are a preadmission PT session we call prehab, social work assessment, joint class, and risk stratification. For an inpatient, the metrics such as distance walked and the number of physical therapy sessions may predict discharge to home.

The following components make up our Home Safely Pathway. The Home Safety Program evaluates motivated patients for the likelihood of success, and then plans hospital and post-acute care to support the decision for safe discharge to home. Figure 3 outlines the levels of the Home Safely Pathway. Approval from the orthopaedic social worker is based on home support, family, home environment, insurance coverage to support the program, prehab outpatient PT visits designed to address function capabilities and any barriers to postoperative discharge to home, and the risk stratification process. The Post-Acute Pathway includes the Penn Home Health Agency, which integrates the components of the care plan at home within 24 hours of discharge.

Summary

In summary, the opportunity to focus on the efficiency of care has allowed us to improve the safety of our patients. We are evaluating readmission, modifiable readmission risk, and safe discharge planning, with the goal of a more complete readmission risk evaluation within the UPHS system, using CMS or prior patient data.

Figure 2. Percent of all patients readmitted and cause (A) prior to “hot joint” pathway and (B) post-implementation of “hot joint” pathway.
The readmission pilot that we are currently evaluating is the low albumin malnutrition process. Our hospital co-management with the hospitalist team focuses on pre-discharge evaluation, medicine reconciliation, and transition of care. The post-hospital process has focused on the “nurse navigator” and improved office access. Successful algorithms such as the Hot Joint Protocol are aimed at common reasons for readmission.

In an effort to lower the rate of SNFs or inpatient rehabilitation discharges, we have considered several measures. The Home Safely Program uses pre-surgery social and home factors to plan hospital and post-acute care to support the decision for patients to return home safely. We are actively evaluating the metrics of hospital activity and distance walked when planning home discharge, which may support a mobility tech. By addressing all these issues, we hope to be successful for BPCI Hip and Knee Arthroplasty service and to improve patient safety.

References

Today, almost one in ten Americans is an armed forces veteran. More than 3.6 million women and men have served during the period of time that we have been directly involved in the Middle East.

George Washington knew that, “The willingness with which our young people are likely to serve in any war, no matter how justified, shall be directly proportional to how they perceive the veterans of earlier wars were treated and appreciated by our nation.”

The Philadelphia VA Medical Center (PVAMC) provides health care to 90,000 veterans living in America’s fifth largest metropolitan area. Our four-fold mission is to honor America’s veterans with world-class health care, advance medical knowledge through research, train health care professionals, and be prepared to serve in the event of a crisis.

We are a tertiary referral center with more than 135 acute care beds, 95 of which are medicine-surgery beds, and total yearly operating budget of more than $380 million dollars. The PVAMC is an eight-minute walk from the Hospital of the University of Pennsylvania. Our Orthopaedic residents and faculty are honored to help care for those who have served their country. Abraham Lincoln articulated the primary mission of the Veterans Administration Penn Orthopaedic Service more than a century ago: “To care for him who shall have borne the battle.”

Perhaps you are familiar with these words attributed to Father D.E. O’Brien:

“It is the soldier, not the reporter, who has given us freedom of the press.

It is the soldier, not the clergyman, who has given us freedom of religion.

It is the soldier, not the poet, who has given us freedom of speech.

It is the soldier, not the campus organizer, who has given us freedom to demonstrate.

It is the soldier who follows the flag into battle, defends our flag, salutes our flag, and whose coffin is draped with our flag.

It is the soldier. It has always been the soldier, and it will always be the soldier.”

The VA is the largest health care system (122 medical facilities) supporting graduate medical education in the United States and the second largest funding source for resident training (31,000 resident physicians) after the Centers for Medicare and Medicaid Services. It is affiliated with 107 of the nation’s 129 medical schools. That network of facilities allows VA to deliver care to veterans from the greatest generation of World War II to the latest generation from Afghanistan and Iraq.

The University of Pennsylvania Orthopedic rotation at the Philadelphia VAMC allows our PGY-2 and PGY-5 residents to care for veterans in an intensive, general orthopedic practice setting under the direct supervision of Drs. Ahn, Bernstein, Ecker, Esterhai, Farber, Gentchos, Hume, Kelly, Kunzt, Sheth, Steinberg, and Zgonis. Dr. Harvey Smith, our spine surgeon, teaches and works with a PGY-3 resident. Dr. Levin volunteers his time without compensation. The veterans who require care at a level of sophistication that we cannot provide are referred to sub-specialists in the City or within the University of Pennsylvania Health System at Pennsylvania Hospital or Penn-Presbyterian Medical Center.

In addition to their dedication to direct patient care and resident education, Drs. Bernstein, Esterhai, Kunzt, Steinberg, and Zgonis have each applied for or been awarded research funding through the Veterans Administration competitive grant system. Under the direction of Drs. Mauck and Dodge our department’s Translational Musculoskeletal Research Center has five Merit Grants. Dr. Smith has begun his basic science spine studies under his Career Development Award. Our PVAMC clinical faculty members collaborate actively with intra and extra mural physicians and basic scientists including Drs. Jonathan Black, Jason Burdick, George Dodge, Paul Ducheyne, Dawn Elliott, Kurt Hankenson, Annamarie Horan, Russ Huffman, Robert Mauck, Samir Mehta, Lachlan Smith, and Lou Soslowsky.
Drs. Mauck and Dodge direct our Translational Orthopedic Research Facility, in 4500 square feet of superbly equipped research space. They have energized collaboration with Rheumatology and Physical Medicine and Rehabilitation scientists. More about that in this volume of the UPOJ.

We have been able to improve our preoperative patient evaluation process to expedite surgery scheduling with the addition of preadmission testing offices immediately adjacent to our clinic, improved peri-operative pain management and post-operative floor care. We look forward to opening another operating room on Wednesdays and adding OR and PACU personnel to extend the operating room duty day.

Mitchell (Chip) Staska and John Wheeler, our superb Physician Assistants, provide seamless, exemplary, tender care from initial patient referral through appropriate triage, outpatient evaluation, scheduling of appropriate testing and consultations, surgery, and post hospitalization care. Chip and John provide immediate, timely interaction with referring physicians and outside consultants, coordination of pre-bed evaluations, surgery scheduling, interaction with the primary care providers, liaison with VA referral health centers, acute and chronic pain management, and assist in the operating room! John coordinates Dr. Smith’s Orthopaedic spine care for our veterans.

We have the best electronic medical record system in the country. All records including consent forms and imaging studies are electronic. In-patient and out-patient progress notes, laboratory results, and imaging studies are available at the workstations on the in-patient units, offices, and outpatient care areas and individual examination rooms from local and satellite VA care facilities across the country.

We have patient office hours on Mondays, Wednesdays, Thursdays, and Fridays allowing us to provide more than 5200 patient visits each year. New patients are scheduled within thirty days of their primary physician’s request for consultation. The Emergency Room is very busy. We perform scheduled surgery four days each week, averaging more than 450 major procedures yearly. Orthopedics performs more major surgeries than any other service. None of this would be possible without the professional expertise and wisdom of the Chief of Surgery, Lew Kaplan, and the nurses, administrative support personnel, and physician staff of the PVAMC.

Vince Lombardi said, “The achievements of an organization are the results of the combined effort of each individual.” By God’s providence and the hard work and daily diligence of everyone in anesthesia, instrument processing, nursing, and orthopaedics the infection rate for our total joints replacement patients has remained excellent. Several factors specifically contributed, including: improved pre-operative patient screening and preparation, rigorous instrument processing and packaging, heightened awareness of potentials for intraoperative contamination, perioperative antibiotic dosing, and patient retention for on site rehabilitation before discharge to the patient’s home. In this time of increasing financial restraint and federal budget review we will likely be called upon to deliver more direct care and perform more research with fewer resources.

Today there are 26.5 million veterans of whom 1.7 million are women. Seventy-five percent served during at least one war time period with Vietnam era veterans accounting for 8.3 million; WW II, 4.8 million; Korea, 3.7 million; and the Gulf Wars 3.6 million.

Many of the veterans for whom we care commute a long distance from central and northeastern Pennsylvania, southern New Jersey, Maryland, and Delaware. Many have significant co-morbidities such as HCV and difficult psychosocial environments. Many have had multiple operations making reconstructive surgical approaches and wound healing more difficult. Not infrequently they have had a difficult time reintegrating into society after their military service. It has been said that “a veteran is someone who wrote a blank check, payable to the United States of America, for an amount up to and including his own life.” Providing Philadelphia-level, state of the art, complication free, compassionate care requires extra, special diligence. It is a worthy goal to which we are fully committed.
Penn Orthopaedics provides its patients with the most advanced comprehensive diagnostic, surgical, and rehabilitative treatments. In tandem with Penn Medicine’s mission to extend programs and projects to vulnerable populations in communities ranging from those in its own West Philadelphia backyard to those in need around the world, the clinical team at Penn Orthopaedics is committed to all patients, no matter how serious their injury or condition.

**Patient Care Volume in 2014**

A total of 36 clinical faculty, 42 medical residents, and 7 fellows offer a range of services through nine sub-specialties customized to treat patients with varying orthopaedic conditions in 10 locations throughout Pennsylvania and New Jersey. Below is the patient care volume for 2014:

- Total Patient Visits: 89,525
- Total Inpatient Cases: 5,368
- Total Outpatient Cases: 4,824
- Total Cases: 10,192

**2014 Total Cases**

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Total Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint Replacement</td>
<td>3,287</td>
</tr>
<tr>
<td>Trauma and Fracture</td>
<td>1,434</td>
</tr>
<tr>
<td>Hand and Wrist</td>
<td>1,541</td>
</tr>
<tr>
<td>Sports Medicine</td>
<td>1,360</td>
</tr>
<tr>
<td>Foot and Ankle</td>
<td>949</td>
</tr>
<tr>
<td>Shoulder and Elbow</td>
<td>934</td>
</tr>
<tr>
<td>Spine</td>
<td>419</td>
</tr>
<tr>
<td>Neuro-Orthopaedics^</td>
<td>151</td>
</tr>
<tr>
<td>Orthopaedic Oncology</td>
<td>117</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10,192</strong></td>
</tr>
</tbody>
</table>

^Includes volume from the Children’s Hospital of Philadelphia

**Patient Satisfaction**

Penn Orthopaedics has improved patient satisfaction by embracing innovation, implementing Concierge Check in with iPads, a series of scheduling questionnaires, online scheduling for patients and the MyPenn experience. Improvements in patient satisfaction can also be traced to recent operational efforts to improve system-wide access, enhance referral communication, and implement an innovative same-day appointment initiative. As a result, the overall patient satisfaction scores for Penn Orthopaedics is 89.3.

**The Penn Musculoskeletal Center**

The highlight from the past year was the opening of the Penn Musculoskeletal Center in August 2014. The Center brings clinicians together from orthopaedics, rheumatology, physical medicine and rehabilitation, pain medicine and musculoskeletal radiology to provide comprehensive musculoskeletal care. Physicians collaborate as a team – with access to the latest diagnostic techniques and an onsite surgery center – to deliver the most advanced surgical and non-surgical treatment options available.

Penn Orthopaedics is a top program in the Greater Philadelphia region and is ranked among the nation’s best by US News & World Report.

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**Physician Relationships**

The entire Penn Orthopaedics team values its extensive and collegial relationships with peers in the medical community. To help disseminate relevant information for physicians on both a local and national level, “Clinical Briefings™” highlight unique cases and novel approaches through a series of clinical reports. Similarly, the annual newsletter, “Excellence in Motion,” provides an overview of the entire department, including research activity. The PhysicianLink® platform (877-937-PENN, www.PennMedicine.org/PhysicianLink) facilitates patient consults, referrals, and transfers through an integrated continuum of treatment to optimize the standard of patient care. This includes the difficult and complex cases that require highly advanced expertise and clinical resources. Physicians from 24 states across the US consulted with Penn Orthopaedics on behalf of their patient.
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.

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 nine attending surgeons from various sub-specialties to populate the orthopaedic clinic on the first floor of the Cathcart 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. Atul Kamath returned to Penn after completing his fellowship in Adult Reconstruction at the Mayo Clinic. He also completed a six month traveling fellowship throughout Europe focusing on hip preservation.

With such a dramatic increase in operative volume, PAH is now staffed by a PGY-1, PGY-2, PGY-4 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. The nurse practitioners also staff the floors at night to provide round-the-clock patient care.

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 held every day in the morning. With a rigorous, structured curriculum, specialty specific conferences include spine, foot and ankle, trauma and arthroplasty.

The administration at Pennsylvania hospital has been 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.
It has been an exceptional year for the Department of Orthopaedic Surgery at Penn Presbyterian Medical Center (PPMC). There is now a greater physical presence of the department on the PPMC campus as two new facilities have opened. In addition the development of the musculoskeletal service line has led to multiple initiatives allowing continued advancements in patient care.

Penn Medicine at University City (PMUC) located on 3737 Market Street opened in August 2014. The Department of Orthopaedic Surgery moved its clinical and administrative offices from PPMC and the Hospital of the University of Pennsylvania (HUP) to the new 150,000 square foot facility. The gala opening was held on September 12th and was well attended including many dignitaries throughout the region. An Excellence in Orthopaedic Surgery Symposium took place the following day with lectures by leaders in the field including Bruce D. Browner, MD, William P. Cooney, MD, Michael Gagnon, MD, Richard H. Gelberman, MD, Joseph P. Iannotti, MD, Marvin E. Steinberg, MD, Peter J. Stern, MD, Thomas P. Vail, MD, and Gerald R. Williams, MD.

The Department of Orthopaedic Surgery is now an integral component of the Penn Center for Musculoskeletal Care located in PMUC. The center allows an integrated unified approach in the treatment of patients with musculoskeletal disorders and injuries. The orthopaedic clinical space encompasses the seventh and eighth floors of the building and is arranged in modules according to department section. A concierge service streamlines the patient visit which includes interactive educational material. The facility houses a comprehensive array of services including physical medicine, radiology, rheumatology, internal medicine, neurology and physical therapy. The proximity of the various departments improves the bidirectional communication of information critical for patient care as well as the coordination of combined lectures and research initiatives. In addition medical imaging, diagnostic testing services and a pharmacy are available at the facility allowing one stop service for patients.

The ambulatory surgery center has opened this year at PMUC with six operating rooms for out-patient same day surgical procedures. The state of the art operating suites are equipped with the latest in video technology for minimally invasive procedures. The highly efficient center has the benefit of a talented regional block anesthesia service led by Drs. Nabil Elkassabany, MD and Jiabin Lui, MD. The high quality service provided is evident by the notable patient experience data.

Outpatient rehabilitation therapy is performed through Good Shepherd Penn Partners, a partnership developed between Good Shepherd and the University of Pennsylvania Health System. The therapy division includes 22 physical therapists and six occupational therapists residing on the second and third floors. The unit encompasses over 28,000 square feet of space and provides a full range of services including a therapeutic pool with variable depths and an underwater treadmill. A satellite occupational therapy unit within the hand surgery module allows same day appointments and direct transition of care.

At noon on February 4, 2015 the regional level I trauma center for Penn Medicine switched from HUP to PPMC. On the morning of the move, several city streets were closed to allow for the transfer of the trauma in-patients from the HUP to the new center which includes the Advanced Care Hospital Pavilion on the corner of 38th street and Powelton Avenue. The new 178,000 square foot building at PPMC houses the facilities for critical care, emergency and surgical trauma including the John Pryor Trauma Bay. The new trauma resuscitation area for patient evaluation and stabilization has upgraded emergency and radiology services for improved efficiency. In addition a helipad is available for the Penn Star flight program for transportation of critically injured patients.

The musculoskeletal service line has been organized with the new transition. A component of the service line structure includes the Quality and Patient Safety Committee led by Dr. Eric Hume with the support of Ms. Finnah Pio. The group has been instrumental in the implementation of multiple initiatives for improvement in patient care. A Penn Chart Acute Transfer Tool has been developed to facilitate the transfer of patient information and communication with post-acute providers. The Penn Arthroplasty Post-Acute Pathway has also standardized the peri-operative process and provides information regarding wound care, activity level with mobility plan and goals for the care team. In addition a care and communication pathway for patients with a post-operative
fever or a potentially infected joint has been developed. The algorithm uses readily available criteria including the patient’s temperature, heart rate, white blood cell count, and C-reactive protein levels to determine the likelihood a patient will require an orthopedic evaluation and re-admission. These highly successful efforts have allowed the various care team members to provide consistent safe care limiting unnecessary hospital admissions. The remarkably low department 30 days unplanned readmission rate is one metric confirming the success of these projects. Other initiatives underway through the service line include Pre-admission Center Testing Enhancement with the support of Fabian Marechal, Trauma Clinical Variations led by Dr. Samir Mehta, and Joint Replacement Development led by Dr. Charles Nelson.

This is an extraordinary time for the Department of Orthopaedic Surgery at PPMC. The group has taken another step forward as it expands its role as the leader in musculoskeletal medicine.
Penn Orthopaedics Does Not Rest On Its Laurels

Dan Gittings, MD
Brian J. Sennett, MD
Chief, Division of Sports Medicine

“Penn Orthopedics does not rest on its laurels.” Dr. L. Scott Levin opened with this statement while recruiting the nation’s best and brightest young men and women to join the Penn Orthopedic Surgery team. Dr. Levin’s statement could not be truer. During the 2014-2015 academic year, the Penn Orthopedics and Sports Medicine team not only continued its tradition of excellence but also made monumental additions to the department to build an even brighter future. The Sports Medicine Department revamped the resident education curriculum, established the new Musculoskeletal Center, and continues to lead in research.

The Sports Medicine resident curriculum has grown tremendously over the past several years. It has evolved to become a curriculum that includes both structured didactics and hands-on human tissue laboratory sessions for surgical skills. Dr. Miltiadis Zgonis, now a Penn Sports Medicine faculty member, exemplifies how Penn Orthopedic Surgery’s residents drive innovation within the department. While Dr. Zgonis was a junior resident at Penn, he laid the groundwork to create the human tissue laboratory residents can now utilize to refine their operative techniques. Through the help of industry sponsors and the advent of the Human Tissue Laboratory by Dr. Levin, Dr. Zgonis’ plan became reality. The Sports Medicine team now meets several times each month to walk surgeons from all levels of training through both bread and butter cases and complex operative techniques. The lab includes fresh cadaveric human tissue along with equipment and implants used in the functional operating rooms in order to have the most realistic simulation possible in preparation to deliver world-class patient care.

The new Musculoskeletal Center at Penn Medicine University City opened its doors this year and solidifies Penn Orthopaedic’s role as a leader in both patient care and research. The Musculoskeletal Center is the first of its kind in the region to integrate comprehensive musculoskeletal care. The building has 110 patient exam rooms, six outpatient operating rooms, and an outpatient medical imaging and diagnostic testing center. This facility has allowed the Sports Medicine team to offer high quality surgery to a greater number of patients each day. In addition to cutting edge clinical work, the Musculoskeletal Center has enhanced research within the Sports Medicine department. The new center houses the Penn Center for Human Performance, which helps patients of all ability levels regain range of motion and improve their performance. Furthermore, researchers are able study musculoskeletal pathology with innovative techniques not available anywhere else in the region. Some of the capabilities of the center include motion analysis, neuromuscular testing, electromyography, and a metabolic measurement system. These resources allow Penn to remain at the forefront of Sports Medicine technology and research.

The Penn Orthopedics and Sports Medicine team will be hosting both the Advances in Throwing Symposium and the Cartilage Repair Symposium to share advancements within sports medicine with international leaders within the field. The Throwing Symposium on January 31, 2015 will feature Dr. James Bradley from Burke and Bradley Orthopedics and Dr. Craig Morgan from the Morgan Kalman Clinic, both leaders in shoulder reconstruction. Dr. Bradley will be presenting a discussion about “Superior Labral Anterior-Posterior and Posterior Instability in throwers”. Furthermore, Dr. Morgan will be discussing the “Disabled Throwing Shoulder”. Both surgeons care for professional athletes at the highest level of play, including National Football League players, Major League Baseball players, Olympic-level athletes, and professional golfers. At the Cartilage Repair Symposium, Dr. James Carey and Dr. Robert Mauck will showcase new directions in osteochondral repair and treatments of focal articular cartilage defects and osteochondritis dissecans. Both symposiums illustrate Penn Sports Medicine’s ability to stay at the forefront of the latest and greatest advancements and collaborate with other leaders within the field.

Sports Medicine at Penn has remained active over the past year in sports medicine education, clinical care, and research. The Sports Medicine program shows signs of continued growth and improvement ahead with state of the art operative training facilities, technology for research, and collaboration with other leaders in the field. The Penn Orthopedics and Sports Medicine team truly “does not rest on its laurels.”
The Division of Orthopedic Surgery at the Children’s Hospital of Philadelphia enjoyed another year marked by change and growth. Our clinical and research programs have continued to expand in line with our goal of improving the quality of care we provide to patients. In 2014, CHOP was named the number one children’s hospital by US News and World Report, a distinction we have held for 10 consecutive years.

In December, CHOP announced the selection of Dr John M. “Jack” Flynn, MD as the new division chief. Dr Flynn has previously served as associate chief of Orthopedics since 2005. Dr Flynn succeeded Dr John Dormans, MD FACS who led the division for over 18 years.

Next year will also mark the opening of two new state-of-the-art facilities. The new Specialty Center at King of Prussia (Figure 1) will open later this summer. The 115,000 square-foot facility will house an ambulatory surgery center to provide outpatient general and specialty surgical services. One of the many CHOP expansion projects in the region, the center acts to expand our reach into areas surrounding Philadelphia and to provide these communities with the best possible care. Construction of the Buerger Center for Advance Pediatric Care is on schedule, and the building will open in July 2015 (Figure 1b). The outpatient facility on CHOP’s main campus features 12 floors of integrated clinical care facilities along with patient oriented features including ‘wait, play, learn’ areas for patients and siblings and a roof garden. The two facilities are exemplary of CHOP’s commitment to being a world leader in patient care.

Clinical Program

Our orthopaedic faculty continues to expand and is currently comprised of twenty six total providers, including eighteen specially trained pediatric orthopaedic surgeons (twelve operative and four non-operative), four pediatricians with sports medicine training, and five transition to adult care faculty.

CHOP Orthopaedics is pleased to announce the addition of Dr Brian Vernau (Figure 2a), a pediatrician with sports medicine training. Dr Brian T Vernau joined the Division in fall 2014 after his completion of a sports medicine fellowship at CHOP. He is the team physician for Kennett High School and has provided medical care to the University of Pennsylvania and West Chester University. Dr Vernau obtained his medical degree from Pennsylvania State University College of Medicine in University Park, PA and completed his pediatrics residency at Nationwide Children’s Hospital in Columbus, OH. Dr Apurva Shah, MD MBA (Figure 2b) will be joining the division in August, 2015. Dr Shah is an orthopedic hand and upper extremity surgeon with interest in brachial plexus surgery, traumatic and congenital problems in the hand, and cost-effectiveness, outcomes, and economics of healthcare and orthopedics.

In the past year, the Division of Orthopedics has made a significant impact on the management of pediatric concussions at a local and national level. Five non-operative primary care sports physicians see concussion patients throughout the extensive CHOP Network in PA and NJ. Collaboration with CHOP’s Center for Injury Research and Prevention continues...
with funding from the CDC to study the epidemiology of pediatric concussion, as well as funding from the NIH CHOP/ Penn Clinical Translation Science Award to study the genomics of concussion. In May, Dr Christina Master traveled to the Washington, DC with CHOP President and COO Madeline Bell to attend President Obama’s White House Summit on Concussion. The work that CHOP is doing in developing a comprehensive pediatric concussion registry was highlighted in the White House press release on the summit. Overall, the Minds Matter research endeavor resulted in 5 publications in 2014, ranging from a review article in Annals of Internal Medicine, to studies describing visual and vestibular deficits in pediatric concussion, with 3 more in press already for 2015, including an article in the upcoming Special Issue of Developmental Neuropsychology highlighting concussion work within the Big 10-Ivy League consortium.

Teaching

CHOP Orthopaedics currently funds four one-year clinical fellowship positions, and three one-two year research fellowship positions. The 2014-2015 clinical fellows are Andrew Georgiadis, MD (Figure 3A); Aristides Cruz, MD (Figure 3B); Peter Fabricant, MD (Figure 3C); and Mark Seeley, MD (Figure 3D). Following completion of their clinical fellowships, Dr Georgiadis will be completing a fellowship at the Royal Children’s Hospital in Melbourne, Australia, where he will train with international CP guru Kerr Graham. Dr Cruz will be joining the faculty at Brown University Orthopedics, focusing on pediatric sports surgery. Dr Fabricant will be completing a sports medicine fellowship at Boston Children’s Hospital, then plans to return to HSS. Dr Seeley will be an attending surgeon at Geisinger Health System in Wilkes-Barre, PA. This year’s research fellows are Nariman Abol Oyoun, MD from Egypt (Figure 4A) and Emmanouil Grigoriou, MD from Greece (Figure 4B). After completing their research fellowship, Dr. Abol Oyoun will be returning to Assiut University in Egypt where she was an attending orthopedic surgeon, and Dr Grigoriou will be starting an orthopedic surgery residency program in the US.

Research Program

Basic Science

The past year has been productive, exciting and far-reaching for our Orthopaedic Basic Research Program, led by Maurizio Pacifici, Ph.D. (Figure 5) with new activities and research goals related to a number of skeletal pathologies. Our faculty members and their young associates continue to work diligently on the goals of our several current NIH...
R01 grants, one Department of Defense (DOD) grant and one Veterans Administration (VA) grant to understand basic fundamental aspects of skeletal formation and growth and in turn, pathogenic mechanisms that may subside pediatric and adult conditions including Heterotopic Ossification (HO), Hereditary Multiple Exostoses (HME) and other musculoskeletal pathologies. Work supported by the Muscular Dystrophy Association (MDA) and led by one of our faculty members—Dr. Masahiro Iwamoto—continues to make progress using a novel pharmacological treatment to enhance muscle tissue repair after trauma or in congenital conditions such as muscular dystrophies. In a related development, our faculty member Dr. Eiki Koyama has joined forces with a faculty member in the CHOP Division of Plastic and Reconstructive Surgery—Dr. Hyun-Duck Nah—to understand the development and growth of the temporomandibular joint and to identify possible therapeutic means to treat TMJ osteoarthritis, a condition particularly common in women and quite debilitating. The data and insights stemming from their work have led to the publication of several important studies, and all their work and dedication have now been rewarded by a new 5 year NIH R01 grant.

An equally important area of research led by another faculty member—Dr. Motomi Enomoto-Iwamoto—and supported by a R21 grant from the NIH focuses on tendon and ligament biology and aims to stimulate structural and functional repair in those essential structures when damaged by trauma or overuse. Dr. Enomoto-Iwamoto also received a grant from the Arthritis Foundation last year to study a cell membrane protein that affects the behavior and function of surface cells in articular cartilage, cells that are essential for the frictionless movement of the joints. The outcome of the work will shed new light on the biology of those cells and will suggest ways to maintain their function during aging or restore it in chronic conditions including osteoarthritis and acute joint injury in pediatric and adult patients. In a related development, Dr. Pacifici joined forces with Dr. Robert Mauck in the Department of Orthopaedic Surgery at Penn to study whether progenitor cells isolated from developing embryonic synovial joints may have articular cartilage regenerative capacity superior to that of currently used cells such as bone marrow-derived mesenchymal stem cells. Such highly innovative studies are supported by a new grant Drs. Pacifici and Mauck just received from the VA.

Our basic research work on HO has directly led to a phase 2 clinical trial to treat children affected by Fibrodyplasia Ossificans Progressiva (FOP), a congenital and very severe form of HO. Papers we published in 2010 and 2011 showed for the first time that synthetic agonist ligands for nuclear retinoic acid receptors are very potent inhibitors of HO in experimental animal models of the disease. The Canadian-based pharmaceutical company Clementia working closely with us and our colleagues at the UPenn FOP Foundation—Drs. Fred Kaplan, Bob Pignolo and Eileen Shore-launched the clinical trial in July of the past year.

Our clinical Division remains a major national and international center of diagnosis, care and surgical treatment for children affected by hereditary multiple exostoses (HME). Our Basic Research Program is actively engaged in understanding the molecular pathogenesis of HME, using animal models and cells in vitro and funding from the NIH. To extend these basic research efforts and accelerate the pace of research toward translational medicine outcomes, a senior investigator—Dr. Paul Billings—joined our Division last year to create new cell-based bioassays to screen chemical libraries and identify drugs able to correct a specific polysaccharide deficiency that causes HME. Such pharmacological treatment could be used in combination with surgical interventions to provide a more effective and comprehensive therapy for HME patients in the future. This investment is paying off with new insights into the mechanisms of action of that polysaccharide in regulating cell function and into assays by which its function and production could be modulated by agents to elicit therapeutic outcomes.

Genetic Research

CHOP Orthopaedics is also working 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 obtained from patients and families with a variety of orthopaedic conditions, including targeting families with multiple individuals affected with adolescent idiopathic scoliosis (AIS), osteochondritis dissecans (OCD), and HME. A collaborative effort between the genetic, basic science and clinical teams indicated a putative genetic connection between the type 2 diabetes associated allele within TCF7L2 and EXT1 and EXT2, genes which are known to account for the primary genetic component of HME. The findings which published in Bone in early 2015, suggest a possible shared pathway between the two pathogeneses. Efforts to understand the genetic basis of adolescent idiopathic scoliosis also continue through efforts at CHOP and multi-center collaborations.

Biomechanical Research

Our division welcomed Saba Pasha, PhD to the research team in 2013. Dr Pasha is leading projects with a focus on orthopaedic biomechanics through extramural funding. In 2014, our research team integrated using EOS imaging with a pressure mat that permits association between skeletal deformities and patients’ balance during the course of the skeletal deformity progression and after surgery. She also initiated a 3D data registry to better investigate the pathomechanisms associated with juvenile knee abnormalities.

Clinical Research

The CHOP Orthopaedic Surgery division is currently conducting 124 ongoing, IRB approved clinical research projects. This includes 49 prospective randomized clinical trials, observational studies or clinical databases on patient care. Investigators within the division have been awarded funding from both internal and external sources to conduct these studies. In 2014, the division produced 125 publications in major orthopedic journals including JBJS, Spine, JPO and CORR. Abstracts were presented at the major national and
international meeting in the field including AAOS, POSNA, SRS, and AAP. Several projects were nominated for best papers at national meetings, and Ben Fox Scholar Christine Goodbody, (Perelman Penn Med ’15) won the Young Investigator in Training Award at AAP-Orthopaedics Section.

In 2009, our division initiated an annual Benjamin Fox Scholarship Award for current medical students who are interested in conducting a year of clinical research within Orthopaedics. In June, our department awarded Alex Gornitzky (Figure 6a) and Joseph Yellin (Figure 6b), both upcoming fourth year medical students at the Perelman School of Medicine at the University of Pennsylvania with this scholarship. While at CHOP, Alex has focused his research on the management and outcomes of development hip dysplasia (DDH), the genetics of osteochondritis dissecans, and Adolescent Idiopathic Scoliosis, including the psychosocial factors influencing bracing and postoperative management using the Rapid Recovery Pathway. Joe has concentrated his research on treatment of pediatric femur fractures and severe supracondylar humerus fractures, rehabilitation following ACL reconstruction, and neuromonitoring during spinal fusion in patients who may be neurologically compromised. He is also interested in examining infection rates and appropriate/efficient treatment surrounding VEPTR surgeries and osteomyelitis, respectively.

Recognitions and Achievements
Our Attendings have assumed several leadership roles within the pediatric orthopaedic community over the past year:

Keith Baldwin, MD is the director of clinical research in the Division of Orthopedics Surgery at CHOP. Dr Baldwin is also the Health Policy Chair of the Orthopedic Rehabilitation Association, Associate Editor for Rehabilitation of the Journal of Bone and Joint Surgery Reviews (JBJS), Editorial Board Member for World Journal of Orthopaedics, and Associate Editor for the Journal of Orthopaedic Trauma (JOT).

Robert Campbell, MD has continued to expand and develop the Center for Thoracic Insufficiency at CHOP. In August 2014, Dr Campbell co-directed the FDA Reviewers Pediatric Spine Course at CHOP. The course provided FDA reviewers with an understanding of surgical concepts, indications, and clinically important efficacy and safety parameters. The interactive sessions allowed for discussion on the use and approval of current and future pediatric spinal devices. Additionally, the VEPTR/VEPTR II received 510(k) clearance by the FDA in 2014. Dr Campbell, an inventor of the VEPTR, believes this will allow for increased availability of the device.

John P. Dormans, MD, FACS, Chief Emeritus of Orthopaedic Surgery at CHOP, is the current President of the Scoliosis Research Society (SRS) and will host the SRS’s 50th Anniversary meeting in Minneapolis, Minnesota in September 2015. He is also the Secretary General of the SICOT Foundation, Treasurer of SICOT International, and President of SICOT’s World Orthopaedic Concern (WOC).

Jack Flynn, MD, Chief of the Division of Orthopedics Surgery, served as the President of the Pediatric Orthopaedic Society of North America (POSNA) in 2013-2014 and hosted the 30th Annual meeting of POSNA in Hollywood, California in April, 2014. Dr. Flynn was elected to serve a 10 year term on the American Board of Orthopaedic Surgery and served as Burton Visiting Professor at Rochester and the Pediatric Orthopaedic Society of New Zealand visiting professor. He is one of the co-editors of Rockwood’s Fractures in Children, 8th ed. published in 2014, and serves as co-Chair of the International Pediatric Orthopaedic Symposium and is the Chair of the AAOS CME Courses Committee. He continues his service on the Board of Directors of the Children’s Spine Study Group, and is active in the Harms Study Group, a multi-center collaboration of researchers studying care improvements for pediatric spine deformity surgery.

Theodore J. Ganley, MD, is the Sports Medicine Director at CHOP supporting the clinical, research and outreach initiatives which continue to grow. Dr. Ganley recently collaborated on the creation of the new Penn/Children’s Hospital of Philadelphia orthopedic sports medicine fellowship with Dr. Sennett. He was an advisory board member for the International Pediatric Orthopaedic Symposium. Dr Ganley co-founded the Research in OCD of the Knee (ROCK) group and is on the board which developed the Pediatric Research in Sports Medicine (PRISM) group. He was also selected as a visiting Professor and invited lecturer this past year at Harvard Boston Children’s, Case Western Reserve University, Union Memorial Hospital, and The Mexican Society of Pediatric Orthopedics.

B. David Horn, MD is the current chair of the AAOS Pediatric Evaluation Committee and is currently in the process of editing the 2016 Pediatric Self Assessment Examination. He also co-edited the textbook Current Surgical Management of Fractures and Complications in Children, published in 2014.

John Todd Lawrence, MD, Ph.D, through an OMeGa grant, recently completed the development of a distal radius fracture model (patent pending) which will improve resident performance in fracture reduction and casting techniques. The model is currently being validated in conjunction with a multicenter pediatric simulation group.

Dr Christina Master, MD, continues to work to expand Minds Matter: Concussion Care for Kids at CHOP and the clinical and research enterprise continues to grow, as described above. In addition, in the fall of 2014, Dr. Master became certified in the new ABMS subspecialty area of Brain Injury Medicine with the

Figure 6. (A, B) From left to right, the 2014-2015 Benjamin Fox Research Fellows: Alex Gornitzky and Joseph Yellin.
Conditions and Injuries in Austere Settings. The textbook provides case-based information for surgeons in developing nations with limited resources in the context of public health, cultural differences, and historical precedents. In January 2014, Dr Spiegel was an invited lecturer at the inaugural Lancet Commission on Global Surgery Conference. He is also heading the AAOS International Scholar Program.

Lawrence Wells, MD became the Associate Director the Sports Medicine Performance Center at CHOP and Director of Quality, Safety, Value and Patient Experience in the Division of Orthopedic Surgery in 2014. He is the section editor for the orthopaedic section of Nelson's Textbook of Pediatrics 20th edition which will be published in 2015. Dr. Wells is the Vice President of the Philadelphia Orthopaedic Society and a member of the executive committee for the section on Orthopaedics for the American Academy of Pediatrics.

Wudbhav Sankar, MD is the Director of the Young Adult Hip Preservation Program at CHOP. Dr Sankar is a member of the Board of Directors for the Pediatric Orthopaedic Society of North America (POSNA) and served as the program chair for the at the 2014 Annual Meeting. Dr Sankar was also a faculty presenter at International Pediatric Orthopaedic Symposium (IPOS) and the AAOS/AAHKS/POSNA Open and Arthroscopic Techniques for Adolescent and Young Adult Hip Preservation Course. He is the section editor of the spine section of Operative Techniques and Orthopedics Surgery’s 2nd Edition, which will be published in 2015.

David Spiegel, MD, is the co-editor of the recently published textbook, Global Orthopedics: Caring for Musculoskeletal After 18 years of distinguished leadership, Dr. John P. Dormans, MD, FACS will be stepping down as Chief of Orthopaedic Surgery at Children’s Hospital of Philadelphia. In his tenure, Dr Dormans oversaw the division’s significant expansion in faculty from five to 25 and facilitated a robust basic and clinical research program. He continued to develop the ACGME-approved pediatric orthopedic surgery fellowship, increasing the number of positions from one to four. As director of the fellowship program, he has trained 51 clinical fellows and 37 research fellows and provided the next generation of surgeons with the skill needed to be leaders in the field. Clinically, Dr Dormans is internationally recognized for his work in treating pediatric spinal deformities and musculoskeletal tumors, and promoting safety in spinal surgery. He oversaw the development of the Spine Program, the Sports Medicine and Performance Center, the Center for Thoracic Insufficiency syndrome, the Neuromuscular Program, the Cerebral Palsy Program and the Young Adult Hip Preservation Program. In addition to his clinical appointments, Dr Dormans is active in a number of national and international organizations. He served as the President of the Pediatric Orthopedic Society of North America (POSNA), Scoliosis Research Society (SRS), and SICOT’s World Orthopedic Concern, Treasurer of SICOT International and Secretary General of SICOT’s Foundation during his tenure as division chief. He was also the president of the Medical Staff of CHOP (1999-2001) and Children’s Surgical Associates (3 terms). He has published more than 340 peer reviewed articles, written or edited five textbooks, 140 abstracts and 150 editorials, reviews or chapters.

Dr Dormans was a driving force behind the division’s growth for nearly two decades. His contributions to CHOP will continue to make a lasting impact on our staff and patients, and we will continue to celebrate his leadership.
The themes for Penn Orthopaedics Human Subjects Research (HSR) in FY15 are growth and collaboration. Starting in July 2014, the clinical research program of Penn Orthopaedics joined forces with the Department of Anesthesiology & Critical Care (ACC) to take advantage of the overlap in our patient populations and complementary research goals. Since the last edition of the UPOJ, our team of Orthopaedic Clinical Research Coordinators (CRCs) has nearly doubled and we have additional shared CRC resources with ACC. It is my pleasure to introduce the research team and summarize their roles for our readers.

Denise Knox, BS has been with Penn Orthopaedics for almost 8 years. She started as a CRC in Adult Reconstruction and has significantly matured in her role. She will be assuming the leadership of all studies for Penn Orthopaedics and ACC that are based out of the Penn Presbyterian Medical Center campus and will supervise all CRCs and assistants based out of Penn Medicine University City (PMUC) and Weightman Hall. As always, Denise has worked tirelessly on the numerous studies in Adult Reconstruction. Currently, there are six extramurally sponsored studies out of PMUC as well as five prospective cohorts and about twenty-five retrospective studies ongoing for the division. The partnership between Denise and Dr. Israelite has led to enthusiastic recognition from Zimmer on enrollment and the quality of data submitted to the sponsor in support of the post marketing follow up study of the Persona Personalized Knee System®. Quality improvement projects are also in place to identify, manage, and prevent risk for our patients. Under the leadership of Dr. Rod Eckenhoff in collaboration with Dr. Gwo-Chin Lee, Denise will be the lead coordinator in an investigator initiated study to study the effects of anesthesia on delirium in the adult reconstruction population. Dr. Hume’s efforts on two DePuy studies are supported by Denise as well, and the department is about to launch our affiliation with the American Joint Replacement Registry (AJRR). Dr. Hume’s effort in coordinating the information technology to make participation in AJRR possible should also be singularly recognized. We look forward to more fully engaging the Pennsylvania Hospital Adult Reconstruction team in research in the upcoming year.

In July of 2014 Lisa Gardo, BSN joined the Fibrodysplasia Ossificans Progressiva (FOP) research team to be the Nurse-Cordinator for the Clementia Pharmaceutical sponsored research program in FOP (Dr. Kaplan, Global PI; Dr. Pignolo, Site PI). She was joined a few months later by Shannon Chester, BS, who serves as the CRC on a series of critical multicenter international studies to test the safety and efficacy of palovarotene as an adjunct treatment for preosseous flare-ups in adults with FOP. The logistic complexity of these trials is astounding and the team has

Team FOP, (A–C) from top, Lisa Gardo, BSN, Shannon Chester, BS, and Kamlesh Rai.
will be joining forces with other faculty to engage in clinical research. New to the team and the world is Ms. Ava Marie Marcoon, who was born 11/15/2014. We anticipate that Ava’s training in clinical research will commence sometime after she finishes preschool. Congratulations to Shannon, and welcome Ava!

Exciting developments have been going on with Upper Extremity HSR as well as Orthopaedic Oncology and Foot & Ankle, all led by Kara Napolitano, BS. Kara joined Penn Orthopaedics in FY15 as the Upper Extremity CRC and in the past year she has become quite the generalist. Kara has been continuously engaged in Hand (NIH funded WRIST study, PI Dr. Bozentka) and Shoulder & Elbow studies, including Dr. Huffman’s work on the molecular assessment of Propionibacterium Acnes (\(P. acnes\)), the Auxilium-sponsored frozen shoulder study (Dr. Kelly co PI and Shannon Marcoon co-CRC), developing an industry collaboration with Dr. Glaser for the study of frozen shoulder, and managing Dr. Kuntz’s McCabe funded multimodal management of post-operative pain (MP3, Nabil Elkassabany, MD, co-PI). Additionally, Kara has been uniting the east and west sides of campus by working on the STAR study under Dr. Wapner as well as tirelessly engaging Genentech/Roche to enable us to begin an interventional study for pigmented villonodular synovitis (PVNS) under Dr. Kristy Weber. We are hoping to have Kara’s home base at the Cathcart Pavilion to enable her to continue supervising Foot & Ankle as well as solidifying the engagement of the Cathcart practice in HSR.

OrthoTraumaTeamSix@uphs.upenn.edu is no stranger to any resident rotating through Ortho Trauma. Patrick Hesketh, BS and Evan Bannister, BS, aka OrthoTraumaTeamSix

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

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

(A) Patrick Hesketh, BS and (B) Evan Bannister, BS, aka OrthoTraumaTeamSix
collaborations have strengthened the relationship between the two departments and hopefully will support funded multicenter studies in the near future.

It is now my pleasure to introduce our ACC partners in HSR. Kim Lacy, BSN has been a vital member of ACC research and has worked with Dr. Michael Ashburn for years at Penn Medicine Rittenhouse. In the past year, Kim, Marlon Schwarz, MD with assistance from TeamSix have been engaged in supporting Dr. Ben Kohl’s study based out of the Hospital of the University of Pennsylvania (HUP) that investigates the intraoperative use of exenatide in cardiac surgery patients to prevent post-operative complications. Kim and Marlon have been extremely active in HUP-based studies. Dr. Marlon Schwarz, however, will be leaving the research team in May 2015 to join ACC as a resident. Best wishes to Dr. Schwarz and we look forward to continued research collaborations with him. The most recent addition to ACC HSR is Rebekah Williams, BS. Rebekah joined ACC in July of 2014 as a research assistant under Dr. Elkassabany and was working on the Kuntz-Elkassabany MP3 study as well as on a project for Dr. Jack Gutsche. In February 2015 Rebekah assumed a new role in ACC where she will now serve all of ACC HSR projects based out of HUP.

Thank you to all the named staff above as well as the leadership of Penn Orthopaedics and Anesthesiology & Critical Care for developing the shared resources plan for the two departments. 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, Lori Gustave and Dennis Harris. Additional staff will be forthcoming to support this collaborative effort so look forward to ever more exciting and meaningful work in the years to come.
The McKay Orthopaedic Research Laboratory of the Department of Orthopaedic Surgery in the Perelman School of Medicine continues to explore important problems in musculoskeletal research. The research facility, including labs and offices, occupies just over 15,000 sq. ft. of space on the 3rd, 4th and 5th Floors of Stemmler Hall. There are over 100 full- and part-time staff and trainees now in the labs. It is an active, thriving research and educational environment.

Currently, the lab has an annual research budget from extramural grants, gifts, and endowments over $7,000,000 and 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 2014 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 awarded this year. These are:

• George Dodge, Ph.D. and Robert Mauck, Ph.D. are PI’s of a VA grant titled “Cartilage response to compression injury: A platform for therapeutics discovery.”
• John Esterhai, M.D. and Lachlan Smith, Ph.D. are PI’s of a VA grant titled “Engineered Multi-Functional Nanofibrous Meniscus Implants.”
• Sherry Liu, Ph.D. is PI of an Institute on Aging grant titled “The stimulation of modeling-based bone formation in estrogen-deficient bone.”
• Robert Mauck, Ph.D. and Lachlan Smith, Ph.D. are PI’s of a VA grant titled “Bioactive Injectable Implants for Functional Intervertebral Disc Regeneration.”
• Robert Mauck, Ph.D. is PI of a renewed NIH grant titled “Multi-scale biomechanics of engineered and native fibrous load-bearing tissue.”
• Robert Mauck, Ph.D. is PI of a renewed NIH grant titled “Dynamic Fibrous Scaffolds for Repairing Dense Connective Tissues.”
• Robert Mauck, Ph.D. is PI of a renewed NIH grant titled “Engineering developmental microenvironments: Cartilage formation and maturation.”
• Faye Mourkoti, Ph.D. is PI of a McCabe grant titled “A stem cell therapy intervention in diseased skeletal muscles.”
• Faye Mourkoti, Ph.D. is PI of a PCMD pilot grant titled “A Novel Molecular Mechanism in Chronic Skeletal Muscle Injury.”
• Robert Pignolo, M.D., Ph.D. is PI of a new clinical trial titled “A Phase 2 Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of aRARα-Specific Agonist (Palovarotene) in the Treatment of Preosseous Flare-ups in Subjects with Fibrodysplasia Ossificans Progressiva (FOP).”
• Harvey Smith, M.D. is PI of a VA grant titled “Tissue-Engineered Constructs for Treatment of Intervertebral Disc Degeneration.”
• Andy Kuntz, M.D. is PI of a McCabe grant titled “Development and Evaluation of a Multimodal Analgesia Protocol for Postoperative Pain Management in Shoulder Surgery.”
• Andy Kuntz, M.D. is PI of an Institute on Aging grant titled “Effects of Autologous Juvenile, Adult, and Aged Tenocyte-Seeded Nanofibrous Scaffolds in Rotator Cuff Repair.”
• Andy Kuntz, M.D. is PI of a VA grant titled “Genetic Response in the Adaptation of Supraspinatus Tendon and Muscle to Load.”
• Lou Soslowsky, Ph.D. is PI of an NIH R01 titled “Injury Response in Normal and EDS Tendons: Regulatory Roles of Collagen V.”
• Lou Soslowsky, Ph.D. is PI of an Orthofix, Inc SRA titled “Pre-Clinical Rotator Cuff Study: Effects of PEMF on rotator cuff repair in a rodent model.”

In addition to the above-mentioned new grants this year, each of the McKay Laboratory faculty remains well-funded through existing research grants not identified in this new grants list. Further, there were several new grants and clinical trials for our surgeon faculty this year. These are:

• Joshua Gordon, M.D. is PI of an AANA grant titled “The Association between Adhesive Capsulitis and Diabetes Mellitus: A Genome Wide Analysis of Expression.”
• G. Russell Huffman, M.D. received another Surgical Shoulder and Elbow Fellowship from DePuy.
• Craig Israelite, M.D. is PI of a clinical trial from Zimmer titled “TKA Outcomes Study Prospective Multicenter Study of the Persona Knee System.”
• Brian Sennett, M.D. & Dr. Milt Zgonis received fellowship grants from DePuy Mitek, Conmed, and Arthrex.
• David Steinberg, M.D. received a Hand & Upper Limb Fellowship from ASSH.
• Jaimo Ahn, M.D. is PI on an OTA grant titled “Disruption of TSP-CD47 Pathway to Enhance Ischemic Fracture Healing,” an FOT grant titled “Acceleration of Geriatric Fracture healing by local activation of notch signaling,” and a clinical study from Design Science titled “DePuy Synthes Trauma Intramedullary (IM) Nail Ethnographic Market Research.”
• David Bozentka, M.D. is PI of a clinical trial from Axogen.
We have also received several grants from Synthes for residents to attend various courses.

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

- John Esterhai, M.D. is PI of a clinical trial from Johns Hopkins titled “Outcomes Following Severe Distal Tibia, Ankle and/or Foot Trauma: Comparison of Limb Salvage vs Transtibial Amputation Protocol (OUTLET Study).”
The University of Pennsylvania Department of Orthopaedic Surgery is pleased to announce the opening of the Biedermann Lab for Orthopaedic Research. This lab has been made possible through a generous donation from the Biedermann family to celebrate the 100th anniversary of their involvement in orthopaedic medicine. Now in its fourth generation, since Max Biedermann first began his work in prosthetics in 1916 (Figure 1), the Biedermann family continues to work and dedicate their lives to orthopaedic research and development. Throughout the years, the Biedermann family has always maintained a strong belief that research is the basis for the development of meaningful novel and innovative treatment concepts. Based on this tenet, a partnership has been established with the University of Pennsylvania to develop a world class biomechanics laboratory.

The goal of the Biedermann Lab is to provide a venue to test novel treatment concepts, existing and new technologies, and unproven theories to get quantifiable and unbiased results that will improve the standard of care and the quality of life for patients. The lab will be located on the 10th floor of Penn Medicine University City, making it easily accessible to surgeons and residents at Penn. The lab will also open its doors to clinicians and researchers throughout the rest of the world, making it a one-of-a-kind environment for collaborative research and innovative exploration in the field of orthopaedics. To this end, the facility will have the capabilities to perform research that includes, but is not limited to: mechanical and biomechanical testing, cadaveric specimens, animal studies, finite element analysis, and dynamic computational modeling.

Scheduled to open in June of 2015, the lab will consist of over 3200 square feet of office and laboratory space (Figure 2). It will be equipped with the tools needed to perform cutting edge research, including: five dissection tables, two universal testing machines, a mobile C-arm, a 3-D motion capture system, a 3-D printer, and an on-site machine shop. Michael Hast, who earned his Ph.D. from the Pennsylvania State University in Mechanical Engineering with a focus on Biomechanical Computational Modeling, has been named the Director of the lab and will oversee day to day operations. Samir Mehta, MD will act as the primary clinical delegate for the Department of Orthopaedic Surgery and will work in conjunction with Surena Namdari, MD (former University of Pennsylvania Orthopaedic resident and current faculty member at Thomas Jefferson University) as the clinical members of the research advisory board.

The Biedermann Lab for Orthopaedic Research has been designed with long-term research goals in mind. Specifically, the lab space has been built so that it can accommodate a growing staff and provide biomechanical testing services to a large spectrum of research interests simultaneously. Initially, the current group will focus on projects that seek to improve clinical outcomes of orthopaedic procedures complicated by osteoporosis. As the size and capabilities of the lab grow in the future, it will be able to facilitate testing for an increasing number of research collaborations.

If you are interested in learning more about the Biedermann Lab, please feel free to contact Michael Hast by emailing him at hast@upenn.edu.
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 have introduced incredible life-saving technologies, an increasing number of our wounded soldiers return home with damaged limbs and joints. 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 five years have witnessed a dramatic growth in VA-sponsored MSK research across the nation, with one of the largest increases occurring at our Philadelphia VA Medical Center (PVAMC). Physician investigators, basic scientists, and engineers at the PVAMC, 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 PVAMC 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 >6,000 sq. ft. of newly renovated research space at the PVAMC. Drs. Robert Mauck and George Dodge co-direct this new enterprise with input, advice, and support from a joint PVAMC/PennTMRC Advisory Committee.

The goal of the TMRC is to develop a focused, internationally recognized research center at the PVAMC 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 PVAMC 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 $3 million in equipment to outfit this new facility, including state-of-the-art devices such as in vivo micro-CT, fluoroscopy, atomic force microscopy, and super-resolution confocal imaging. Over the past year, the TMRC has continued to grow, with new Merit Awards (R01 equivalents), awarded to Dr. Mauck, Dr. Dodge, and Dr. Esterhai. Additionally, the TMRC received its first CDA2 Award -- a five year career development award awarded to Dr. Harvey Smith from Orthopaedic Surgery. Most recently, both Dr. Carla Scanzello (Rheumatology) and Dr. Andy Kuntz (Orthopaedic Surgery) received funding through the SPIRE Award mechanism (equivalent to an NIH R21) in support of their growing research programs. Finally, Drs. Mauck and Dodge, along with the entire team, contributed to the submission of a Shared Equipment Grant, and recently heard that that...
subside. This equipment grant will support the acquisition of a new high resolution microCT specimen scanner and associated computing resources (at a cost of $500,000) for use by TMRC investigators and their collaborators across the Penn community. 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 VA Funding at the TMRC

<table>
<thead>
<tr>
<th>Type</th>
<th>PI</th>
<th>Amount &amp; Duration</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merit</td>
<td>D. Steinberg</td>
<td>$275,000 per year for four years (2012-16)</td>
<td>Cartilage Repair with Stem Cell Seeded Hyaluronic Acid Hydrogels</td>
</tr>
<tr>
<td>Merit</td>
<td>J. Bernstein</td>
<td>$275,000 per year for four years (2013-17)</td>
<td>The Role of Local NSAID Administration and Inflammation on Tendon Healing</td>
</tr>
<tr>
<td>Merit</td>
<td>G. Dodge</td>
<td>$275,000 per year for four years (2014-18)</td>
<td>Cartilage Response to Compressive Injury: A Platform for Therapeutic Discovery</td>
</tr>
<tr>
<td>Merit</td>
<td>R. Mauck/L. Smith</td>
<td>$275,000 per year for four years (2014-18)</td>
<td>Bioactive Injectable Implants for Functional Intervertebral Disc Regeneration</td>
</tr>
<tr>
<td>Merit</td>
<td>J. Esterhai/R. Mauck</td>
<td>$275,000 per year for four years (2014-18)</td>
<td>Engineered Multi-Functional Nanofibrous Meniscus Implants</td>
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<tr>
<td>CDA2</td>
<td>H. Smith</td>
<td>$400,000 per year for five years (2014-19)</td>
<td>Tissue-Engineered Constructs for Treatment of Intervertebral Disc Degeneration</td>
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<tr>
<td>SPiRE</td>
<td>R. Mauck</td>
<td>$100,000 per year for two years (2014-16)</td>
<td>Cartilage Repair with Synovial Joint Precursors</td>
</tr>
<tr>
<td>CPPF</td>
<td>A. Kuntz</td>
<td>$50,000 over one year (2014-15)</td>
<td>Genetic Response in the Adaptation of Supraspinatus Tendon and Muscle to Load</td>
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<tr>
<td>SPiRE</td>
<td>C. Scanzello</td>
<td>$100,000 per year for two years (2015-17)</td>
<td>The Impact of CC-Chemokine Receptor 7 (CCR7) on Synovitis and Osteoarthritis</td>
</tr>
<tr>
<td>SPiRE</td>
<td>A. Kuntz</td>
<td>$100,000 per year for two years (2015-17)</td>
<td>Effect of Scaffold-Delivered Growth Factors on Rotator Cuff Repair</td>
</tr>
</tbody>
</table>
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