The University of Pennsylvania Orthopaedic Journal

Volume 24 June 2014

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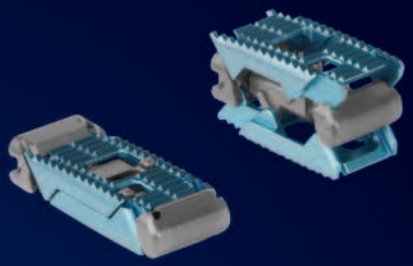

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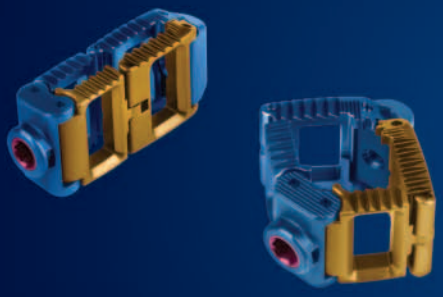

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The University of Pennsylvania Orthopaedic Journal

Volume 24, June 2014

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The University of Pennsylvania Orthopaedic Journal

Volume 24, June 2014

Table of Contents

CLINICAL ARTICLES

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1. DePuy Synthes Joint Reconstruction 2014. Data on File.

BASIC SCIENCE ARTICLES

Biomechanics of Ligament and Tendon

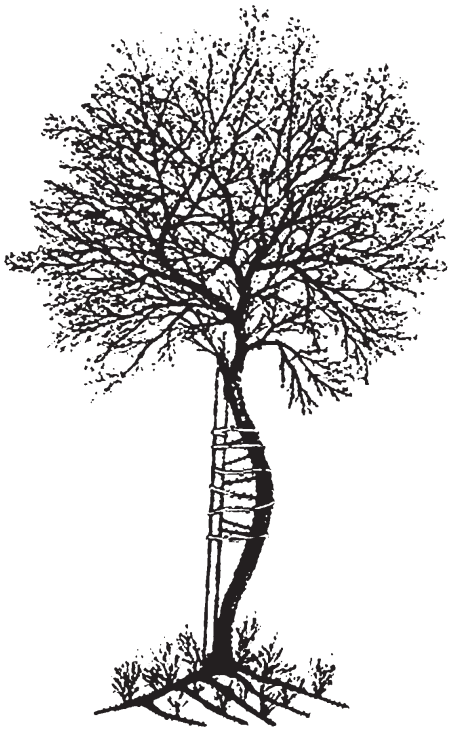
Musculoskeletal Tissue Engineering

Stem Cell Mechanobiology

Fracture Healing

Cartilage and Bone Biology

Translational Animal Models



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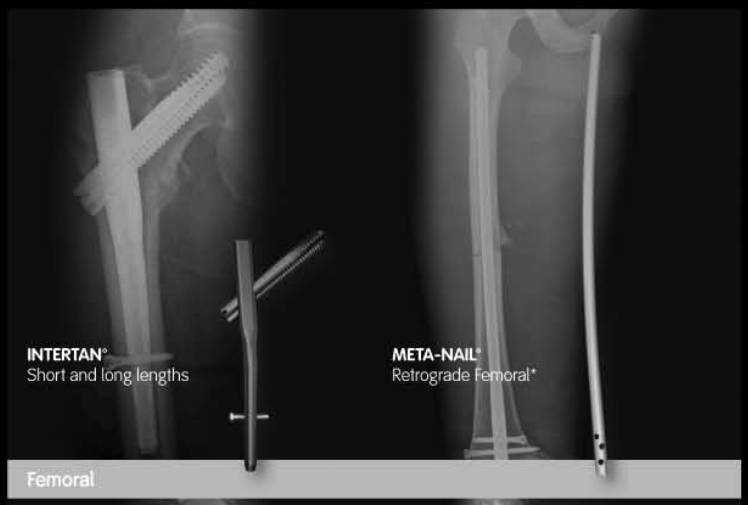
EDITORIALS

DEPARTMENTAL ITEMS

HEALTH SYSTEM UPDATES



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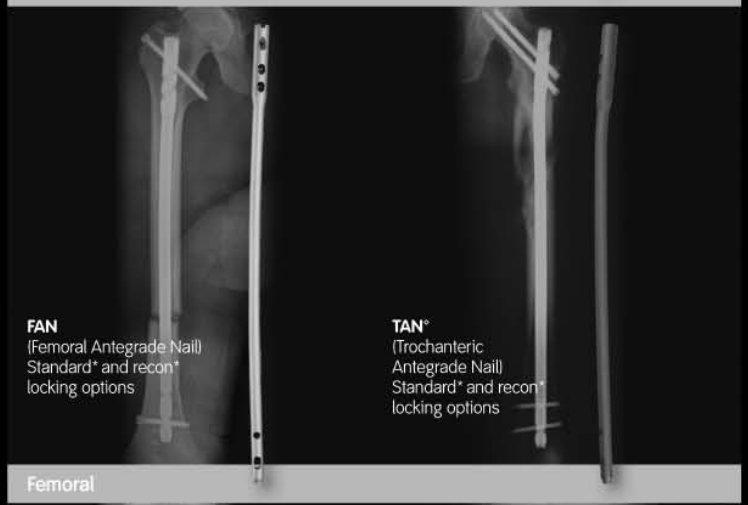

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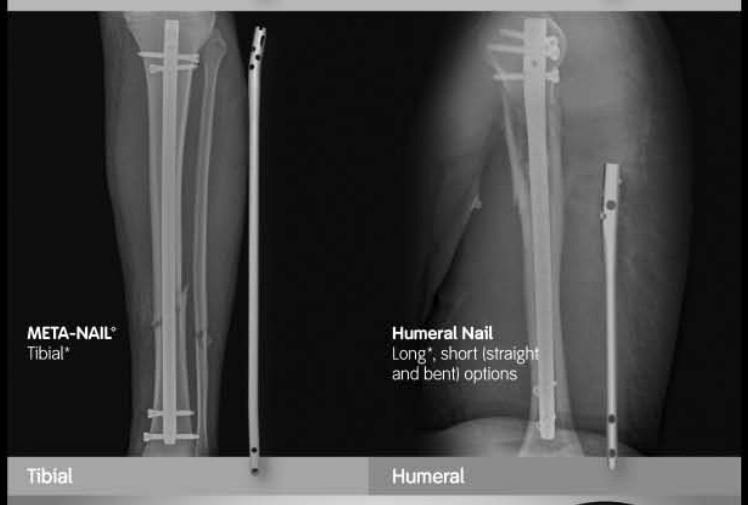

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Letter from the Editors-in-Chief

We are proud to present the 24th edition of the *University of Pennsylvania Orthopaedic Journal (UPOJ)*. The *UPOJ* began in 1985, during the leadership of previous Chairman, Dr. Carl T. Brighton. Since then, the *UPOJ* has been published annually, except for a brief hiatus from 1993 to 1997. Thus, with the publication of the 24th edition, we celebrate the 29th anniversary of the nation's oldest fully resident-run orthopaedic journal.

We proudly dedicate this edition of the *UPOJ* to Ernest J. Gentchos, MD, a towering figure at Penn, and a man whose actions have spoken volumes about his genuine nature and seemingly limitless generosity. After a career of service to Penn spanning four decades, Dr. Gentchos retired from his nonoperative clinic at HUP last year. However, he continues to staff the orthopaedic clinic at the Philadelphia VA, where he imparts more than a half-century of wisdom and knowledge to residents. Indeed, Dr. Gentchos serves as a constant reminder of the values of education, service, and philanthropy. This edition is but a small tribute to an individual who has served Penn so loyally for so many years.

On a more somber note, publication of the *UPOJ* also allows us to reflect on those we have lost over the past year. This winter, the Penn Orthopaedics family lost a dear friend, colleague, and teacher. Anthony "Tony" Searles passed away after a long battle with cancer. For decades, Tony and his smile were constant figures in the clinic at HUP. He taught generations of attendings, residents, and medical students the art of casting and splinting, skills that are often underappreciated, yet paramount to excellent patient care. In this edition of the *UPOJ*, we feature a tribute to Tony Searles, written by Dr. Frederick Kaplan, one of his close friends and a leading figure at Penn Orthopaedics.

This year, we are continuing to structure and format clinical and basic science articles in the "extended abstract" process that was begun last year by our predecessors, Andrew Milby and Sarah Yannascoli, and was a rousing success. Along with presenting information and ideas in a succinct manner, the extended abstract format also allows our authors to submit their work to the *UPOJ* without restricting their ability to submit full-length versions of their work to other peer-reviewed journals.

Although we are proud of the *UPOJ's* legacy as a print journal, this edition ushers the *UPOJ* into the age of digital media. We are thrilled to introduce the revamped *UPOJ* website designed by Daniel Steinberg, founder of Hyaline Creative. As Daniel's father is David Steinberg and his grandfather is Marvin Steinberg, this marks three generations of Steinbergs who have served Penn Orthopaedics well. We hope that the new website provides a more attractive and far-reaching platform for our current and past articles. We urge you to visit us at www.upoj.org.

Since 1997, the *UPOJ* has been financially independent from the Department of Orthopaedic Surgery. Thus, this journal would not be possible without the financial support of our advertisers. We extend our gratitude to our industry and commercial sponsors whose generous contributions further our mission of musculoskeletal research and education.

Publication of the *UPOJ* would also not be possible without the support of our Chairman, Dr. L. Scott Levin, and Program Director, Dr. Craig L. Israelite. We are also indebted to our faculty advisors, Drs. Samir Mehta and Jaimo Ahn, for their mentorship and guidance. We give a hearty thanks to our content editors for their hard work and enthusiasm, for they help to make the journal what it is: Drs. P. Maxwell Courtney and Christopher Melnic (adult reconstruction); Dr. Stephen Liu (hand surgery); Dr. Jonathan Slaughter (spine); Dr. Michael McGraw (sports medicine); Dr. Jason Anari (trauma); Dr. Russell Stitzlein (shoulder and elbow); and Dr. Alexander Neuwirth (pediatrics).

On behalf of our fellow authors, editors, and mentors, we proudly present the 24th edition of the *UPOJ*. Within this edition, you will find some of the latest ideas and trends in clinical and basic science, as well as editorial features on progress in the Department and beyond. We hope you enjoy.

Sincerely,
Vishal Saxena, MD, and Joshua A. Gordon, MD
Editors-in-Chief
The University of Pennsylvania Orthopaedic Journal
Volume 24

Dedication to Ernest J. Gentchos, MD

Vishal Saxena, MD, and Joshua A. Gordon, MD

It is our great honor and privilege to dedicate the 24th edition of the *University of Pennsylvania Orthopaedic Journal* to Ernest J. Gentchos, MD, a man whose commitment to education and service to the University of Pennsylvania and beyond are unparalleled.

Dr. Gentchos was born in Greece in 1937. The Greece of his early childhood knew only war and occupation by the armies of Mussolini and Hitler. Many Greeks perished during this occupation, including some of Dr. Gentchos's closest childhood friends. The end of WWII brought no respite, as Greece soon became engulfed in a devastating civil war which lasted until 1953. Due to the conflict and political instability, Dr. Gentchos did not see his father until the age of 11. His father traveled back and forth between the US and Greece and was not allowed back into Greece during the occupation and subsequent civil war. Dr. Gentchos remained in Greece where he lived with his mother and large extended family. In 1948, Dr. Gentchos and his mother escaped Greece and emigrated to the US where they could be reunited with his father.

Dr. Gentchos's first exposure to medicine was as an orderly at his community hospital. He gained an exceptional foundation in human anatomy and pathology by participating in every autopsy he could. He did his undergraduate studies at Benedictine University in Illinois, where he first developed his interest in physics. He then attended medical school at St. Louis University School of Medicine. Again, war dominated his early adulthood. After completing his internship at Albert Einstein Medical Center in Philadelphia, Dr. Gentchos joined the Army and was eventually deployed to Vietnam, where he spent 13 months.

Upon returning from Vietnam, Dr. Gentchos completed a surgical residency at the University of Pennsylvania under the guidance of Dr. William Blakemore and furthered his interests by completing an orthopaedic residency with Dr. Edgar Ralston. Giants walked the earth in those days. Upon completing residency, Dr. Gentchos went into private practice for eight years. He then did a fellowship in spine surgery at Beth Israel Hospital in Boston, MA. After fellowship, Dr. Gentchos returned to private practice in New Jersey but remained active in Penn Orthopaedics through teaching medical students. In 1997, Dr. Gentchos returned home and joined Penn Orthopaedics as a full-time faculty member. For a decade, he staffed the nonoperative clinic in the Shoulder and Elbow Service, working side-by-side with Drs. Gerald Williams, Joseph Iannotti, and Matthew Ramsey. He then staffed the general nonoperative clinic at HUP.

In 1948, Dr. Gentchos was the 61st American citizen evacuated from his region of Greece since the start of WWII.

Dr. Gentchos at age 10.

Dr. Gentchos's commitment to education and lifelong learning is matched only by his generosity. Fifteen years ago, he began endowing scholarships to medical students, undergraduates, and high school students. Currently, he funds scholarships for four medical students at two medical schools, two undergraduates, and one high school student. Over the years, Dr. Gentchos has enabled dozens of students to pursue their dreams. Scholarship recipients have gone into numerous fields, and they have given back as well. And many of them continue to keep in touch with the man whose generosity knows no bounds.

Dr. Gentchos retired from HUP last year, but he can still be found regularly at Friday clinic at the VA. It is only fitting that after a life dominated by war, Dr. Gentchos still dedicates his time to the care of our veterans. Dr. Gentchos remains a vibrant participant in the Penn Orthopaedic community. He is the first person present at HUP Trauma Conference on Mondays and Tuesdays, and he is a regular presence at Orthopaedic Grand Rounds. Whenever we discuss patients who have failed primary and revision surgical intervention, you can always find Dr. Gentchos shaking his head wistfully and reminiscing about the era in which he trained and practiced, one in which physicians had to rely more on their resourcefulness and skill in nonoperative management to overcome limitations in their implants. In a time when we have the latest and greatest implants and technology at our disposal, Dr. Gentchos serves as an invaluable reminder that the simplest solutions still often work the best. Thus, we are proud to honor and dedicate the 24th edition of the *UPOJ* to Ernest J. Gentchos, MD, a fitting tribute to a man who has impacted generations of physicians at Penn Orthopaedics and throughout the medical community.

Letter from Dr. Ernest J. Gentchos

I am humbled to be honored by the *University of Pennsylvania Orthopaedic Journal*. Heaven knows that I don't deserve it. Honors are reserved to celebrate recognition and accomplishments.

I am not JJ Thomson, the third Director of the Cavendish Laboratory in Physics at Cambridge University, England. He discovered the electron. This was the first fundamental nuclear particle. The atom no longer stood whole and alone. For this he received a Nobel Prize. The laboratory went on to attract English as well as foreign students, who demonstrated enthusiasm, curiosity, and open-mindedness. Seven of his students, along with his son, went on to each receive the Nobel Prize, and 27 of his students were accepted to the Royal Society of England, a testament to a great teacher and mentor.

There are also other kinds of awards. They honor philanthropic donors, who are noble and should be honored. Some donors, however, come top heavy with strings attached. They come with hidden agendas. They are the kind that seek access to the corridors of power, influence, and privilege. We have seen and know them: the kind that compromise great institutions as well as individual physicians. They are the kind that seduce us. Where have the legal system, insurance industry, and government taken us? Did I forget to mention we are no longer doctors but only providers? What would Dr. Edgar Ralston say? What would Dr. Jonathan Rhoads say?

Like many doctors from my era, my summers throughout high school and college were spent in community hospitals working as orderlies. Beginning in the emergency room, I then went on to the pathology department. I learned a great deal of anatomy and pathology by assisting in autopsies.

Finally I worked up to surgical assistant in the OR. The surgical staff recognized that I wanted to be a doctor. They became my teachers. I was seventeen years old when I did my first appendectomy, of course under supervision.

In the early 1950s, there was no heart-lung machine. Open surgery for congenital heart disease in children was performed under hypothermia. I was the junior member of the hypothermia team. This presented a great opportunity for me to meet the prominent cardiac surgeons. They were good and fast. This team of cardiac surgeons, headed by Dr. Charles Bailey, made the cover of *Time* magazine in the 1950s. I will always be grateful to the staff of our community hospital for all that they taught me.

I applied to medical school during my second year of college. I was accepted during my third year. I attended St. Louis University School of Medicine in St. Louis, MO. During my second year of medical school, I was plagued with bouts of recurrent bowel obstruction and periodic bleeding. On numerous occasions, I was considered a candidate for a large bowel resection. I have generalized diverticulosis of the colon. The chairman of the GI service was opposed to a partial or total colectomy since the exact site of the bleeding could never be determined at that time. In 2007, I had massive GI bleeding requiring transfusion of eight units of blood. Bleeding spontaneously stopped – no surgery performed.

After finishing medical school and internship, I served in the United States Army for two years. I was stationed at Fort Campbell, KY, with the 101st Airborne Division. The 101st Airborne Division is on alert 24 hours a day, ready for worldwide deployment. The paratroopers from this division can jump from less than 1200 feet with accuracy to the drop zone. During the Cuban Missile Crisis, the mission of the 101st was to capture Havana Airport. All members of the 101st Airborne Division were expected to jump, including the doctors. Fortunately, war was averted. Thank God, as the casualty rate was expected to be 30-40% in such an operation.

My second posting was to Fort Benning, in Columbus, GA, the home of the 2nd Infantry Division. Martin Army Hospital at Fort Benning has a large orthopaedic service. In addition to being the site of the paratrooper jump school, Fort Benning was also the training area for the helicopter pilots and crew who were to form the new First Air Cavalry Division. These groups provided a wealth of orthopaedic injuries. Our civilian consultant was Dr. Jack Hughston of Columbus, GA, a premier orthopaedic surgeon. The 15th Medical Battalion was formed in support of the First Air Cavalry Division, and off we were to Vietnam, where I spent 13 months.

Upon my return, I met with Dr. William S. Blakemore at Penn. He advised me to attend the postgraduate school of surgery of the University of Pennsylvania for one year and then enter surgical residency as a second year with him. The postgraduate school of surgery was a magnificent year of education. There was yearlong surgical anatomy taught by Dr. Michael Hardy, a renowned orthopaedic anatomist, and physiology taught by the Department of Physiology. The year also included classical surgical procedures performed on dogs. Follow-up care was given to our canine patients, and the dogs were expected to recover. We also observed surgery by Penn physicians at HUP and Pennsylvania Hospital.

At the conclusion of this year, having passed the written exam, I entered second year surgical residency with Dr. Blakemore. At the completion of my second year of surgical residency, my interest returned to orthopaedics. When I met with Dr. Blakemore and expressed my interest in orthopaedics, he immediately, in my presence, phoned Dr. Edgar Ralston and told him he had a young man for his program. Dr. Ralston replied, "Send him over." During my final two years of orthopaedic residency, I served as Chief Resident. In 1985, I took a fellowship in Spine at Beth Israel Hospital in Boston, MA, a Harvard University program, with Dr. Gus White.

If we are lucky in our school years and are blessed with at least one teacher who becomes our true mentor, the path of our lives is influenced and defined with inspiration and dignity in a way we have not imagined. During my career, I have been fortunate to benefit from several outstanding teachers and mentors. Dr. Blakemore was a very intimidating person. His Saturday morning Grand Rounds were legendary and lasted for hours. Each patient in the ward was seen, his history was presented, and any complication was discussed in an open forum.

Dr. Ralston, the Chairman of the Department of Orthopaedic Surgery, was a deep thinker, highly intelligent, a gentleman with great integrity. He hardly ever gave a lecture. In fact, I don't remember even one. He never called attention to himself, but you knew you were in the presence of a great man. He led by example. As Chief Administrative Resident for two years, I had the privilege of working closely with him. He had a very kind heart. He left it to me to deal with problems.

Dr. Zachary Friedenberg was truly a genius. He was extremely disciplined, well-read, and athletic. His surgeries were slow but technically superior. I spent every day with him for six months during my senior rotation. I miss him so.

Dr. Marvin Steinberg is a man for whom I have the greatest admiration. He has been a friend, fellow physician, and mentor. He has a heart of gold. Our discussions to this day are legendary, especially when we have opposite views.

Dr. Richard Lackman will always be remembered for saving our residency program. His commitment to education can never be forgotten.

To quote Shakespeare, "Some are thrust into greatness." Dr. Scott Levin has a lot on his plate. He has been called to lead this historic University of Pennsylvania Department of Orthopaedic Surgery, the first in the nation. Our residency program is second to none, attracting the best and brightest. Our young faculty shows great promise. The research program under Dr. Lou Soslowsky is outstanding. The new orthopaedic institute is about to become a reality. We proudly support and salute the accomplishments of Dr. Levin. He is our General George Patton. He will get the job done.

With tremendous support and the generosity of many of my patients as well as our family and friends, I have established endowed scholarships in support of medical, college, and high school students. These include scholarships at two medical schools, two colleges, and two high schools as well as one endowed medical lectureship.

These endowed scholarships are more than just financial. They demonstrate our significant commitment to education. By this, we hope that the students who receive these scholarships will be motivated to succeed and consider future generations of students.

My life has had value not only to my family but also to others whom I had the opportunity to help. If you ask what my personal philosophy is, I would answer, *What you do for others matters most.* That is how I live my life..

Letter from the Chairman

L. Scott Levin, MD, FACS

July 1, 2014, at 06:00, will mark my completion of five years as Chairman of the Department of Orthopaedic Surgery at the Ruth and Raymond Perelman School of Medicine at the University of Pennsylvania. As I look back on the last five years, I take tremendous pride in the accomplishments of our faculty, residents, fellows, researchers, medical students, staff, and Allied Health personnel who have contributed to our continued success. The missions of our academic medical center that encompass clinical care, education, and research are all flourishing. However, our work is never done.

I also pause to reflect on surgical lessons learned. In 1982, I served as an intern in general thoracic surgery under the leadership of Dr. David C. Sabiston, Jr. Dr. Sabiston was legendary for emphasis on "attention to detail" and his commitment to excellence, always setting the bar higher despite great achievements by his department. I believe this defines my style of leadership.

Over the years, I have also shared with you my enthusiasm for the lessons of Jim Collins, author of *Good to Great*. One of the key principles that Collins emphasizes in all of his books is the importance of "getting the right people on the bus before the direction of the bus can be established."

Over the last five years, the momentum and trajectory of the Department has been positive, with recruitment of young faculty and retention of world-class, established surgical scholars. Currently there are 31 clinical faculty and 6 tenure-track PhD research faculty. This represents double digit percentage growth in both clinical and basic science research faculty members. We now have "the right people on the bus."

It is important to realize that growth for the sake of growth alone is often detrimental to the balance of a department or enterprise, particularly if there is little need for extra clinical or research faculty. The trajectory of Penn Orthopaedics has been positive. Due to our excellence in clinical care, patient demand for our expertise has increased. We have recruited faculty with specialized talents and enthusiasm for our clinical missions. We have continually diversified and added to our basic science capabilities in the McKay Orthopaedic Research Laboratory.

My philosophy has been not only to build "depth" on our bench but also to hire individuals with unique skills that will help differentiate Penn Orthopaedics in a competitive market locally and attract attention to our clinical, research and educational advancements nationally and internationally. This year, Foteini Mourkioti, PhD, will join us from Stanford. She is an expert in muscle physiology and will be instrumental in establishing liaisons with other basic science departments at Penn to study muscle function in a variety of musculoskeletal conditions.

In keeping with our rapid growth of the Adult Reconstructive Service, we recently recruited Atul Kamath. He returns to Penn, having completed his Adult Reconstructive fellowship at the Mayo Clinic, followed by the prestigious Maurice Mueller Traveling Fellowship. He will complement our Adult Reconstructive Service and add a hip preservation service to the division. He will also work closely with Wudbhav Sankar, further strengthening the Penn/CHOP partnership. This will attract patients not only locally but nationally and internationally for hip preservation and care from "cradle to adulthood." This partnership is supported by John Dormans, Chief of CHOP Orthopaedics, along with other combined Penn/ CHOP programs in sports medicine, tumor, and hand surgery.

As part of our hip preservation program, we have introduced a unique treatment for avascular necrosis of the hip, particularly in young patients. CHOP and Penn are now offering vascularized fibular grafting for avascular necrosis of the femoral head in young patients. The vast experience popularized by Jim Urbaniak from Duke is now available in Philadelphia. Dr. Sankar and I are receiving referrals from the northeast region for this unique and important adjunct for hip preservation.

We have recruited Dan Farber to work with Keith Wapner and Wen Chao in the Foot and Ankle Section. Dr. Farber comes from the University of Maryland, where he was highly regarded as a tremendous educator, and is in charge of the national fellowship program for AOFAS. He has more than ten years experience in practice and has already been embraced as a great educator and clinician by our residents and faculty members.

Perhaps the biggest change in our department's evolution has been the formation of our musculoskeletal service line within Penn Medicine. I have had the privilege of helping develop this service line with Lori Gustave, our Chief Operating Officer. The service line includes integration of orthopaedics, rheumatology, neurosciences, pain management, musculoskeletal imaging, physical medicine and rehabilitation, and physical and occupational therapy. The silo concept of an orthopaedic department in an academic system has evolved into a service line that extends across multiple departments in our health system for optimization of patient care, cost containment, efficiency of care, and the provision of increased value in musculoskeletal care delivery.

In parallel with the development of the service line will be a history-making addition for our department, founded in 1889 by DeForest Willard. In August 2014, our new Musculoskeletal Center will open at 3737 Market Street, a 14-story building predominantly dedicated to musculoskeletal care.The identity of the Department will be further defined by giving us our own space in a brand new building designed for advanced musculoskeletal care and use of cutting-edge technology,

such as the "Just in Time" delivery systems of Toyota as well as Microsoft and Apple software innovations.

To complement our new Musculoskeletal Center, a new trauma center is being constructed on the campus of Penn Presbyterian Medical Center, across the street from the Musculoskeletal Center. These new buildings will serve to redefine Penn Orthopaedics not only in 2014, but for decades to come. The planning of these buildings included creating new aspects of patient care as it relates to information systems, patient flow (such as same day appointments), as well as clinic and operating room efficiency. We will redefine our purpose and goals that further differentiate us not only in the greater Delaware Valley but nationally and internationally. Examples of amenities in this building will be two unique features that are unprecedented for any musculoskeletal center. First, we will establish the Penn Human Performance Laboratory, which will include gait analysis, virtual reality, motion sensors, video analysis, and equipment to measure body mass index. Our patients will be tested preoperatively as well as postoperatively after musculoskeletal intervention. This lab will be fully integrated into our Musculoskeletal Center and will give patients a unique opportunity to perform at their "personal best" following nonoperative or operative treatment. Proceeds from this year's Philadelphia Antique Show will benefit Penn Orthopaedics and will be used to provide funds for equipment in the Penn Human Performance Laboratory.

In addition to our strong clinical performance, which has facilitated reinvestment into our research and educational missions, we have also been successful at philanthropy. Lutz Biedermann of Biedermann Motech has pledged $3.25 million to Penn Orthopaedics over five years to establish the Max Biedermann Biomechanics Laboratory. Similar to the relationship of the Perelman Center for Advanced Medicine and the Translational Research Center, Penn Orthopaedics will duplicate the physical relationship between our research labs and our clinics, basically adjacent to each other, one floor apart. This will locate our residents, fellows, and faculty in close proximity to our research labs. The lab is established to provide biomechanical testing and answers to questions regarding implants, fracture fixation, and a multitude of other musculoskeletal conditions. We will have the ability to answer questions almost immediately and literally walk across the hallway and share this knowledge with our patients. Both the Human Performance Laboratory and the Biedermann Biomechanics Laboratory will be integrated into the Musculoskeletal Center. Not only will this enhance care and advance the practice, this will also demonstrate to our patients the unique aspects of Penn Orthopaedics. Hans Joerg Wyss has also pledged $3.25 million over five years to support orthopaedic genomics and limb transplant research. His foundation's endorsement of our Department is a true honor.

As successful as the Department has been, the performance of the Penn Health System has been strong. The future changes that we know are coming in healthcare are welcome. Our integrated health system and the ability of support to be transferred from the hospital system to the medical school as well as clinical departments will continue under the leadership of Larry Jameson, our Dean, and Ralph Muller, our CEO. Strategically Penn has purchased Chester County Hospital, and we will expand our orthopaedic profile to this region of Delaware Valley with the support and guidance of CEO Michael Duncan.

Our research program under the direction of Louis Soslowsky, PhD, has never been stronger. The continued success of peer-reviewed funding (which is the gold standard for a tenure-track scientist) continues to be exemplary with Lin Qin obtaining her first R01 this year. Sherry Liu has been awarded an R03 grant, and Robert Mauck and Louis Soslowsky have been awarded additional R01 grants, adding to their already outstanding portfolios. We welcome the addition of Foteini Mourkioti to McKay Laboratory this July. We have also recruited George Dodge, PhD, in the research track in McKay to further contribute to our efforts at the VA. Under the direction of Robert Mauck and George Dodge, musculoskeletal research at the Translational Musculoskeletal Research Center (TMRC) at the VA has put the Philadelphia VA on the national map. VA grants totaling over $4 million support our faculty, which includes Neil Sheth, Paul Ducheyne, John Esterhai, Robert Mauck, Jason Burdick, George Dodge, David Steinberg, Milt Zgonis, Andrew Kuntz, Louis Soslowsky, and Joe Bernstein. This VA Center of Excellence in Musculoskeletal Research is multidisciplinary and includes our rheumatology colleagues who partner with us in the TMRC. Our world class cartilage program under the basic science leadership of Robert Mauck and the clinical leadership of Jim Carey allowed us to host the third annual Cartilage Repair Symposium in April, which attracted international faculty such as Peter Verdonk, MD, PhD, from Belgium, who served as Keynote Speaker.

Along with our NIH and VA merit grants, I am pleased to announce our vascularized composite allotransplantation (VCA) program, which is funded by a $2 million grant from the Department of Defense to support VCA and research studies aimed at improving transplant procedures in those suffering from traumatic injuries, such as limb loss and severe burns. This is done in conjunction with Wayne Hancock (CHOP) and Matt Levine, Abraham Shaked, and Kim Olthoff from the Transplant Institute and represents a huge advance in the development of our VCA program.

Our faculty also has continued to be recognized for their contributions and achievements. For example, Keith Baldwin was named the Health Policy Chair for the Orthopaedic Rehabilitation Association. Gwo-Chin Lee has been awarded membership in the Knee Society. Kristy Weber is serving as President of the Musculoskeletal Tumor Society, and I am serving as Regent of the American College of Surgeons, in addition to my other responsibilities in the Hand Society and as President of the World Society of Reconstructive Microsurgery and Treasurer of the International Hand Composite Allotransplantation Society. Brian Sennett was awarded the Penn Master Clinician Award this spring.

Our international outreach continues to thrive. Vincent Arlet was awarded over $200,000 in funding for outreach to foreign countries to deliver spine care. Dr. Arlet routinely travels to Trinidad, and our trauma division (Derek Donegan,

Jaimo Ahn, and Samir Mehta) travels to Nicaragua for outreach care and humanitarian efforts, accompanied by our residents. The Biedermann family has pledged half a million dollars for these efforts, which will greatly enhance our residents' experiences abroad.

Our educational program under the direction of Craig Israelite and assistant and associate program directors, Jaimo Ahn and Samir Mehta, has continued to be outstanding. In order to enhance our resident education, the Department has purchased mini iPads for all residents that have been programmed with our core curriculum, lectures and didactics from our faculty and visiting Grand Rounds speakers, as well as manuals for implants and prostheses. Implementation of an online curriculum has been a great advance in the efficient education of our residents. With over 800 applicants, our recently matched class includes a diverse workforce of women and underrepresented minorities from institutions such as Harvard, Johns Hopkins, and other schools that make our residency sought after on a regular basis. Our finishing residents are getting the finest fellowships, often their first choice in trauma, adult reconstruction, shoulder, and other specialties based on their interest and inspiration from our excellent faculty.

Finally I want to recognize our Vice Chairman, Brian Sennett. This past year under his leadership, Penn Sports Medicine was chosen to be the official Sports Medicine Provider of the Philadelphia 76ers with Dr. Sennett serving as Head Team Physician.

We are going not only from good to great, but indeed from "excellence to eminence," which is the motto of Amy Gutmann, President of the University of Pennsylvania. I am honored to lead this team. Please do not hesitate to contact me if you have suggestions for continued improvement in our missions.

Letter from the Program Director

Craig L. Israelite, MD

With each year, I look forward to the publication of *The University of Pennsylvania Orthopaedic Journal*. The reason is that it gives me pause for reflection on the past and present academic year. As importantly, it acknowledges the continued growth and strength under the leadership of our Chairman, Dr. L. Scott Levin, MD.

For many of you that may be unaware, much more documentation is required by the ACGME. In addition to making sure that all residents receive the greatest depth and experience in all areas of orthopaedics, there is the requirement of documenting milestones of certain core procedures. Each resident is required, prior to graduation, to be deemed both academically and technically proficient in these chosen procedures. Core values of professionalism and ethics are also documented. This leads to an even more robust evaluation of residents providing them with feedback on their journey through residency.

If you think this is a lot of additional work, you are absolutely correct! Fortunately Drs. Samir Mehta, MD, and Jaimo Ahn, MD, PhD, have stepped up and have been named Associate and Assistant Program Director, respectively. For those of you who have been part of this program over the past decade, you know that these two educators have enormous energy, intelligence and passion. Their efforts along with the continued direction of Barbara Weinraub have let us navigate through this new litany of documentations.

As a result of the aforementioned program directors, Barbara Weinraub, Dr. Levin, along with each and every attending and resident, we have been granted, effective as of January 2014, full accreditation for the next ten years. This is the maximum term allowable. There were very few areas of concern, and we have already begun corrective action.

But as always, the strength of any program, in addition to its dedicated and stellar faculty is the residents themselves. Once again, last year's residents achieved the most prestigious fellowships in the country. It is obvious that the top fellowship programs of this country are well aware of the excellent quality and training here at Penn. I am happy to report that last year's graduating residents are doing well in their current fellowship programs. Eileen Crawford, MD, is doing sports medicine at the University of Michigan. Andre (Nic) Gay, MD, is doing foot and ankle at Oakland Bone and Joint Specialists. Jason Hsu, MD, is training in shoulder and elbow at Washington University in St. Louis. Tae Won Kim, MD, is doing tumor at Memorial Sloan Kettering. Amun Makani, MD, is in the sports medicine program at Massachusetts General Hospital. Min Park, MD, is doing hand at Stanford. Amy Sewick, MD, is in sports medicine at UCLA. Roshan Shah, MD, JD, is doing his adult reconstruction fellowship at Rush in Chicago. Obviously the quality of the fellowship programs speaks to the advanced training that the residents receive here at the University of Pennsylvania. I expect many of these graduating residents to become leaders in their fields.

Additionally, the current group of residents has continued to push the academic frontiers of orthopaedics. Obviously I cannot detail each and every achievement, but during this past academic year there have been 73 peer-reviewed journal articles, 29 book chapters, 43 abstracts at national conferences, four OREF grants, as well as numerous national awards. This is a credit to the industriousness of our residents, the quality of our faculty, and the research engine which continues as strong as ever under the stewardship of Dr. Lou Soslowsky, PhD.

Finally, I would be remiss if I did not give credit where much of the current credit is due. While it is obvious that we continue to matriculate the best and brightest applicants (again receiving approximately 700 applications for this upcoming year), special recognition goes to our Academic Chiefs, Drs. Mara Schenker, Adam Griska, and Chancellor Gray. All have done a stellar job. However special recognition, gratitude, etc., goes to Mara. I have been at Penn for a dozen years, and her continued enthusiasm and program development are unequaled. Again, I would like to thank each and every administrator, faculty member, resident, and support staff in the Department of Orthopaedics. Each has contributed to what is an outstanding program which is sought after by all applicants, and we continue to be leaders in our fields. I am excited about the upcoming academic year and look forward to reporting once again in the *UPOJ* next year.

Penn Presbyterian Medical Center Hip and Knee Risk Reduction Program Overview

Eric L. Hume, MD
Atul F. Kamath, MD
P. Maxwell Courtney, MD
Finnah Pio, MS
Laura Kosseim, MD
Craig L. Israelite, MD

University of Pennsylvania,
Philadelphia, PA

Introduction

In this overview, we will review the recent effort of Penn Presbyterian Medical Center (PPMC) toward improving the safety of hip and knee arthroplasty patients. The large volume and growing complexity of these cases increases the difficulty in maintaining the safety of patients undergoing elective surgical procedures. We see increasing prevalence of obesity, renal disease, and other medical comorbidities. We also see more patients with more complex orthopaedic problems. Orthopaedic comorbidity at present is addressed simply by the number of revisions. Our focus has been on standardizing pre-hospital and hospital care around best practices and the tools to implement them.

Risk Stratification Tool (RST) Overview: Origin, Development, and New Data

RST Development: Hip Arthroplasty 2007 to 2009

RST development is described in a consecutive hip procedure case-control analysis published in the *Journal of Arthroplasty* by Kamath, *et al.*[1] The study group was comprised of 1,259 consecutive total hip arthroplasty (THA) patients, both primary and revision, who underwent procedures at PPMC between 2007 and 2009. The effort was driven by the recognition of the need to improve morbidity and mortality. Although concern about mortality was the driving factor, the low number of deaths would not have provided statistical significance for stratification of risk variables. Unplanned admission to the surgical intensive care unit (SICU) and rapid responses were selected as proxies for morbidity and mortality. The risk factors that were most predictive for unplanned SICU admission were: 1) age greater than 75 years, with an odds ratio of 2.6; 2) creatinine clearance less than 60 ml/min, with an odds ratio of 6.5; 3) prior myocardial infarction, with an odds ratio of 7.2; 4) BMI greater than 35, with an odds ratio of 2.9; and 5) revision surgery, with an odds ratio of 5.8. If two risk factors were present, the risk of SICU admission was approximately 75%. To maximize sensitivity, two or more risk factors was selected as the threshold for a planned SICU admission, but that threshold meant that only one of three patients would truly need to be in the SICU.

A second guiding principle was the operational benefit of pre-hospital prediction allowing SICU admission planning. Therefore, the risk stratification tool would have to be completed before hospital admission to allow planning for SICU admission.

Kamath, *et al* described the importance of surgical variables which predict the need for SICU admission. Intraoperative use of vasopressors and transfusions during a surgical procedure were both predictive variables. The odds ratio for intraoperative vasopressors was 5.9, and the odds ratio for intraoperative transfusions was 7.1. Although these were important variables recognized in this study, day-of-surgery factors were not included in the original model because the goal was to develop a pre-hospital risk evaluation that could be used to plan care.

Although there were no knee data, we extrapolated the RST to patients undergoing total knee arthroplasty (TKA), with the reasonable expectation of similar risk relationships to hips. Some data were collected starting in November 2011.

RST Early Experience: Hip Arthroplasty November 2011 to April 2012

In 2013, Kamath, *et al* described a post-intervention group of 175 consecutive THA patients who were triaged by the RST.[2] This post-intervention group was compared to the pre-intervention group comprised of 1,259 cases described by Kamath, *et al.*[1] The outcomes of interest were unplanned SICU admissions, rapid responses or codes, major complications, and death. The information contained in this article was based in part on the Clinical Database/ Resource Manager (CDB/RM) maintained by the University HealthSystem Consortium (UHC).

The major complication rate with this small group of RSTed THA patients fell from 12.5%, pre-intervention, to 2.0%, post-intervention. The mortality rate dropped from 4.77 observed-to-expected, pre-intervention, to 1.62, post-intervention. The 11.4% post-intervention rate of total SICU admissions was a modest increase from the historical rate, but the mean SICU length of stay decreased from 2.55 days, pre-intervention, to 1.70 days, post-intervention. After implementation of the triage model, the rate of unplanned SICU admissions dropped

Corresponding author:
Eric L. Hume, MD
Department of Orthopaedic Surgery
University of Pennsylvania
Penn Presbyterian Medical Center
1 Cupp Pavilion
51 N. 39th Street
Philadelphia, PA. 19104
Eric.Hume@uphs.upenn.edu

from 7.1%, pre-intervention, to 2.2%, post-intervention (P=0.013). The complication rate fell significantly from 12.5% to 2%, post-intervention.

RST Two-Year Experience: Hip and Knee Arthroplasty January 2012 to December 2013

Two years of consecutive hip and knee arthroplasty patients, both primary and revision, were stratified prospectively by the RST. Although developed for hip patients, RST was applied to knee patients as well, with the expectation of a similar risk relationship but without specific knee data. These two years of data from primary and revision cases for hip and knee replacements illustrate outcomes specific to the Penn Presbyterian Medical Center when stratified for perioperative risk.

The control group is composed of patients who had hip or knee arthroplasty in 2010 and 2011. There were eight deaths in 2,308 patients. The full study group consisted of 2,853 patients who had hip or knee arthroplasty in 2012 and 2013. The study group included 2,294 patients who were RSTed and 559 patients who were not RSTed owing to urgent admissions or insufficient data. There were no deaths among 2,294 RSTed during the index admission. There was one death for an RSTed patient during readmission for sepsis and liver failure. Of the 559 patients who were not RSTed, there was one death in the urgent group and one death in the insufficient data group. The combined complete group had a mortality rate of 0.11% (3/2,853 deaths), whereas mortality in the control group was 0.35% (8/2,308 deaths), for a Fisher exact two-tailed statistic of p = 0.072 comparing both groups.

UHC data, shown in Table 1, include 15 months of consecutive patients before RST and 24 months after implementation of RST but includes RSTed and urgent patients. The combined Mortality Index dropped from 1.42 to 0.51 after intervention. A Mortality Index of 1.00 indicates that observed mortality equals expected mortality based on UHC criteria. Raw mortality rate dropped from 0.22% to 0.08%, and there were no early deaths after RST was initiated.

Further Development: Penn Arthroplasty Risk Score (PARS) Data

Courtney, *et al*[5] evaluated a recent consecutive subset of patients for care requiring SICU stay. The currently used RST demonstrated moderate specificity, which prompted the consideration of unnecessary SICU admissions. A consecutive series of 295 patients was evaluated for need for critical care intervention. The PARS was developed to include intraoperative risk factors and to improve the specificity of the RST. Based on this retrospective data, PARS was prospectively validated over a consecutive series of 738 patients. The study found that while 176 patients were in the ICU (24%), only 50 patients (6.7%) required critical care intervention. Weighted risk factors in this model included estimated blood loss (EBL) greater than 1000mL, intraoperative vasopressors, COPD, CHF, BMI greater than 35, and revision hip arthroplasty.

Although we expected a RST positive predictive value (PPV) of about 0.3, we found the RST PPV to be 0.22. Evaluation of PARS data shows that a model with higher PPV could be based on the operative events of transfusions and blood loss risk factors for SICU care with a subset of RST variables of heart and pulmonary disease. Both the PARS data and the original RST data[1] show that EBL and intraoperative pressor use are strong predictors for the need for SICU care. PARS data tighten the prediction of need for the SICU by including intraoperative blood loss and vasopressor treatment.

This PARS stratification could only be completed postoperatively, whereas pre-hospital planning for SICU admission was the central theme of RST. Pre-hospital planning probably has value beyond reserving the SICU bed, but even with the planning supported by RST, there are occasions when an SICU bed is not available. The SICU decision is then based on resources such as prolonged PACU monitoring, observations, and discussion among the anesthesia, orthopaedic, and SICU teams. We have the sense that a pre-hospital planning component is valuable and that day of surgery variables and clinical judgment must be part of appropriate triage to SICU or floor care.

Table 1. Information about all consecutive THAs and TKAs before and after implementation of RST. LOS: length of stay. ICU cases included both planned and unplanned ICU admissions. Mortality Index: ratio of PPMC mortality rate to UHC expected mortality rate; less than 1.0 is favorable.

	Pre-RST	Post-RST		
	All THA/TKA 10/2010 – 12/2011	All THA/TKA 1/2012 – 12/2013	THA 1/2012 – 12/2013	TKA 1/2012 – 12/2013
Cases	1,386	2,664	972	1,692
Mean LOS	3.79	3.61	3.84	3.47
LOS Index	1.01	1.00	1.08	0.95
ICU Cases	8.4%	21.4%	23.0%	20.4%
Mean ICU Days	1.70	1.52	1.67	1.42
Deaths	0.22%	0.08%	0.00%	0.12%
Mortality Index	1.42	0.51	0.00	0.80
Early Deaths	0.14%	0.00%	0.00%	0.00%

A blended model would maintain sensitivity and increase specificity. A modified RST including preoperative weighted PARS variables maintains the pre-admission planning value based on new data. The first step would be modified risk stratification with more predictive weighting of patient comorbities and would improve the RST PPV. The second step would be postoperative stratification which would further improve PPV by a final adjustment based on EBL and pressor treatment. Patients with borderline RST scores would be included or excluded from SICU admission in a final postoperative stratification based on PARS values.

Based on this new analysis, the newly proposed risk stratification is more predictive due to weighting of the variables that have been used in the prior risk stratification tool. It has become clear that the prediction for SICU admission of patients who require SICU interventions is stronger using the two variables of intraoperative blood loss and intraoperative vasopressors. Patients who were triaged to the floor but who have blood loss greater than a liter and who required intraoperative use of vasopressors should be managed in the SICU. Patients who are stratified to the SICU based on age, weight, and revision but who have a low blood loss and no use of intraoperative vasopressors may be sent safely to the floor. This second phase postoperative evaluation further increases the sensitivity, specificity, and PPV beyond pre-hospital risk stratification while maintaining strong negative predictive value (NPV, Table 2).

Limitations of RST

An important limitation identified is the infrequent occurrence of certain diseases such as hemophilia, liver disease, complications in transplant patients, and pulmonary embolism. We noted especially that for two of the three deaths during the RST period, the patients had severe liver disease directly contributing to their demise. There were 18 cirrhosis patients in the 14 months of data we collected. Death is too rare to allow statistical significance. In addition, some diseases or patient types may be clinically important but also are too rare to show statistical significance, such as transplant patients, cancer survivors, hemophiliacs, and adults with congenital heart disease.

Orthopaedic disease burden is poorly evaluated at present. We evaluated hip and knee revision arthroplasty and found that hip revision alone is predictive. Because there is great variability in complexity among revisions, we do not have the tools to further risk stratify revisions. A simple hip cup or

Table 2. Sensitivies and specificities of the RST and Post-op PARS.

RST			
	Needed ICU Care		
	Yes	**No**	**Total**
Sent to ICU	36	126	162
Sent to Floor	14	562	576
Total	50	688	738
Sensitivity	0.720		
Specificity	0.816		
PPV	0.222		
NPV	0.975		

Post-op PARS			
	Needed ICU Care		
	Yes	**No**	**Total**
Score ≥ 3	36	52	88
Score < 3	14	636	650
Total	50	688	738
Sensitivity	0.720		
Specificity	0.924		
PPV	0.409		
NPV	0.978		

stem revision has lower risk than a revision for major bone loss. Thus, a good metric for orthopaedic disease burden is needed.

Other Safety Initiatives During the RST Period

Other changes contributed to improved safety outcomes during the past two years. Although we have standardized venous thromboembolism prophylaxis, the RST process allows us to tailor prophylaxis for higher-risk patients. The MP3 preemptive pain protocol has increased the use of non-narcotic analgesics, lowered the use of narcotics overall, and allowed us to limit PCA use while maintaining or improving pain control. The RST process leads to better recognition of and care for patients at risk of delirium, alcohol withdrawal, and sleep apnea. The Hawthorne effect may be important by increasing safety discussion and awareness. Active ongoing discussions among the teams are inherently valuable to improve safe care.

Summary

These efforts have been recognized by UPHS Risk Reduction Initiatives, Joint Commission, and the IBC. We feel that preoperative risk stratification has improved safety for hip and knee arthroplasty patients but at the cost of a 20% rate of ICU admission. We are now evaluating the PARS data to develop an improved stratification model which keeps the high negative predictive value of RST with improved positive predictive value. We look forward to evaluating the new model which lowers the rate of "unnecessary" SICU admissions while maintaining safety.

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Multimodal Analgesia for Total Joint Arthroplasty

[1]Rosemary MG Hogg, MBChB
[1]Jiabin Liu, MD, PhD
[2]Eric Hume, MD
[1]Nabil M. Elkassabany, MD, MSCE

[1]Department of Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA

[2]Department of Orthopedic Surgery, University of Pennsylvania, Philadelphia, PA

Introduction

Despite the advances in surgical techniques and the improved safety of anesthetic practice, a large percentage of patients continue to experience inadequate postoperative pain relief.[1] Several recent surveys have found that more than 60% of patients report moderate to severe pain after surgery.[2,3] Most treatment regimens for managing postoperative pain include significant doses of systemic opioids. Opioid-related side effects, including sedation, nausea, vomiting, pruritus, ileus, and respiratory depression, continue to be a major source of patient discomfort, dissatisfaction, and morbidity in the postoperative period.[4] The demographics of patients scheduled for total joint arthroplasty is changing. Patients are getting older and have higher body mass index, which makes opioid-related side effects more challenging.[5]

Multimodal analgesia (MMA) is defined as the combination of different analgesics and techniques that act by different mechanisms, resulting in additive or synergistic analgesia with lowered adverse effects (Figure 1), compared to sole administration of an individual pharmacological agent.[6] Initially described by Kehlet *et al* over 20 years ago,[6] many different regimes have been described in the literature with some consensus found in large international working groups.[5,7] The American Society of Anesthesiologists task force on acute postoperative pain management recommends using multimodal analgesia whenever possible.[8]

Through close collaboration between the Departments of Orthopedic Surgery and Anesthesiology at Penn Presbyterian Medical Center (PPMC), an evidence-based MMA protocol has been designed and implemented to facilitate

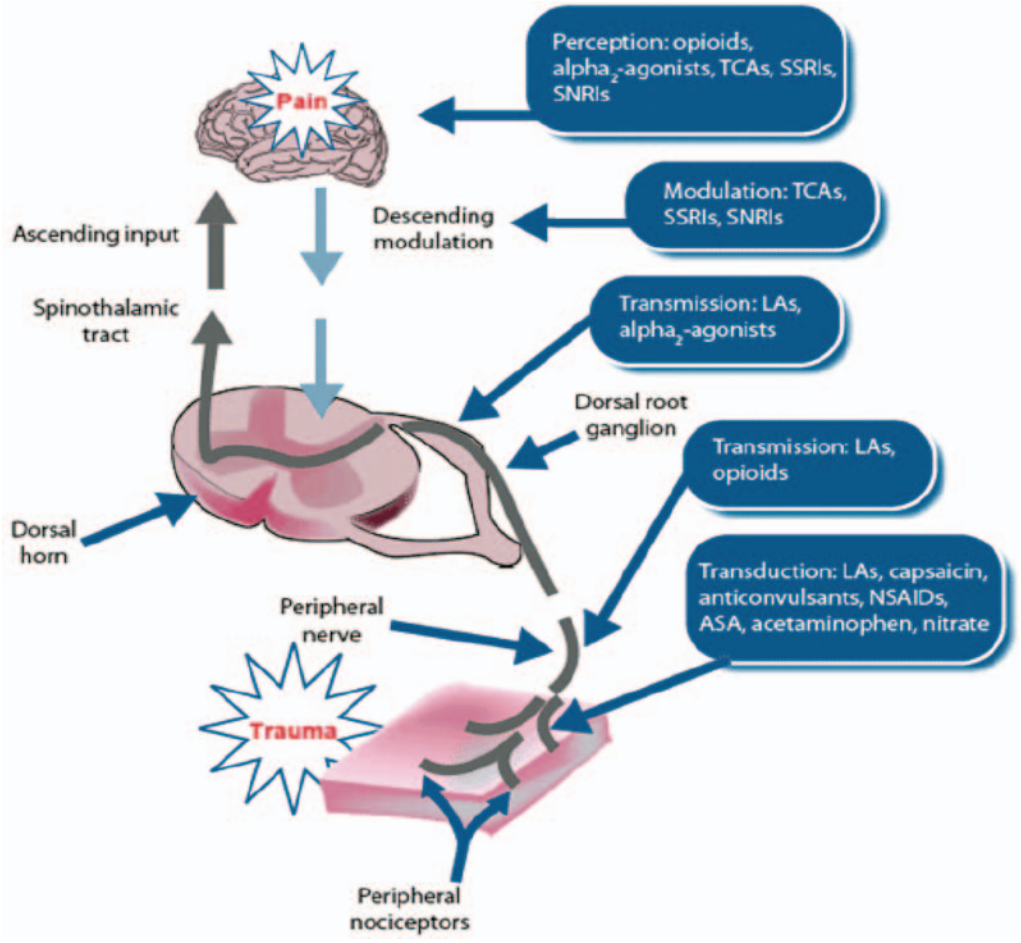


Figure 1. Site of action of different agents involved in multimodal analgesia and the receptors involved in the pain pathway. Adapted from Kehlet *et al*.[6]

Corresponding author:
Nabil M. Elkassabany, MD, MSCE
Department of Anesthesiology and Critical Care
University of Pennsylvania
3400 Spruce St.
Philadelphia, PA 19104
Nabil.Elkassabany@uphs.upenn.edu

Table 1. MP3 multimodal analgesia regimes for use after primary total joint arthroplasty at PPMC. +2hrs before procedure. *Avoid or reduced dose in patients >70yrs; the duration of therapy is extended to two weeks in opioid-tolerant patients. #Avoid in patients with GFR<60, Creatinine >1.4, sulfa or NSAID allergy.

Total Knee Arthroplasty (TKA)	Total Hip Arthroplasty (THA)
Preoperative+	Preoperative+
Gabapentin 300mg PO + Celecoxib 200mg PO + Acetaminophen 1g PO	Gabapentin 300mg PO + Celecoxib 200mg PO + Acetaminophen 1g PO
Intraoperative	Intraoperative
Spinal anesthesia preferred using 10-15mg bupivacaine	Spinal anesthesia preferred using 10-15mg bupivacaine
Femoral nerve or adductor canal block with 20- 30mls 0.2% ropivacaine with insertion of an indwelling catheter	Single shot Lumbar plexus or Fascia iliaca block or ketamine 0.5mg/kg to be considered for patients with chronic pain, high opioid usage or intolerance to opioids.
Consider ketamine/sciatic nerve blockade for patients with chronic pain, high opioid usage or intolerance to opioids.	
Postoperative	
Continuous Femoral nerve or adductor canal block infusion – 0.2% Ropivacaine @ 8-10mls/hr	Postoperative
Oxycodone 10mg Q4-6hrs	Oxycodone 10mg Q4-6hrs
Oxycontin 10-20mg Q12hrs	Oxycontin 10-20mg Q12hrs
Gabapentin 300mg PO Q8 for 7 Days*	Gabapentin 300mg PO Q8 for 7 Days*
Celecoxib 200mg PO for 72 hrs#	Celecoxib 200mg PO for 72 hrs#
Acetaminophen 1g PO for 72 hrs	Acetaminophen 1g PO for 72 hrs
IV opioid for breakthrough pain	IV opioid for breakthrough pain

both improved analgesia and expedient rehabilitation in patients undergoing total joint arthroplasty. This protocol has been branded as the Multimodal Perioperative Pain Protocol (MP3). It consists of specific guidelines to be implemented throughout the perioperative period and allows for adaptation depending on specific patient requirements (Table 1).

Preoperative Regime

The use of preemptive analgesia is commonplace in most surgical settings and aims to prevent the establishment of central sensitization secondary to the surgical insult. In recent years, it has developed into an integral part of pain management, particularly in those institutions which employ "fast-track" surgical protocols.[9]

Pain control after surgery starts with patient education before surgery. A preoperative discussion with the patient should include the patient's previous experiences with pain management and give the patient information about pain management therapies that are available as well as the rationale behind their use. During this discussion, the importance of a factual report of pain and avoiding stoicism or exaggeration should be emphasized. Setting the patient's expectations right, especially when it comes to pain relief versus "pain-free status," can positively impact the patient's overall experience and improve satisfaction.[10] In our institution, we are working on making patient education material available through the internet and in the surgeons' offices.

Gabapentin has been shown to interact with central voltage-sensitive sodium and calcium channels, increase the concentration of GABA in neuronal synapses, and decrease monoamine oxidase expression.[11] Its role in acute postoperative pain management originated from its use in management of chronic pain conditions, such as fibromyalgia, in which it is thought to limit the development and propagation of dysfunctional neurons. Earlier clinical trials with gabapentin for early postsurgical pain have shown improved analgesia with opioid-sparing effect. In addition to its role in acute postoperative pain, gabapentin has been shown to improve movement and reduce chronic postoperative pain in TKA at both 3 and 6 months.[12] Side effects, such as sedation or delirium, can be observed in elderly patients, and dose adjustments may be required

The use of COX-2 inhibitors is considered somewhat controversial for perioperative pain management due to the increased risk of cardiovascular events in patients on long-term treatment.[13] Celecoxib, however, has been shown to reduce opioid requirements by up to 40% with significantly improved visual assessment scale (VAS) scores and higher active range of motion over 72 hours in patients undergoing TKA and is not associated with the same cardiovascular risk.[14] Concerns regarding the use of NSAIDs in orthopedic surgery center mainly around the potential for decreased bone healing in fracture patients. However, it has been shown that the short term use of celecoxib has no effect on bone healing in total joint arthroplasty.[15]

Acetaminophen is thought to act primarily by inhibiting central prostaglandin synthesis without the side effects of NSAIDs. Despite recent FDA warnings concerning patient use of multiple medications containing acetaminophen, it has repeatedly been shown to reduce morphine consumption by up to 40% with minimal complications, particularly when used

as an intravenous preparation due to increased cerebrospinal concentrations.[16,17] At PPMC, the use of acetaminophen is within the daily dosing limits set by the FDA.

Intraoperative Regime

The use of regional anesthesia (RA) in orthopedic surgery in general and specifically in total joint replacement has been demonstrated in numerous studies to improve patient outcomes, including decreased mortality and length of stay in the hospital. RA is also associated with lower incidence of significant morbidity indices, including pulmonary complication, venous thromboembolism, acute renal impairment, and postoperative infectious complications.[18-20] Spinal anesthesia is more cost-effective than general anesthesia for orthopedic surgery and is associated with similar or higher overall patient satisfaction with the anesthetic technique.[21] Monitored sedation is commonly used in addition during the procedure to improve patient comfort and reduce anxiety.

The use of single shot or continuous nerve blockade for postoperative analgesia after total joint replacement has been an integral part of postoperative analgesia protocols for a number of decades. The choice of which block is largely driven by the culture of the institution and the emphasis on postoperative mobility and rehabilitation protocols. Traditionally, a combined femoral and sciatic nerve block was advocated for TKA to eliminate discomfort arising from the complex innervation of the knee joint. This technique has decreased in popularity due to the increased likelihood of motor weakness with the potential for subsequent delayed mobilization, fall risks, and the need for prompt assessment of sciatic nerve functionality in the postoperative period.[22] At PPMC, sciatic nerve blocks are only reserved for patients who are having major difficulty in pain control with our conventional protocol or patients in whom opioid use may be detrimental.

Continuous femoral nerve block (FNB) provides effective analgesia in the postoperative period, significantly reducing opioid requirements, particularly when a continuous catheter technique is employed.[23] It does, however, have the potential to cause quadriceps weakness at higher concentrations of local anesthesia. Recently, the use of continuous adductor canal blockade (ACB), which aims to avoid motor weakness by solely targeting the saphenous nerve, has been shown to provide equivalent analgesia to FNB but with significantly greater preservation of quadriceps strength (52% vs. 18%).[24] A recent study by Memtsoudis *et al* has shown that peripheral nerve blockade is not correlated with the incidence of postoperative falls in patients undergoing joint replacement surgery.[25] The acute pain and regional anesthesia service in our institution works closely with the physical therapy and rehabilitation team in designing protocols to minimize the risk of falling. With development of protocols for fast-track recovery after TKA, the ACB may have a role in these protocols as they continue to evolve.

Local wound infiltration with low dose, high volume local anesthesia has been increasing in popularity in recent years with optimum results demonstrated when used with femoral nerve blockade in TKA.[26,27] It is, however, pertinent to note that significant volumes of local anesthesia must be injected (up to 100mls of 0.1% ropivacaine), particularly in the posterior compartment, to produce these analgesic effects in TKA. Peripheral nerve block for total hip replacement may be facilitated in the form of lumbar plexus or fascia iliaca nerve block or local infiltration. However, it is commonly agreed that these may be reserved for patients with complex pain issues or those at increased risk of complications from opioid medications.

Ketamine is used as an adjunct in patients with preexisting chronic pain due to antagonism of the N-methyl-D-aspartate (NMDA) receptor and potentiation of opioid analgesia. It has been shown to reduce morphine usage by up to 32% when given alone and by 51% when used in combination with gabapentin after THA.[28] It is rarely used as a sole analgesic agent due to its potential to produce psychotomimetic side effects, although these are rarely seen when lower doses are used as part of a multimodal regime.

Postoperative Regime

The continuation of the multimodal regime into the postoperative period allows for a reduction in opioid usage and, in particular, aims to reduce the need for PCA or intravenous bolus-dose opioids and their concomitant side effects. The continuous nerve block infusion may be commenced in the immediate postoperative period to allow a smooth transition after the resolution of the spinal and initial femoral nerve blockade.

Oral slow release preparations, such as oxycodone, can significantly reduce the need for intravenous opioids in patients undergoing joint replacement.[29] This method of preemptive analgesia management has the potential to facilitate physical therapy, improve sleep, and decrease the incidence of chronic postoperative pain.[30] While these medications are potentially associated with significant side effects, patient

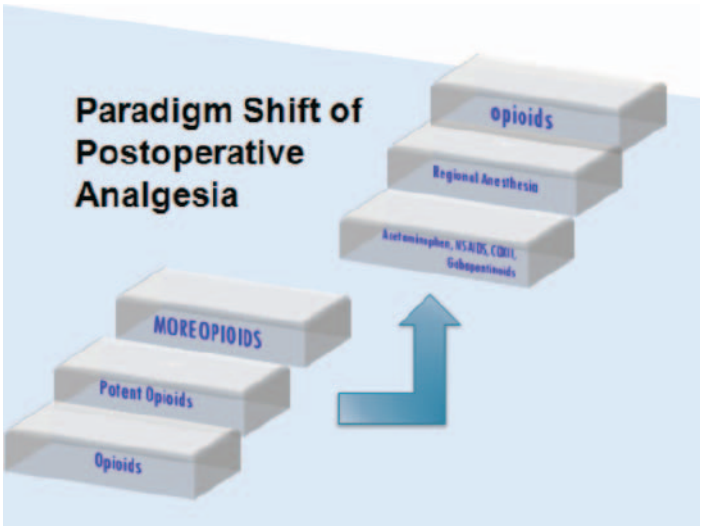


Figure 2. Paradigm shift in postoperative analgesia.

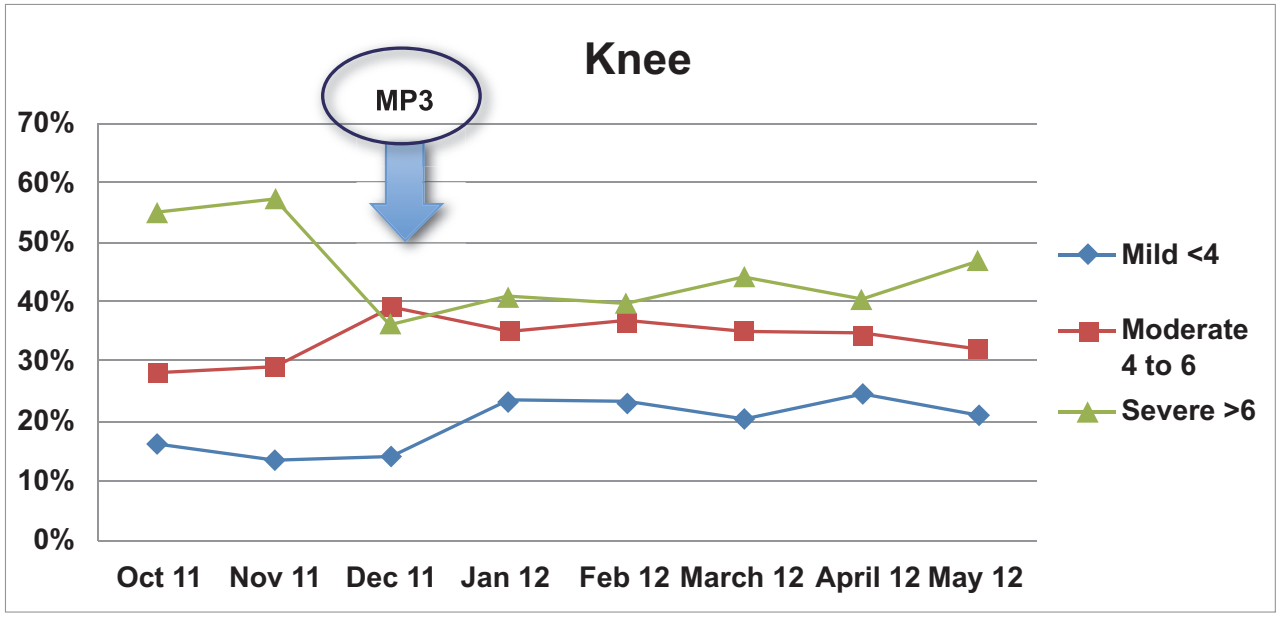
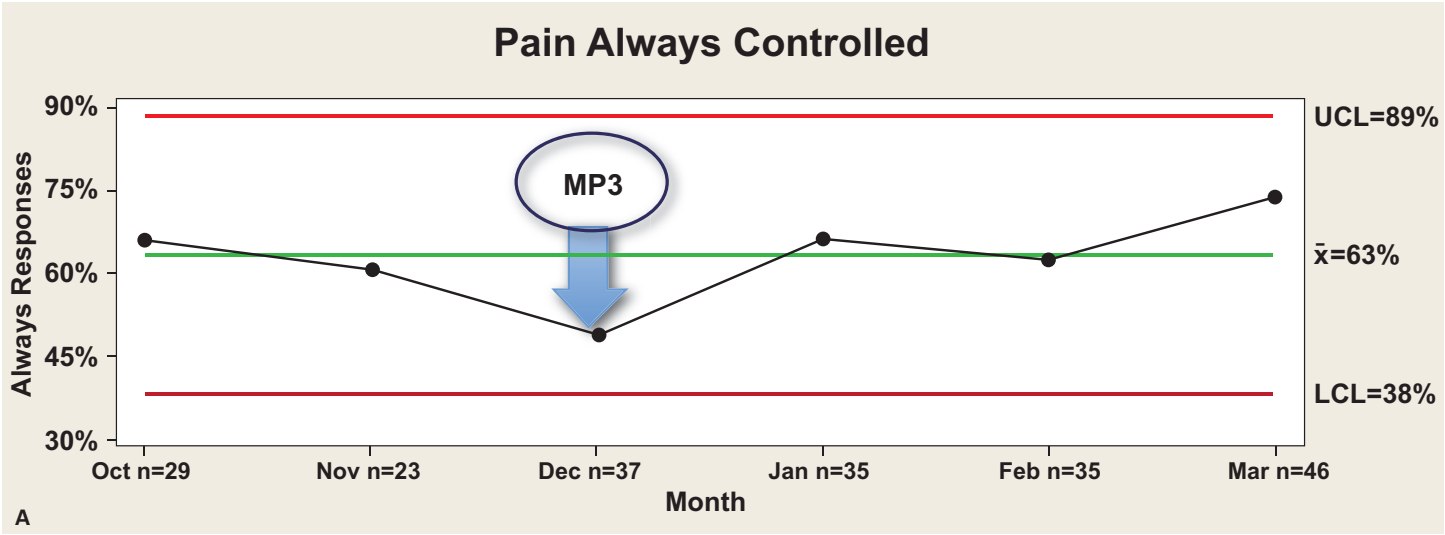


Figure 3. Percentage of patients with severe pain, as assessed by VAS, decreased after implementation of the MP3 protocol starting January, 2012.



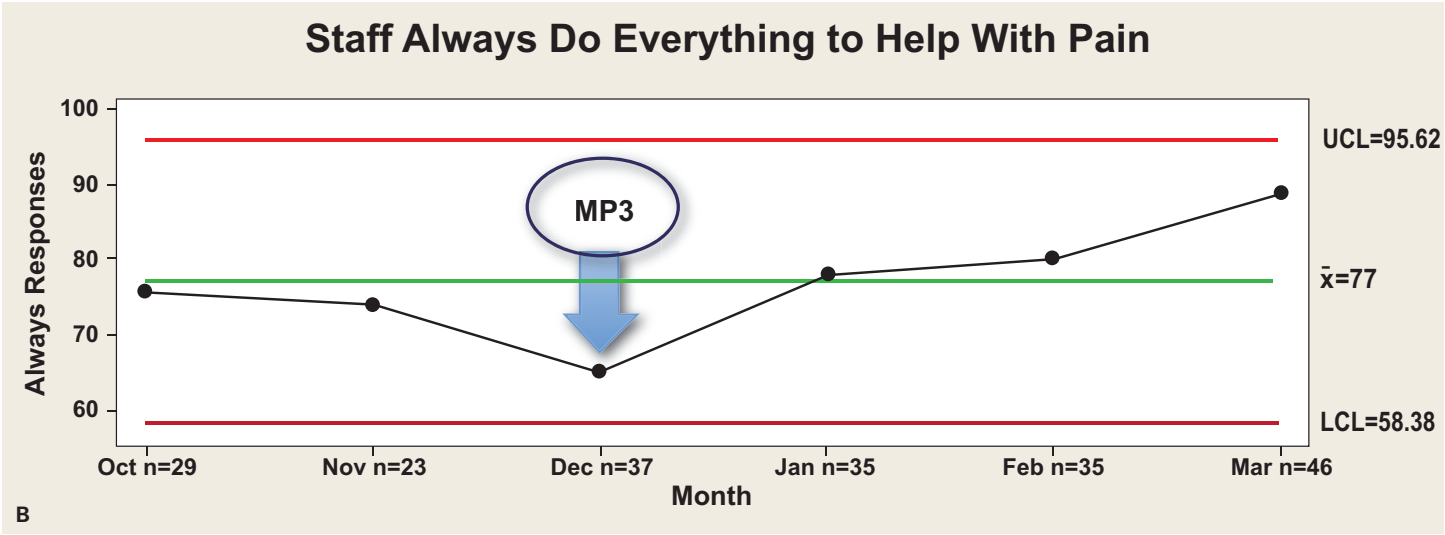


Figure 4. (A) The number of patients answering the question (How often your pain was always controlled?) increased after January, 2012. (B) The number of patients answering the question (Did you feel the staff always did everything to help with your pain?) also increased after January, 2012.

and healthcare staff education may allow responsible use of these medications while avoiding potential complications and prolonged dependence. Patients with complex chronic pain issues should be assessed on a case-by-case basis and a perioperative pain management program instigated with the assistance of orthopaedic surgeons, anesthesiologists, and chronic pain physicians.

Implementation of the MP3 Protocol at PPMC

Implementation of the MP3 protocol at PPMC was a true collaborative effort between the Departments of Anesthesiology, Orthopedic Surgery, Internal Medicine, Pharmacy, Nursing, Physical Therapy, and Physical Medicine and Rehabilitation. The protocol was implemented in January of 2012, and since then, it has been a huge success and resulted in a large paradigm shift (Figure 2). After putting the protocol together, we relied on a core group of individual super users, representing their respective disciplines within the institution, to be the liaisons to their departments and to do the necessary education for all those who are involved with implementation of the protocol. We were able to eliminate relying predominately on intravenous narcotics and have seen a decrease in patient pain scores after total joint arthroplasty. In the first few months after implementation of the MP3 protocol, the number of patients with severe pain after TKA decreased (Figure 3). The HCAHPS survey has a pain domain to assess the percentage of patients answering that their pain was always controlled and who affirm that everything was done, from the patient perspective, to control their pain. The number of patients whose pain was always controlled increased in the first three months after implementation of the MP3 protocol as well as the percentage of patients stating that the staff did everything to help them with their pain (Figure 4A-B).

In summary, the concept of multimodal analgesia will continue to spread as it is not exclusive for total joint arthroplasty. Other service lines within the Department of Orthopaedic Surgery are starting to apply the concept to both inpatient and outpatient procedures.

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An Analysis of the Demographic and Technical Characteristics Associated with Iliac Cortical Perforation During Insertion of Iliosacral Screws

[1]J. Stuart Melvin, MD
[2]Nicholas Pulos, MD
[2]Keith Baldwin, MD, MPH, MSPT
[3]Amer Mirza, MD
[3]Michael J. Gardner, MD
[2]Samir Mehta, MD

[1]OrthoCarolina, Charlotte, NC, USA

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

[3]Department of Orthopaedic Surgery, Oregon Health & Science University, Portland, OR

[4]Department of Orthopaedic Surgery, Washington University, St. Louis, MO

Introduction

After initial resuscitation and stabilization, anatomic reduction of the pelvic ring with stable fixation leads to earlier patient mobility, decreased pain and improved outcomes.[1-4] Iliosacral screws have become the standard for fixation of most injuries to the posterior pelvic ring and have generally been associated with limited blood loss as well as low rates of infection and nonunion.[5-10] Reports of complications for iliosacral screws have focused on nerve and vessel injury.[5,11-15] Perforation of the outer cortex of the ilium during the final tightening of iliosacral screws has long been observed but seldomly reported. This complication may compromise the fixation of pelvic ring injuries. The aim of this study was to identify risk factors associated with breach of the outer iliac cortex during iliosacral screw insertion.

Methods

One hundred and forty-two consecutive patients who had undergone iliosacral screw fixation of the posterior pelvic ring from July 2006 to June 2010 and had post-operative CT scans were retrospectively identified from three Level 1 trauma centers. Charts were reviewed for potential epidemiologic risk factors such as age, time from injury to surgery, smoking status, and diagnosis of diabetes. All pelvic radiographs and CT scans were reviewed for number of screws, laterality of screws, screw thread length (partial vs. fully threaded) and for intrusion of the screw and washer through the outer iliac cortex. Injury patterns were classified according to the OTA classification.

Results

Two hundred and thirty-six iliosacral screws with washers were inserted for an average of 1.66 screws per patient. Twenty-eight screws (11.8%) in 26 patients (18.3%) perforated the outer cortex of the ilium (Figure 1A-B). Patients with screw perforation were significantly older (52.61 years vs. 38.6 years; p=0.0002) and were more likely to be diabetic (p=0.0071). Additionally, perforated screws were more often fully threaded (p=0.0315), and patients with a perforated cortex had significantly more screws inserted (1.92 vs. 1.60; p=0.037). Cortical perforation on univariate analysis was not influenced in our series by gender (p=0.40), time to surgical fixation (p=0.30), laterality (p=0.45), smoking status (p=0.99), OTA Classification (p=0.932) or attending surgeon (p=0.206).

Discussion

Percutaneous iliosacral screw fixation of unstable pelvic ring injuries has become standard. This study demonstrates that perforation of the outer iliac cortex is relatively common during insertion of iliosacral screws and is associated with additional screws being inserted. Factors that may predispose to poor bone quality, such as age and diabetes, are associated with increased rates of cortical perforation. These factors should be kept in mind when performing final tightening of iliosacral screws. Interestingly, fully threaded screws were found to be significantly more likely to breach the iliac cortex compared

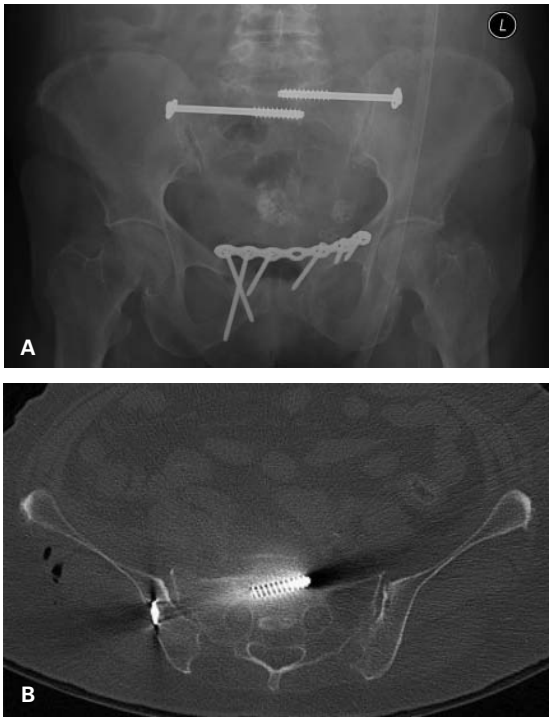

Figure 1. (A) AP pelvis demonstrating screw with intact iliac cortex on left and breach of iliac cortex by screw and washer on right. (B) Axial CT image depicting breach of the right iliac cortex by screw and washer.

Corresponding author:
J. Stuart Melvin, MD
OrthoCarolina
354 Copperfield Blvd.
Concord, NC 28025
Stu.melvin@gmail.com

to partially threaded screws. Further research is warranted to evaluate the effect of cortical perforation on reduction, healing and outcomes.

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U·P·O·J

Safety of Bilateral Total Knee Arthroplasty: Simultaneous Versus Staged at a Week Interval

P. Maxwell Courtney, MD
Christopher M. Melnic, MD
Hassan Alosh, MD
Roshan P. Shah, MD, JD
Charles L. Nelson, MD
Craig L. Israelite, MD.

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

Introduction

The decision to perform simultaneous bilateral total knee arthroplasty (TKA) or a staged procedure in patients with severe degenerative arthritis of both knees continues to be controversial. Simultaneous bilateral TKA offers several advantages to the patient, including an operation done under one anesthetic and a single rehabilitation period. Some orthopaedic surgeons recommend against performing bilateral simultaneous TKA and suggest performing the two procedures staged at least a few months apart during two separate admissions. The optimum timeframe between staged procedures continues to be of much debate. Few studies have addressed the safety of staged bilateral TKA one week apart,[1,2] but this time frame may represent a compromise between faster recovery and patient safety.

The primary purpose of this study is to determine if higher risk patients with bilateral knee osteoarthritis selected to have a staged procedure at a one week interval have different rates of complications compared to healthier patients having simultaneous surgery.

Methods

We retrospectively reviewed the department's arthroplasty database for all patients who underwent simultaneous and staged bilateral TKA performed by the two senior authors (CLN and CLI) from 2007-2012. All patients over age 18 who underwent a simultaneous or staged procedure were included in the study. Patients who underwent staged bilateral TKA were admitted following their first procedure. When deemed medically stable, they were transferred to our institution's skilled nursing facility (SNF) to await their second procedure seven days after the first.

Patient demographic data, American Society of Anesthesiologists (ASA) score, preoperative medical comorbidities, and blood transfusions were documented from the medical record. A Charlson Comorbidity Index was calculated for each patient.[2] Inpatient discharge summaries, progress notes, laboratory values, and consultation reports were then reviewed for each patient to identify any perioperative complications during their hospital stay. We classified and stratified each post-surgical complication based on published definitions from the TKA Complications Workgroup of the Knee Society.[3,4] Each complication was graded I to V based on severity as determined by the Workgroup using a modification of the criteria set by Sink et al.[4,5] Grade I complications were excluded while post-operative anemia requiring blood transfusions was documented separately.

We performed an *a priori* power analysis to determine the appropriate sample size before the study. Our primary statistical goal was to determine any significant difference in the rate of complications between simultaneous and staged bilateral TKA. To detect a medium clinically important effect size of 0.30 using a chi-square test with a power of 0.80 and type I error rate of 0.05,[6,7] we would need a sample size of 88 patients in each cohort.

A consecutive series of 235 bilateral TKA patients (470 TKAs) from two surgeons at a single academic institution between 2007 and 2012 were retrospectively reviewed. Of the total, 131 patients (55%) underwent bilateral TKA staged at a one-week interval. There were 69 males (29%) and 166 females (71%) with a mean age of 62.1 years (range 23-87). Patients had a mean Charlson Comorbidity Index of 0.86 (range 0-6) and mean length of stay of 5.69 days (range 3-13). Demographic data of the patient population is presented in Table 1.

Results

Patients who underwent both staged and simultaneous procedures had low overall rates of perioperative complications (6% vs. 13%, $p=0.054$). There was one mortality (grade V) in the staged group that occurred after the second procedure due to a myocardial infarction. The rate of severe complications (grade IV and V) was also low for each group (4 simultaneous patients and 3 staged patients, $p=0.467$). A list of complications and their severity grades from both groups are listed in Table 2.

Patients in the simultaneous group were younger (59.5 vs. 64.2 years, $p<0.001$) and had

Corresponding author:
P. Maxwell Courtney, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Paul.Courtney@uphs.upenn.edu

Table 1. Descriptive statistics of all bilateral total knee replacements in the study.

N=235	Mean		Number (%)
Age (years)	62.1	Male	69 (29)
Length of Stay (Days)	5.69	Female	166 (71)
Preoperative Hemoglobin (g/dL)	13	Staged 1 week apart	131 (56)
Blood transfused (units)	1.58	Simultaneous Bilateral	104 (44)
ASA	2.44	Required transfusion	159 (68)
BMI	34.1	Perioperative Complication	31 (13)
Charlson Comorbidity Index	0.83	Hypertension	173 (74)
		Hyperlipidemia	71 (30)
		Diabetes Mellitus	44 (19)
		Coronary Artery Disease	38 (16)
		Chronic Obstructive Pulmonary Disease	16 (7)
		Chronic Renal Insufficiency	10 (4)
		Human Immunodeficiency Virus	4 (2)
		Hepatitis B or C	15 (6)
		Mortality	1 (0.4)

a lower BMI (31.6 vs. 36.0, $p=0.001$) than those in the staged group. Furthermore, patients who underwent simultaneous bilateral TKA had lower ASA scores (2.35 vs. 2.51, $p=0.038$) and a lower mean Charlson Comorbidity Index (0.53 vs. 1.06, $p<0.001$). Comparative data between bilateral simultaneous and staged TKA is detailed in Table 3.

Univariate logistic regression analysis of the study population revealed a statistically significant correlation between lower preoperative hemoglobin and higher rates of blood transfusion in both the staged ($p=0.001$) and simultaneous group ($p=0.004$). There was no significant correlation with BMI ($p=0.972$) or Charlson Comorbidity Index ($p=0.352$) and rates of complications among the whole study population. While the simultaneous group had a higher preoperative hemoglobin (13.3 vs. 12.7 g/dL, $p=0.007$), there was no statistical difference in the number of patients who received a blood transfusion (71% vs. 65%, $p=0.307$) or in the mean number of units of blood transfused (1.74 vs. 1.45, $p=0.222$).

Table 2. List of complications and grades of severity. Grade I complications were excluded from the study.

Staged bilateral TKA (n=8)	Simultaneous bilateral TKA (n=14)
3 patients - Delirium requiring close monitoring and antipsychotics (grade II)	3 patients - Delirium requiring close monitoring and antipsychotics (grade II)
Bradyarrythmia requiring cardiology consultation and close follow-up (grade II)	Persistent bleeding in hemophiliac requiring factor infusion (grade II)
Atrial fibrillation requiring medical treatment and prolonged index admission (grade III)	Seizure requiring treatment and outpatient monitoring (grade II)
2 patients - Hypoxia requiring ICU transfer (grade IV)	Peroneal nerve palsy requiring orthotics which resolved (grade II)
Death from acute myocardial infarction (grade V)	Pulmonary Embolism requiring anticoagulation and prolonged admission (grade III)
	2 patients - Hypoxia requiring intervention and prolonged admission (grade III)
	Readmission for sepsis unrelated to TKA (grade III)
	3 patients - Hypoxia requiring ICU transfer (grade IV)
	Pulmonary Embolism requiring ICU transfer (grade IV)

Table 3. Comparison of patients undergoing simultaneous bilateral TKA and those staged one week apart.

Patient Data	Staged (n=131)	Simultaneous (n=104)	p value
Age (years)	64.2	59.5	<0.001
Length of Stay (Days)	7.2	3.8	<0.001
Preoperative Hemoglobin (g/dL)	12.7	13.3	0.007
Blood transfused (units)	1.45	1.74	0.222
ASA	2.51	2.35	0.038
BMI	36.0	31.6	0.001
Charlson Comorbidity Index	1.06	0.53	<0.001
Male (%)	30 (23)	39 (38)	0.014
Required transfusion (%)	85 (65)	74 (71)	0.307
Perioperative Complication (%)	12 (9)	19 (18)	0.040
Hypertension (%)	105 (80)	68 (65)	0.011
Hyperlipidemia (%)	39 (30)	32 (31)	0.868
Diabetes Mellitus (%)	38 (29)	6 (6)	<0.001
Coronary Artery Disease (%)	26 (20)	12 (12)	0.085
COPD (%)	14 (11)	2 (2)	0.008
Chronic Renal Insufficiency (%)	8 (6)	2 (2)	0.192
HIV (%)	2 (2)	2 (2)	1
Hepatitis B or C (%)	6 (5)	9 (9)	0.283
Mortality (%)	1 (1)	0 (0)	1

Discussion

Staged bilateral TKA is an option for patients with advanced degenerative joint disease of both knees who desire a single rehabilitation period, and who have medical comorbidities putting them at high risk during simultaneous bilateral TKA. There were several limitations to our study, however. A selection bias exists in the decision to proceed with simultaneous bilateral TKA. Surgeons are much more likely to select younger, healthier patients to undergo a simultaneous operation. Our data confirm this, as the simultaneous group was younger and had lower ASA scores, Charlson Comorbidity Indices, and BMI. Despite being older and having more medical comorbidities, patients who underwent staged bilateral TKA had lower complication rates, which approached statistical significance (p=0.054). While our study identified perioperative complications during the index hospital admission, we did not have long-term follow-up to identify many of their adverse events including osteolysis, bearing surface wear, or periprosthetic fracture. Our data are consistent with prior smaller series demonstrating a low complication rate with a staged bilateral procedures one week apart.[1,8]

Conclusion

Staging bilateral TKA one week apart has low complication rates and is a viable option for patients with advanced degenerative disease and deformities of both knees who desire a single rehabilitation period. Staged procedures are particularly attractive for those with medical comorbidities precluding a simultaneous operation.

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Strategies and Application of Ankle-Spanning Multiplanar External Fixators

Ryan M. Taylor, MD
Matthew P. Sullivan, MD
Derek J. Donegan, MD
Jaimo Ahn, MD, PhD
Samir Mehta, MD

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

Introduction

Complex, high energy, open, periarticular fractures are seen regularly in most Level I and II trauma centers. Practicing orthopaedic surgeons in the trauma call pool should be capable of applying a lower extremity, joint-spanning external fixator for temporary fracture stabilization. There are several advantages to temporary joint-spanning external fixation over acute internal fixation including less vascular compromise to already traumatized bone, minimizing further soft tissue damage, rapid application in emergency situations, and stabilization of open and contaminated fractures until definitive fixation can take place.[1] Applying an external fixator also allows the traumatized soft tissue envelope to improve prior to definitive fixation, resulting in a staged management of the injury.[2]

Techniques regarding the application of joint-spanning external fixators are grounded in biomechanical principles that significantly affect the stability of the construct. The three variables under surgeon control that directly affect construct stability are the bone-pin interface, the components of the fixator, and the fixator configuration.[3] To increase stiffness in the overall construct, one can decrease the distance between the Schanz pins and the fracture, increase the diameter of the Schanz pins, increase the distance between consecutive Schanz pins in the same fracture fragment, decrease the distance from bar to bone, add additional bars, increase the bar diameter, use a triangular or multiplanar frame, align the pins with the major bending axis of the bone, combine limited internal fixation with external fixation, and achieve bone-to-bone reduction.[1,3,4]

There are several principles that orthopaedic traumatologists agree on regarding lower extremity external fixation. One concept involves the need for CT scans in preoperative planning for definitive fixation. However, the utility of a CT scan prior to application of an external fixator is limited. By placing a patient with a periarticular fracture into an external fixator, ligamentotaxis can be utilized to achieve better alignment of the fracture providing for greater information to the operative surgeon. To obtain the greatest improvement in bony and soft tissue alignment, it is important to obtain length, alignment, and rotation. The external fixator will also protect the soft tissue allowing the envelope to heal. Pins should not be placed in the zone of injury or future surgical incisions are hypothesized to lead to increased infection.[5] Issues that are less agreed upon are the use of power in pin insertion, the bar/pin/clamp construct, the brand of fixator used, and overall frame configuration.[5] Here we will discuss the thought process and preferred method for application of an ankle-spanning multiplanar (delta-configuration) external fixator, as would be applied for a tibial plafond fracture or high-energy ankle fracture-dislocation.

Case

VK is a 65 year old female who sustained a left trimalleolar fracture dislocation of the ankle after falling while walking down steps (Figure 1). She was initially evaluated in the emergency department, where the remainder of her trauma workup was negative. Given the instability of the fracture and the large concomitant soft tissue injury, the decision was made to go to the operating room for application of an ankle-spanning external fixator.

Preoperative Considerations

Imaging

Adequate AP, lateral, and mortise views of the ankle and AP and lateral of the ipsilateral knee are imperative before proceeding to the operating room. This helps to both better characterize the injury as well as rule out any concomitant injury at adjacent joints. Should the radiographs reveal a dislocated or subluxated tibiotalar or subtalar joint, reduction should not be delayed until the time of operative intervention. Instead, expeditious reduction should take place. Advanced imaging, such as a CT scan, does not necessarily need to be performed prior to application of an external fixator unless it will directly affect the initial surgery. Some advocate early CT to guide limited articular reduction and fixation through open wounds; however this is not universally agreed upon. By applying an external fixator and restoring appropriate length, the fracture fragments are disimpacted, and overall fracture pattern and location can be better evaluated on a subsequent CT. In addition, ligamentotaxis can help reduce some

Corresponding author:
Ryan M. Taylor, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Ryan.Taylor@uphs.upenn.edu

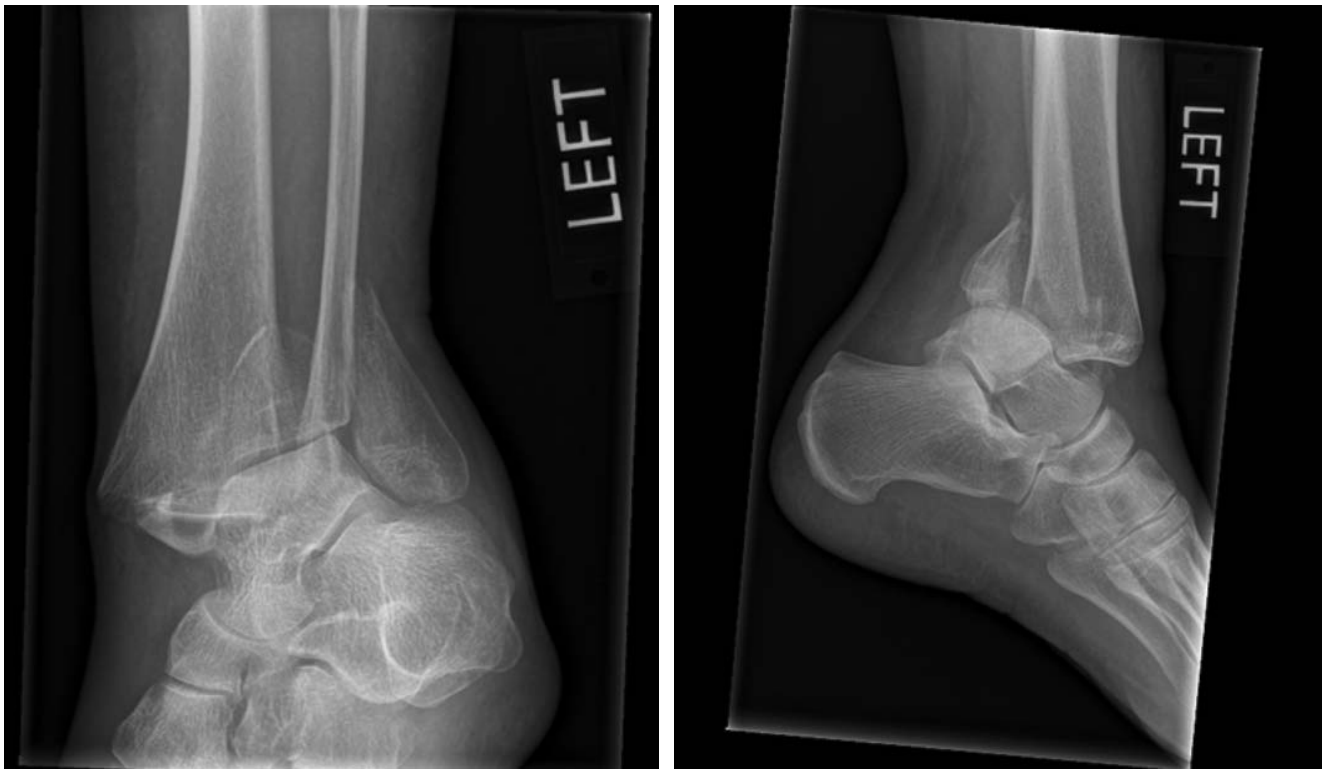

Figure 1. AP and lateral radiographs of a trimalleolar ankle fracture dislocation.

fragments to aid in planning for ultimate anatomic reduction and fixation.

Positioning/Equipment/Fluoroscopy

The patient should be positioned supine on a regular OR bed with a distal table extension to facilitate intra-operative fluoroscopy. Though a flat top radiolucent bed (Jackson table) may facilitate more proximal imaging, getting adequate images of the foot and ankle may be difficult due to the attachments at the foot of the bed. A regular bed with extension also facilitates physical access of the foot from the end of the bed. We prefer using a bump under the operative hip to position the patella pointing directly at the ceiling and an elevated ramp under the operative lower extremity to bring the leg away from the table and facilitate lateral imaging. Fluoroscopy should be brought in from the contralateral side of the table, and all necessary views should be obtained prior to prepping and draping the extremity. By bumping the hip and positioning the patella straight up and down, the AP and lateral shots of the knee and ankle are simplified with the machine able to alternate between positions parallel and perpendicular to the floor.

Implant Selection

The techniques used to apply an external fixator are significantly more important than the manufacturer of the implant. No specialized implants are necessary, and the pins, bars, and clamps used do not affect the stability of the construct as long as they are biomechanically sound and follow principles of fixation.

Prior to beginning the procedure, make certain that there are an adequate number of pins, bars, and clamps. There should be both 5mm Schanz pins for the tibia and a 5mm or 6mm centrally threaded pin for the calcaneus. In our preferred construct, five pin-bar clamps are necessary. Also ensure that there are bars of adequate length to span from the calcaneal pin to the tibial pins. The clamps need not be polyaxial. Though multi-axial clamps facilitate ease of use, they are not necessary for application of an ankle-spanning, multiplanar frame. Other implants to have available include any plating system that might be used for early fixation of the fibula in a pilon fracture. However, the indications and techniques regarding that are beyond the scope of this review. Current recommendations are such that acute fixation of the fibula during external fixation is not routinely performed.

Intraoperative Considerations

Tibial Pin Placement

Placement of Schanz pins should be well thought out before entering the operating room. When planning pin placement, one must consider the definitive surgical procedure. The pins should be well away from the fracture site for several reasons. First, during definitive fixation, the external fixator can be left on and utilized as a reduction tool, and having the construct away from the area of work can facilitate a window in which to work. Second, placement of pins within the zone of final fixation that overlap with permanent implants could lead to increased risk of bacterial inoculation and ultimately osteomyelitis, a devastating complication. Third, incisions for pin placement should be well away from the area of

the incisions being used for definitive fixation. Small skin bridges and increased trauma to an already compromised soft tissue envelope could lead to wound breakdown ultimately necessitating soft tissue coverage. This also ensures that the surgical trauma avoids the zone of injury. Application of an external fixator should be designed to help avoid compromise from any secondary procedure.[1]

There are multiple options for Schanz pin tip design including standard, self-tapping, and self-drilling/self-tapping. We prefer the self-tapping screws that do not self-drill. Self-drilling pins could theoretically lead to decreased pin stability due to the nature of their insertion. Also, the pins should be less than one third the total bone diameter. When the drilling tip engages the far cortex, the threads of the near cortex are stripped, therefore lessening their interference with the near cortex and leaving the pin engaged in only one cortex. In addition, a self-drilling pin will be more prominent through the far cortex with the same thread purchase. We prefer 5mm, self-tapping, non-coated Schanz pins inserted by hand. The surgeon should also know if the pin has a tapered design which can increase pin-bone interface as it moves forward but will be compromised if it is reversed.

The first tibial pin is placed as proximal as three finger breadths distal to the tibial tuberosity (for pilon fractures) or as proximal as the middle third or the shaft (ankle fracture-dislocation) on the medial border of the tibia just off of the apex of the crest. Once the appropriate position has been determined, a 1 cm incision is made, and blunt dissection is carried to the level of the periosteum. A small periosteal elevator can then be used to clear off any remaining soft tissue. The soft tissue protection sleeve (comprised of an outer sleeve, drill sleeve, and trocar) can then be positioned against the cortex of the tibia, making sure that all soft tissue is protected. Initially the sleeve should be at 90° to the medial border of the tibia, but once the drill engages, the trajectory should be shifted to perpendicular to the table, therefore making it straight along the AP plane and perpendicular to the mechanical axis of the tibia (on a lateral view). If the trajectory is not changed, the risk of a "burner" or all cortical pin is high. This is suboptimal, and if the drill is advanced too far past the cortex, the peroneal nerve could be at risk. Once two cortices are drilled, the inner drill sleeve can be removed, and the Schanz pin, loaded on a T-handled chuck, can be advanced. It is of the utmost importance that the trajectory of the outer sleeve does not change as you insert the pin to avoid losing the trajectory that was drilled. The pin will give some resistance as it goes through the first cortex, then continue to advance until the resistance of the second cortex. After several more turns, a lateral fluoroscopic image should be checked to gauge the depth of the pin (Figure 2). The entire tip should have passed through the second cortex with at least one thread engaged and through the far cortex.

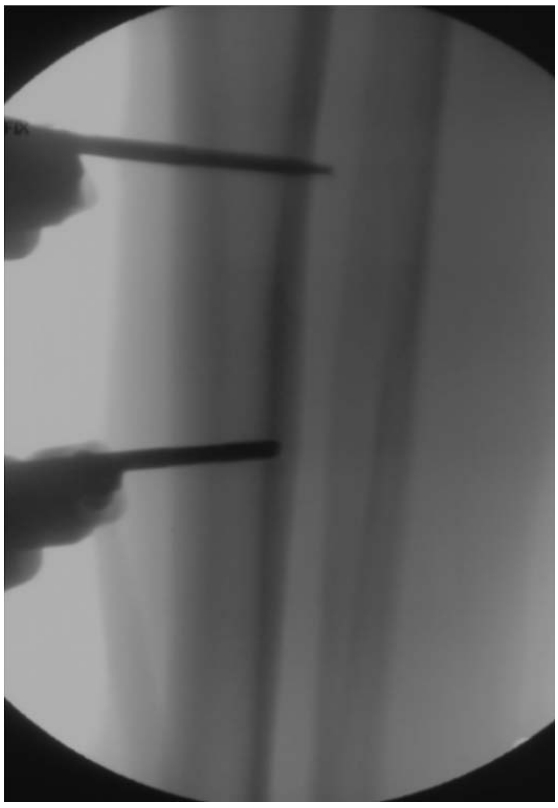

Figure 2. Fluoroscopic view of the tibia after final pin insertion.

Calcaneal Pin Placement

Placement of the calcaneal pin is slightly more difficult given the neurovascular structures in close proximity to the ideal window. The medial calcaneal nerve, the posterior branch of the lateral plantar nerve, and the lateral plantar nerves are at all risk.[6] The pin should be inserted from medial to lateral to avoid injury to the posterior tibial artery, the tibial nerve, and adjacent tendons. The posterior tibial artery should be clearly identified and can even be palpated during insertion to avoid injury. Many textbooks describe the location for the insertion of the trans-calcaneal pin as a point 2 cm posterior to the posterior border of the medial malleolus and 2 cm distal to the distal tip of the medial malleolus. We prefer to place our pins slightly more distal and posterior. This allows the calcaneal pin to abut the physeal scar, which contains the hardest bone in the calcaneus. This also serves to keep the pin further away from at risk neurovascular structures. The pin should be placed orthogonal to the tibial pin and to facilitate positioning of the calcaneus and, if possible, the foot should be supinated and the ankle dorsiflexed to lock the subtalar joint and keep the ankle in neutral.

When inserting the pin, first make a small skin incision and bluntly dissect down to the level of the medial calcaneal wall. Then, position the tip of the pin at the desired starting point and check your position in two planes. Drill only the medial cortex of the calcaneus. After correct positioning is confirmed, insert the centrally threaded pin directly across the calcaneus. We prefer a centrally threaded calcaneal pin that allows bars to be placed both medially and laterally on the same pin. The threads should be inserted slowly so as to not strip them in the soft cancellous bone of the calcaneus. After the pin is inserted, check a perfect lateral of the pin to ensure that it is completely within bone (Figure 3). By pre-drilling

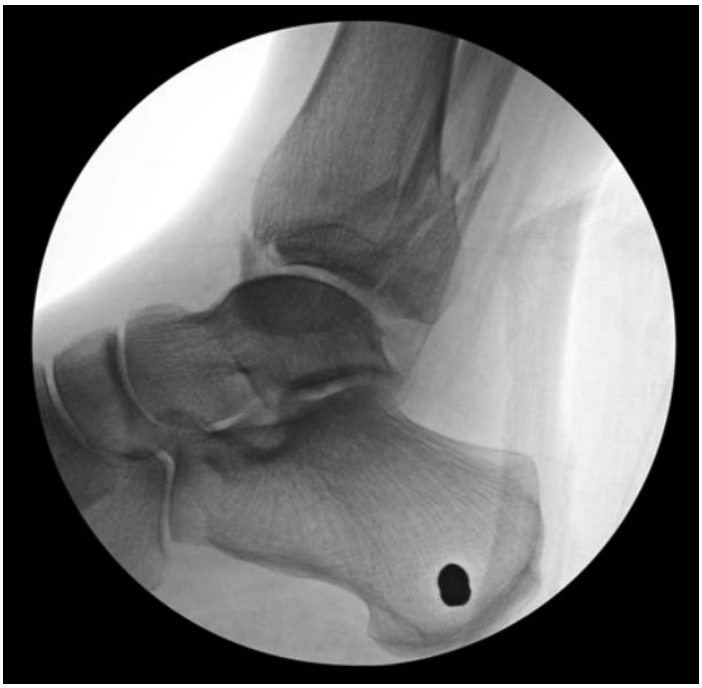

Figure 3. Lateral fluoroscopic view after calcaneal pin insertion.

the calcaneus pin you can ensure a correct trajectory, as well as make real time corrections without leaving a large defect in the cancellous bone, as you would with a misplaced threaded calcaneal pin.

Construct

After confirming the position of both tibial pin and the trans-calcaneal pin, the overall construct can be assembled. Two pin-bar clamps should be placed on the tibial pin and one each side of the calcaneal pin. Our preferred construct is a bar from the tibial pin to the lateral aspect of the calcaneal pin, a bar from the tibial pin to the medial aspect of the calcaneal pin, and an out-of-plane tibial pin connected to the medial bar, added after the reduction has been performed and the rest of the clamps tightened.

The directionality of the clamps is also important. The pin side of the pin-bar clamps should open away from the fracture so that the distraction force is "pushed" through the imbedded pins rather than "pulled." Also, the bar side of the tibial clamps should be positioned with the open side facing posteriorly and the bar side of the calcaneal clamps, with the open side facing anteriorly. This is to decrease the posterior vector force, thereby preventing subluxation. All pin-bar clamps should be left loose on the bar side so that the bars slide through the clamp as the reduction maneuver is performed. Often times, a posteriorly directed force on the distal tibia and an anteriorly directed force through the calcaneal pin will help reduce the subtalar or tibiotalar joint. The ankle should also be dorsiflexed to help reestablish the ankle as the center of rotation.

After the reduction is performed and the ankle is positioned appropriately, the clamps can then be finger tightened and ultimately fully tightened once an acceptable reduction has occurred. The bars should be about two to four finger breadths away from the skin of the calcaneus and should accommodate additional swelling so that there is no risk of contact between the bars and the skin either at the tibia or the calcaneus.

Reduction

Once the pins, clamps, and bars are in place, the reduction can take place. Restoring length, alignment, rotation, and maintaining a reduced ankle are key considerations during this step. Fluoroscopy should be brought into the field and multiple images should be acquired as you perform your reduction. The initial maneuvers should be performed while

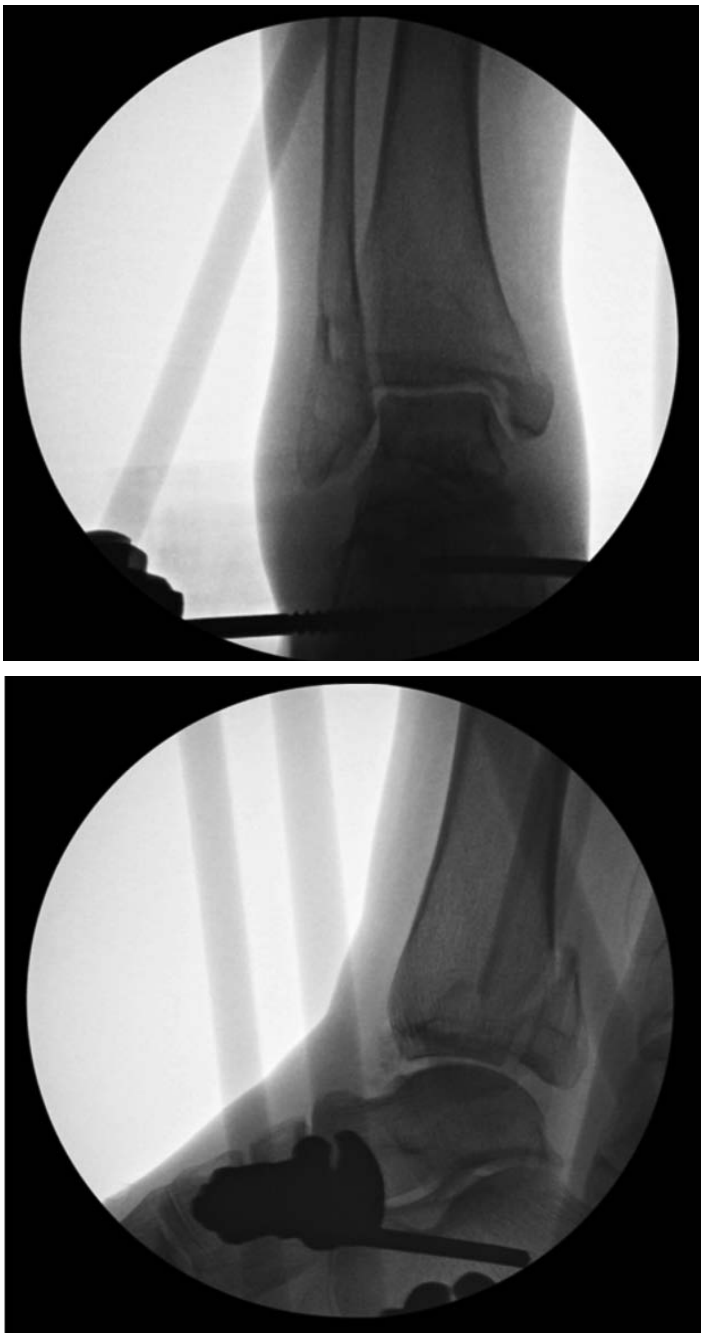

Figure 4. Mortise and lateral fluoroscopic images of the ankle after reduction maneuver.

taking lateral fluoroscopic images to confirm that the talus is reduced under the tibia. Usually axial traction, with slight anterior or posterior translation, and minimal internal or external rotation should achieve an adequate reduction. Once a satisfactory reduction has occurred, tighten the bar side of the pin-bar clamp to hold the reduction and release traction. Take AP, lateral, and mortise views of the ankle to confirm restoration of length, alignment, rotation, and a reduced joint (Figure 4). If the reduction appears satisfactory, tighten all the clamps fully. Never tighten dual-nut clamps with a single wrench, as this may cause the pins to strip out of the bone. Instead, take a second wrench and place counter traction on the opposite side of the clamp to resist increased torque through the pins. Lastly, after the reduction has been performed and all the pins have been fully tightened, use a drill guide that can be mounted on the medial tibial to calcaneal bar, and place a second tibial pin out of plane to the first pin, to give increased stability. After the pin has been inserted but prior to removing the T-handle chuck, the pin can be used to help modify the reduction but only slightly. At this point only small changes in the overall reduction can be implemented given that the rest of the construct is locked. After the reduction is satisfactory, tighten the clamps and recheck fluoroscopy shots. Make sure that all clamps have been fully tightened in order to avoid losing your reduction.

Conclusion

The application of an ankle-spanning multiplanar (delta-configuration) external fixator is a tool that all orthopaedic surgeons should have in their armamentarium. By understanding the biomechanics of building a stable construct, performing adequate preoperative planning, and adhering to strict principles of fracture stabilization and soft tissue management, the application of a joint-spanning external fixator can be used successfully as temporary stabilization of a high energy, comminuted, or open fracture that needs to be managed in a staged fashion.

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Length, Alignment, and Rotation: Operative Techniques for Intramedullary Nailing of the Comminuted, Diaphyseal Femur Fracture

Matthew P. Sullivan, MD
Ryan M. Taylor, MD
Derek J. Donegan, MD
Samir Mehta, MD
Jaimo Ahn, MD, PhD

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

Introduction

Shortened and rotationally unstable femoral shaft fractures can be extremely challenging even for the very experienced. Orthopaedic surgeons taking trauma call should have the necessary technical skills to stabilize a femur fracture with an elementary pattern utilizing an intramedullary device, but they should also be prepared for the occasionally challenging case. This may occur in the high energy trauma patient, who is often young, healthy, and generally tolerant of surgery, but who also has many years of life ahead, making it critical to restore anatomic length, alignment, and rotation. Restoring normal anatomy gives the patient the greatest chance at normal long-term hip and knee function. Incidences of leg length discrepancy and angular malalignment following femoral nailing have been reported as 7% and 9%, respectively.[1,2] Significant rotational deformity occurs in up to 28% of femur fractures.[3] Historically, malrotation less than 15° was thought to be acceptable;[4] however, Karaman and colleagues recently showed that patients with rotational malunion greater than 10° demonstrated significantly worse WOMAC knee and hip scores at long-term follow- up.[5] Additionally, Lee *et al* demonstrated in a biomechanical study that patellofemoral contract pressures increase dramatically with both internal and external femoral malrotation greater than 30 degrees.[6] Finally, femur fractures are the most common cause of litigation in orthopaedic surgery.[7,8] For these and many other reasons, it is critical for those participating in trauma call to be familiar with multiple ways to restore length, alignment and rotation in a comminuted diaphyseal femur fracture. We will review tips and tricks used in order to ensure the best possible reduction following these complex injuries. We will take the reader through a complex case and the decision-making involved in arriving at the desired outcome.

Corresponding author:
Matthew P. Sullivan, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Matthew.Sullivan2@uphs.upenn.edu

Case Report

We present a 26 year-old male who arrived at our trauma center after sustaining an isolated, closed, high energy blunt injury to his left thigh. Primary and secondary surveys were carried out in the trauma bay, and the patient was cleared by the Trauma Service for surgery. Given the high energy nature of the injury, the availability of a ready orthopaedic trauma OR, and a full OR staff, including a trauma-trained orthopaedic surgeon with resident help, the patient was taken expeditiously to the operating room for intramedullary fixation of the femur fracture.

Preoperative Considerations

Imaging

Basic trauma series plain films were acquired in the trauma bay, which included lateral C-spine, chest, and pelvis Xrays. Limited AP and lateral plain films of the left thigh and knee were acquired as well. Radiographic evaluation of the ipsilateral knee and hip are essential, as abnormal native anatomy or intra-articular fracture extension will potentially alter the surgical plan. Our radiographic evaluation revealed a segmental, comminuted, diaphyseal femur fracture involving the subtrochanteric and mid-diaphyseal regions (Figure 1). Additionally, as is standard of care at our institution, this high energy trauma patient underwent a CT scan of the head, neck, chest, abdomen and pelvis, including the ipsilateral proximal femur to evaluate for an occult femoral neck fracture.

Equipment

Preoperative planning for this surgery should include choosing the appropriate operating room table, C-arm position within the room, and ancillary instruments that may be needed for reduction and fixation. The standard at our institution is to use a radiolucent flat-top (Jackson) table with the patient in the supine position with a bump placed under the ipsilateral hip. We utilize distal femoral skeletal traction with traction being applied longitudinally over a pipe-bender. (Figure 2)

Intraoperative Considerations

Length

It is critical to plan the strategies that will be used to restore length, alignment, and

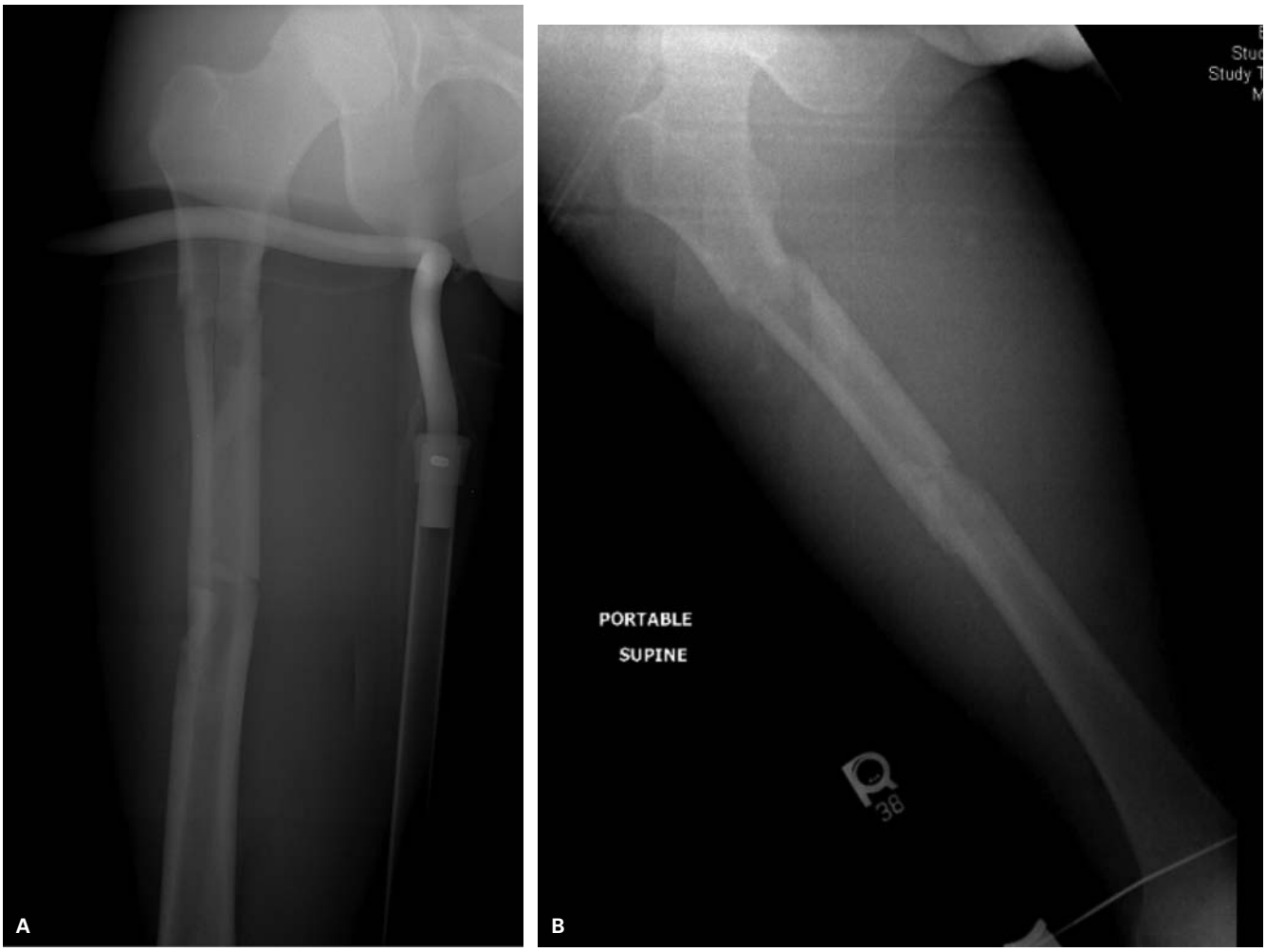

Figure 1. Injury films taken in the trauma bay. The patient was initially placed in a Hare Traction splint (A), followed by skeletal traction (B).

Figure 2. Typical operating room setup depicting a radiolucent flat top table with a black foam ramp for proper positioning. The proximal apex of the triangle is placed at the gluteal fold. A pipe bender is attached to the end of the table on the contralateral side to the injury. Skeletal traction is applied longitudinally over the pipe bender with 10-15 lbs of weights attached to sterile rope.

rotation before the patient is prepped and draped. The first consideration should be restoration of length. When significant cortical comminution exists, length can be gauged from the contralateral leg. However, because of patient positioning on a bump as well as the sterile drapes, intra-operative comparison of the injured extremity to the uninjured extremity is unreliable. With the aid of fluoroscopy, the nail length can be accurately estimated from the uninjured leg before prepping and draping. There are several ways to accomplish this task.

Measuring Tape

One method for restoring length is to measure the distance from the nail entry point in the proximal femur (just distal to the cortex of the piriformis fossa or the tip of the greater trochanter) to where the distal tip of the nail will ultimately be seated (the distal femoral physeal scar or superior pole of patella). A common mistake when measuring this distance is to localize the precise locations with a radio-opaque marker over the extremity on the anterior skin surface. Because of fluoroscopic projection, placing the marker closer to the image intensifier will result in a false increase in the measured nail length. To prevent this, we prefer to use a hemostat placed lateral to the femur at the level of the femur in the anterior-posterior plane. One hemostat is placed proximally at the starting point, confirmed with fluoroscopy, and held in place. Another is placed distally, confirmed with fluoroscopy, and held in place. The distance between hemostat clamps is

measured with a measuring tape. The final image of the distal hemostat should be saved and printed for future reference when determining where to ultimately seat the nail. Of note, when using any technique in which distance is being measured with the aid of fluoroscopy, the reference point must be centered in the C-arm field. Failure to properly center an image can alter a measurement by up to a centimeter.

Metal Ruler

Another method for measuring the nail length is with a metal ruler that occasionally comes in the instrumentation set for the implant system. A common mistake in measuring the length of the nail off of bony landmarks is to follow the contour of the lateral aspect of the thigh. Piriformis nails are straight in the coronal plane, and trochanteric nails have only a few degrees of built-in valgus bend. Measuring along the contour of the thigh will erroneously increase the measured length. Doing so will give the hypotenuse length as opposed to the long leg of the triangle. In general, in order to ensure proper measurement of length, the intraoperative position of the injured limb should be replicated in the uninjured limb. This involves using the same bump and angle of the hip.

Cortical Length

In certain situations, there will be enough cortical bone intact so that length can be assessed by lining up the intact cortices. This method has the potential to be problematic if the cortical read is out of the plane of the beam of the fluoroscope. In the situation in which a precise cortical read is not perfect, the above-mentioned steps should be carried out to ensure restoration of proper length.

Full-Length Imaging

Full-length imaging of the non-injured femur, if available, can be an excellent way to measure nail length. This is possible with plain radiographs or computed tomography. If full-length plain films are going to be used, it is essential to use a 25mm magnification marker at the level of the femur in order to account for radiographic projection. Another useful method to consider is using the CT scout view. All femoral shaft fractures should have a CT of the femoral neck to aid in identifying an occult femoral neck fracture. A scout view scan of the uninjured femur can easily be obtained at this time and used to accurately measure nail length.

Rotation

Along with assessment of length, proper rotation must also be addressed. Unfortunately, rotation is the most common parameter to be malreduced. Rotation, like length, requires careful consideration before the patient is prepped and draped. Additionally, there are intra-operative clues that can be used before the patient is woken up. In similar fashion to length, rotation can be planned from the uninjured extremity.

Lesser Trochanter Method

The lesser trochanter method relies on the rotational relationship between the distal femur and the proximal femur and uses the lesser trochanter to define this relationship. The first step is to evaluate the uninjured femur. The thigh should be bumped up in the standard fashion. We prefer to use a long, black foam ramp. (Figure 2) The C-arm is brought distally to the knee and the beam is oriented perfectly parallel to the floor. A perfect lateral of the distal femur is obtained. The thigh can be moved freely to obtain this view, but once it is acquired the thigh must be held perfectly still. The C-arm is then rotated up exactly 90° and translated up to the hip. Once at the hip, an image centered directly over the lesser trochanter is obtained. This image of the proximal femur centered over the lesser trochanter should be saved, printed, and posted in a visible location for reference later in the case (Figure 3). Once the nail has been passed, the proximal interlocking screw should be inserted. The C-arm is then centered directly over the lesser trochanter with the beam exactly 90° to the floor. Next the image of the lesser trochanter from the uninjured femur is referenced and replicated by gently rotating the proximal femur through the aiming jig. Specifically, the amount of lesser trochanter visible medial to the proximal femur must be perfectly reproduced. Once this is accomplished, the aiming jig is held perfectly still. The next step is to rotate the C-arm beam exactly 90° such that it is parallel to the floor. The machine is translated to the distal femur. With the proximal femur firmly being held in place through the aiming arm the distal femur is rotated until a perfect lateral of the distal femur is acquired. If done correctly, the entire femur will be locked in the equivalent rotation as the uninjured side.

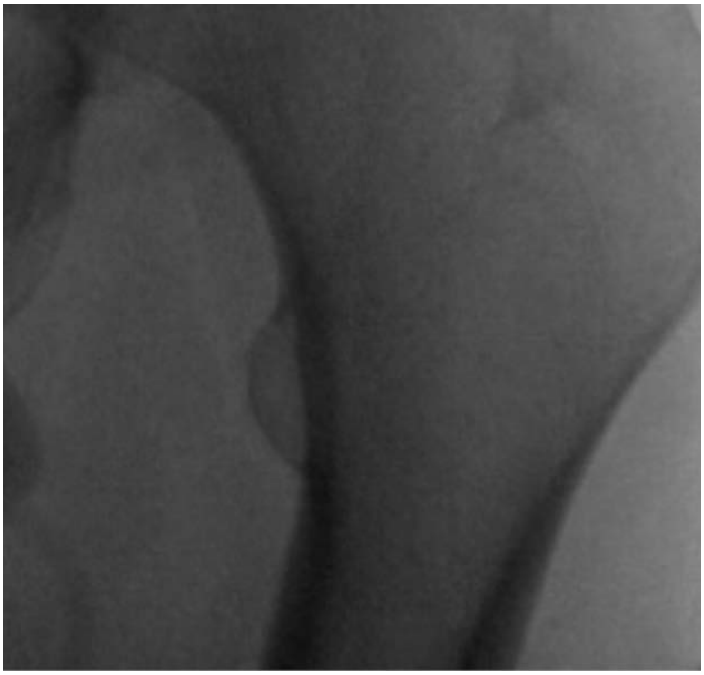

Figure 3. Preoperative fluoroscopic image centered over the lesser trochanter of the *uninjured* extremity. This image is saved and printed for later use in determining anatomic rotation once the nail has been placed. The image can be magnified over the lesser trochanter to more accurately set rotation.

Neck Version Method

The neck version method relies on the same principles as the lesser trochanter method for restoring femoral rotation. The primary difference lies in the anatomic landmark upon which rotation is referenced. In this method, instead of using an AP of the lesser trochanter, the version of the neck is used. As in the previous method, a perfect lateral of the distal femur is obtained. Then the C-arm is arced into a near lateral position until a perfect lateral is obtained of the native version of the neck, and this angle is noted. During the surgical repair of the injured side, the noted neck version can be recreated. These principles can in fact be applied to any two consistent landmarks on the femur, one proximal and the other distal to the fracture site.

Cortical Width Method

The cross sectional anatomy of the femoral diaphysis reveals a non-symmetric circumferential cortical width. In certain circumstances, this finding can be used to judge rotation. The ideal situation in which to use cortical widths to assess rotation is when there is little or no comminution of at least one cortex on AP or lateral imaging or there is a large wedge fragment that allows for assessment of cortical width. Once the nail has been passed and locked proximally, the distal segment may be rotated around the nail until the cortical width of the proximal and distal segments are perfectly equal. This may not be an appropriate method to use when there is significant circumferential comminution or a segmental injury.

Alignment

Limb alignment is critically important to the overall function of the traumatized limb, and restoration of the mechanical axis should be considered a high priority. Unfortunately, alignment is set well before the nail is placed and can be difficult to change once the nail has been passed. The most significant factor affecting alignment is starting point. For a piriformis entry nail, the entry point is constant regardless of the system being used. For a trochanteric entry nail, the starting point varies depending on the proximal bend of the nail. As a result, the technique guide should be consulted for the precise starting point before embarking on nailing a femur with a trochanteric entry nail. However, there are a few techniques that should also be considered to set alignment as anatomic as possible.

As mentioned above, the critical opportunity to set alignment is with the starting point. However, once the starting point has been identified and the femur has been open reamed, there are additional opportunities to adjust alignment. Upon successfully passing the guidewire across the fracture and into the distal segment, the mechanical axis can easily be evaluated. The C-arm is brought to the hip, and a Bovie cord with an attached hemostat is laid directly over the center of the femoral head. This is held perfectly in place. The Bovie cord is tensioned distally, clamped with another hemostat, and laid directly over the center of the ankle (just slightly laterally off center of the tibial plafond). Again, this is confirmed with C-arm, and the clamp/cord is held perfectly in place. Finally, the C-arm is brought proximally to the knee. If the mechanical axis is appropriate, the Bovie cord will lie slightly medially to the center of the knee (Figure 4). If the Bovie cord is translated medial or lateral to this spot, adjustments in alignment should be made prior to femoral reaming. Once the nail has been passed and prior to locking, the same steps should be repeated to ensure that alignment has been maintained.

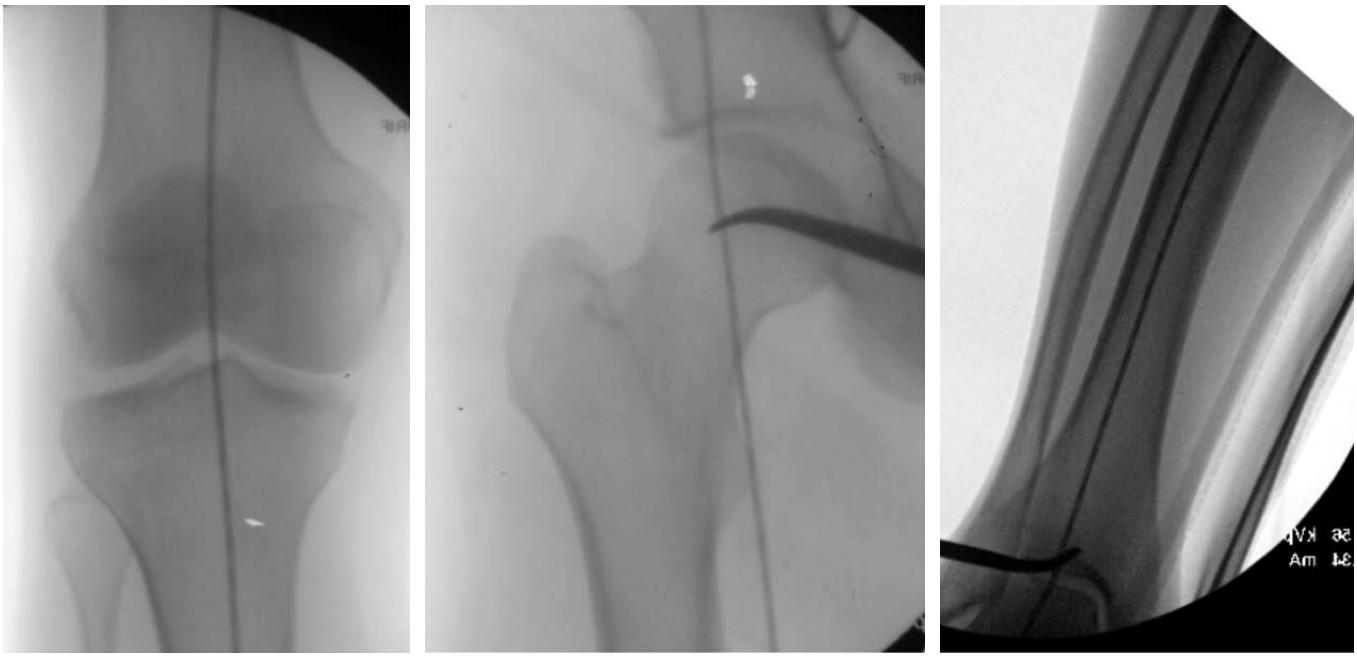

Figure 4. Bovie cord method used for restoring the proper mechanical axis of the limb. The Bovie cord is stretched from the center of the femoral head to the center of the ankle and held in place with clamps. An AP image at the knee is then taken. If the mechanical axis has been properly restored, the cord should pass directly through or slightly medial to the center of the knee.

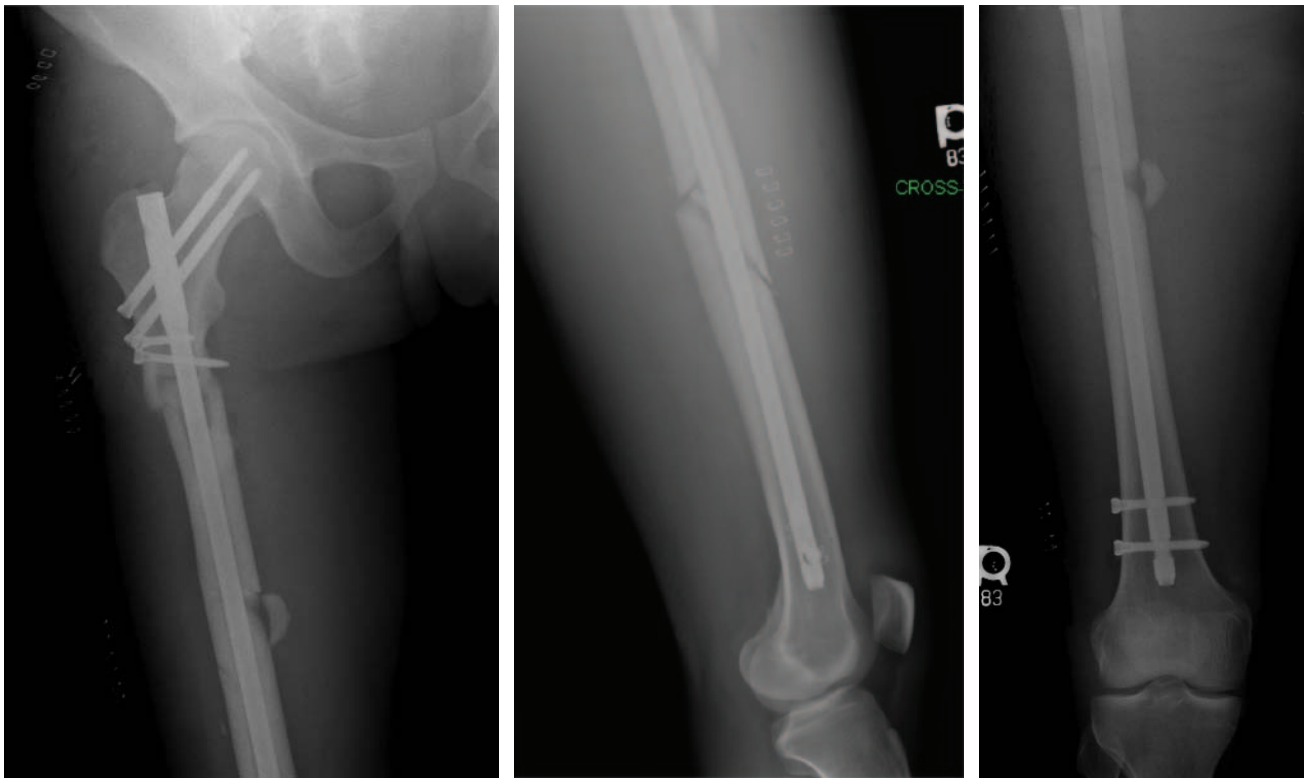

Figure 5. Intra-operative Xrays are performed prior to waking the patient and contaminating the surgical instrumentation. These are essential to ensure extra-articular placement of implants as well as gross alignment. Length and rotation are also evaluated clinically prior to waking the patient.

If the mechanical axis is markedly off due to a malpositioned starting point or loss of reduction of the unstable segment, the nail can be removed, and the starting point may be eccentrically reamed. This can be achieved by temporarily placing a one-third tubular plate into the proximal hole on the opposite side of which you choose to eccentrically ream. The plate will force the reamer in the opposite direction, allowing for the hole to be opened eccentrically. The nail can then be passed again, and alignment must be reevaluated. Another option for adjusting alignment once the canal has been reamed is to utilize cortical replacing screws (also known as Poller screws or blocking screws) in order to translate the bone relative to the nail.

Conclusion

The case presented above demonstrates a common senario that the orthopaedic surgeon may face while taking trauma call. Our management strategy includes many of the methods described above for restoring anatomic length, alignment, and rotation. Specifically, we utilize the measuring tape method for length restoration, the lesser trochanter and cortical width methods for restoring rotation, and the Bovie cord method for restoring alignment. Additionally, this fracture pattern required cortical replacing screws in order to control the mobile proximal segment during nail passage. Examination prior to waking the patient from anesthesia demonstrated anatomic restoration of the aforementioned parameters. Immediate intra-operative plain radiographs are shown in Figure 5. At 6-month follow-up, the patient demonstrated appropriate healing and excellent lower extremity function.

Intramedullary fixation of comminuted diaphyseal femur fractures is extremely challenging, and it is critically important to restore anatomic length, alignment, and rotation. Malreduction and malunion significantly affect long-term function. Here we describe several tips and tricks for restoring normal anatomy. As with nearly all orthopaedic procedures, preoperative planning and careful consideration are paramount.

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Treatment of Thumb Basal Joint Arthritis With Hematoma and Distraction Arthroplasty Compared to LRTI in a Predominantly Male Population

Stephen Y. Liu, MD
Christina F. Endress, MD
David R. Steinberg, MD

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

Introduction

The basal joint, also referred to as the carpometacarpal (CMC) joint, of the thumb is one of the joints most commonly affected by arthritis. CMC joint arthritis can lead to decreased grip and pinch strength and impairment of activities of daily living. The goal of surgical intervention is to relieve the arthritic pain while maintaining thumb function. Simple trapeziectomy was first described in 1949 by Gervis and again in 1960 by Murley but was abandoned due to decreased grip strength.[1,2] Over the past three decades in the United States, a more popular procedure for thumb CMC arthritis has been ligament reconstruction with tendon interposition (LRTI). This procedure was first described by Burton in 1983, in which the flexor carpi radialis (FCR) tendon is used to reconstruct the palmar oblique ligament (POL). Upon review of his cases, with minimum of two-year follow-up, Burton showed 92% excellent results.[3] Reports have shown that the majority of patients are satisfied with pain relief provided by LRTI and have improved ability to perform activities of daily living.[4]

Recent literature has questioned whether LRTI is the ideal treatment option for basal joint arthritis. Studies have shown that the LRTI procedure is not as effective in preventing proximal metacarpal migration as was once thought, yet patient satisfaction remained high. Based on these findings, Gelberman *et al* proposed a new technique in which the ligament was reconstructed but a portion of trapezium was retained ("trapezium-retaining interposition arthroplasty"). They concluded that patients had similar satisfaction compared to LRTI and trapezial height was also maintained.[5]

Other surgeons took a different approach. In 2003, Kuhns *et al* described a technique of trapeziectomy with post-operative K-wire immobilization of the CMC joint, known as "Hematoma and distraction arthroplasty" (HDA, Figure 1). Outcomes showed a stable, pain-free thumb that had superior strength and motion compared to other more complicated procedures for CMC arthritis.[6] Comparative studies in predominantly female patients (86-100%) over the last decade have demonstrated equivalent outcomes for trapeziectomy alone and trapezium resection with tendon interposition with or without ligament reconstruction.[7-10]

The purpose of our study was to compare the results of LRTI versus HDA in a predominantly male population at the Philadelphia Veterans Affair Medical Center (PVAMC).

Methods

A retrospective review was conducted of the PVAMC database between November 2000

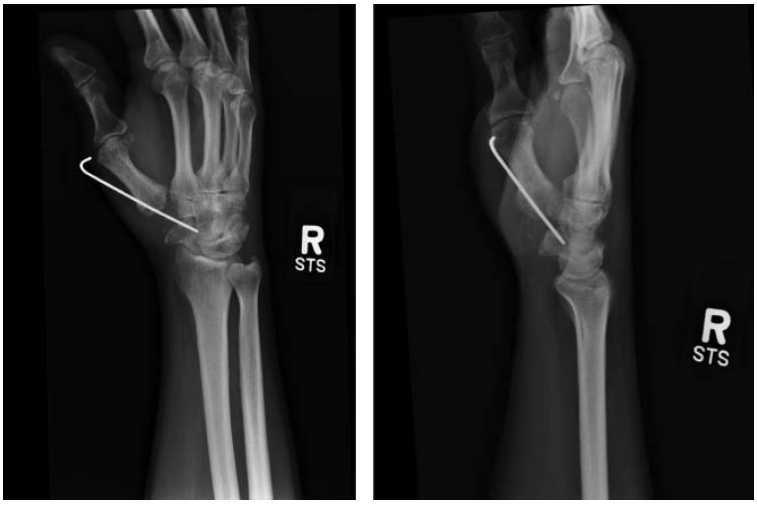

Figure 1. Postoperative imaging showing K-wire fixation in hematoma and distraction arthroplasty.

Corresponding author:
Stephen Y. Liu, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Stephen.Liu@uphs.upenn.edu

and October 2013. All patients who underwent CMC joint arthroplasty for radiographic evidence of basal joint arthritis and pain unresponsive to conservative measures were included in the study. For purposes of this review, patients were further stratified into LRTI and HDA groups. All surgeries were performed by the senior author (DRS). This represents a consecutive series of patients undergoing basal joint surgery. LRTI was performed in all patients in the first part of the collection period, and HDA performed in all patients presenting after July 2010. Data regarding preoperative pain, postoperative pain, postoperative radiographs, comorbidities, number of additional procedures done at the time of surgery, and complications were collected. Post-operatively, patients underwent suture removal and cast application at 1 week, cast and K-wire removal (if applicable) and the start of ROM exercises in an orthoplast splint at 4 weeks, and strength exercises at 8 weeks. Patients were discharged from routine follow-up at 12 weeks. At 12 weeks, pain scores were recorded and radiographs were evaluated for collapse by one surgeon (CFE) looking specifically at trapezial space height and trapezial space ratios. Patient outcomes included pain relief, radiographic collapse, and complications. Significance was calculated using a two sample two-tailed Student's t-test. Chi-squared analysis was used to compare discrete variables.

Results

A total of 31 CMC arthroplasties were performed during the study period, of which 28 were included in the study (25 patients). Twelve were LRTI and 16 were HDA. Eighty-two percent of the patients were male, which was statistically similar in both groups. There was no difference in age, number of additional procedures, comorbidities, pre and postoperative pain scores, and pain relief between the groups (Table 1). The LRTI patients had longer follow-up (5.69 years +/− 2.88 vs. 0.60 +/− 0.91; p=0.003), while the HDA group had significantly shorter tourniquet time (96.9 minutes +/− 7.3 vs. 68.9 +/− 21.5; p=0.0001). There was no difference radiographically between the trapezial space height/ratio on AP or lateral radiographs between the groups (Table 2). The LRTI group was complicated by one case of incisional cellulitis, which resolved with oral antibiotics. The HDA group had one suture abscess from an unrelated surgical site, that resolved with antibiotics, and one incision and drainage for hypersensitivity to gelfoam (only used in this one case) that went on to heal uneventfully.

Discussion

Recent comparative studies have demonstrated similar outcomes for different thumb basal joint surgeries, including trapeziectomy, tendon interposition, and ligament reconstruction. All have been in predominantly female populations (86–100%).[7,9-10]

Our results further support the concept of simple trapeziectomy as a viable treatment option for thumb basal joint arthritis. We found that patients are satisfied with the HDA procedure and have similar pain relief and function compared

Table 1. Demographic data of the study groups, LRTI and HDA. There were significant differences in follow-up (longer in LRTI) and tourniquet time (shorter in HDA).

	LRTI (mean ± SD)	HDA (mean ± SD)	P-value
Age (yr)	61.75 ± 7.20	63.56 ± 6.61	0.5
Male (%)	83.3	81.2	0.89
Follow-up (yr)	5.69 ± 2.88	0.60 ± 0.91	<0.05
# Comorbidities	3.25 ± 2.86	4.31 ± 3.11	0.36
# Extra procedures	0.42 ± 0.67	0.31 ± 0.79	0.71
Tourniquet time (min)	96.91 ± 7.33	68.88 ± 21.50	<0.05
Preoperative pain	7.77 ± 0.65	8.13 ± 1.02	0.28
Postoperative pain	1.45 ± 1.69	1.06 ± 1.06	0.51

Table 2. Postoperative pain relief and radiographic measurements for the LRTI and HDA groups. There were no significant differences found between groups for any of these measurements.

	LRTI (mean ± SD)	HDA (mean ± SD)	P-value
Pain relief (pain score difference)	6.32 ± 1.75	7.06 ± 1.36	0.25
Trapezial space height AP (mm)	7.13 ± 2.01	8.22 ± 2.26	0.28
Trapezial space height lateral (mm)	6.17 ± 1.55	5.71 ± 1.78	0.55
Trapezial space ratio AP	0.21 ± 0.05	0.26 ± 0.08	0.10
Trapezial space ratio lateral	0.20 ± 0.05	0.20 ± 0.06	0.96

to patients who underwent the more complex LRTI. There was no statistical difference in pain relief between the two groups. Men undergoing this procedure can expect results similar to those reported in the literature for predominantly female patients.

There was no statistical difference in metacarpal subsidence between the two groups as determined by the trapezial height ratio. This is an important finding, as one justification for performing the LRTI procedure is that it was thought to provide greater joint stability and less subsidence of the thumb metacarpal.

Limitations of our study include its retrospective nature. The hematoma arthroplasty group had very short-term Xray follow-up. Many of the patients did not have further imaging after their K-wires were removed, as they were clinically doing well. Currently these patients are being reevaluated to document longer-term clinical and radiographic outcomes.

Conclusion

HDA is a reasonable alternative to LRTI for surgical treatment of thumb basal joint arthritis. It is a simpler procedure with less potential complications and requires less tourniquet time. HDA provides equivalent pain relief and function compared to LRTI in a predominantly male population. Men undergoing this procedure can expect results similar to those reported in the literature for predominantly female patients.

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U·P·O·J

Functional Knee Outcomes in Suprapatellar and Infrapatellar Tibial Nailing: Does Approach Matter?

P. Maxwell Courtney, MD
Anthony Boniello, BS
Derek J. Donegan, MD
Jaimo Ahn, MD, PhD
Samir Mehta, MD

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

Introduction

With an incidence of 75,000 per year in the United States alone, fractures of the tibial shaft are among the most common long bone fractures.[1] Techniques using a semi-extended suprapatellar approach can facilitate intraoperative imaging, allow easier access to starting site position and counter deforming forces. While outcomes following traditional infrapatellar nailing have been well documented, there is a paucity of literature regarding outcomes following the use of a suprapatellar approach. By splitting the quadriceps tendon, scar tissue will form superior to the patella as opposed to the anterior knee, which may reduce flexion-related pain or pain while kneeling.[2] The infrapatellar nerve is also well protected during this approach. The purpose of this study was to determine differences in functional knee pain in patients who underwent suprapatellar nailing versus traditional infrapatellar nailing.

Methods

This study received no outside funding and was approved and conducted according to the guidelines set forth by our Institutional Review Board (IRB). We searched our department trauma database for all patients who underwent Current Procedural Terminology (CPT) code 27759 for treatment of tibial shaft fracture with intramedullary implant at a single Level 1 trauma center from January 2009 to February 2013. Radiographs, operative reports, and inpatient records were reviewed. Patients over age 18 at the time of injury and those with an isolated tibial shaft fracture (OTA type 42 A-C) fixed surgically with an intramedullary nail via a suprapatellar approach or a traditional infrapatellar approach were included in the study. Exclusion criteria were a treatment regimen that included fasciotomy, Gustilo type 3B or 3C open fractures, a history of additional orthopaedic injuries or prior knee surgeries, and pre-existing radiographic evidence of degenerative joint disease.

Each patient was contacted via telephone by an investigator who administered the 12 question Oxford Knee Score questionnaire (Figure 1). Investigators were blinded to surgical exposure. Operative time, quality of reduction on postoperative radiographs, and intraoperative fluoroscopy time were compared between the two approaches. We determined quality of reduction by measuring the angle between the line perpendicular to the tibial plateau and plafond on both the anteroposterior and lateral

1. How would you describe the pain you usually have in your knee?
2. Have you had any trouble washing and drying yourself (all over) because of your knee?
3. Have you had any trouble getting in and out of the car or using public transport because of your knee? (with or without a stick)
4. For how long are you able to walk before the pain in your knee becomes severe? (with or without a stick)
5. After a meal (sat at a table), how painful has it been for you to stand up from a chair because of your knee?
6. Have you been limping when walking, because of your knee?
7. Could you kneel down and get up again afterwards?
8. Are you troubled by pain in your knee at night in bed?
9. How much has pain from your knee interfered with your usual work? (including housework)
10. Have you felt that your knee might suddenly give way or let you down?
11. Could you do household shopping on your own?
12. Could you walk down a flight of stairs?

Figure 1. Oxford Knee Score questionnaire administered to each patient via telephone. Each question had specific answers corresponding to a score from 0 (worst function) to 4 (best function).

Corresponding author:
P. Maxwell Courtney, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Paul.Courtney@uphs.upenn.edu

postoperative radiographs. Rotation was determined by measuring the displacement of the fracture by cortical widths.

We conducted an a priori power analysis to determine the appropriate sample size. In order to detect the reported Minimally Clinically Important Difference (MCID) in the Oxford Knee Score of 5.2,[3] estimating an approximate 20% larger patient population in the infrapatellar group, we calculated a need to enroll 24 infrapatellar patients and 20 suprapatellar patients. Our calculations predict this study design would achieve a power of 0.80 with a type I error rate of 0.05.[4] This power analysis was based on an estimated Oxford Knee Score standard deviation of 6, as previously reported in several studies.[5,6]

Results

We identified 176 patients who underwent intramedullary fixation of tibial shaft fractures from January 2009 to February 2013. After analyzing radiographs and medical records, 82 patients met inclusion criteria. Thirty-six of the original 82 patients (45%) were lost to follow-up after attempts to contact them by telephone. Twenty-four patients underwent traditional infrapatellar nailing and 21 patients had a suprapatellar nail placed with approach-specific instrumentation. No significant difference was found between the groups in terms of gender, age, BMI, mechanism of injury or operative time (Table 1). The mean ages for the infrapatellar and suprapatellar group were 37.6 (range 20-65 years) and 38.5 years (range 18-68 years) respectively ($p=0.839$). The average follow-up for the suprapatellar approach (8.0, range 3-33 months) was significantly shorter than the infrapatellar approach (12.8, range 4-43 months, $p<0.001$).

The mean Oxford Knee Score (maximum of 48 points) was 40.1 and 36.2 ($p=0.221$) for the infrapatellar (range 11-48) and suprapatellar groups (range 2-48), respectively. Suprapatellar nailing had improved radiographic reduction (2.90 degrees) in the sagittal plane when compared to infrapatellar nailing (4.58 degrees, $p=0.044$). There was no difference in rotational malreduction (0.32 vs. 0.25 cortical widths, $p=0.599$) or reduction in the coronal plane (2.52 vs. 3.17 degrees, $p=0.280$). The suprapatellar approach did require less operative fluoroscopy time (80.8 seconds, range 46-180) than the standard infrapatellar approach (122.1 seconds, range 71-240, $p=0.003$). Our results data are summarized in Table 2.

Discussion

We present one of the first retrospective cohorts comparing functional knee scores between suprapatellar nailing and the traditional infrapatellar approach. While much has been written about the incidence of anterior knee pain through a patellar splitting or parapatellar approach, the clinical effects of knee pain after suprapatellar nails have yet to be addressed in the literature. Our data show no difference in the Oxford Knee Score between the two groups. Although the suprapatellar approach is intra-articular, approach-specific instrumentation may protect the trochlea and patellar cartilage.

Even though our data did not show a difference in operative time between the two groups, suprapatellar nails required significantly less fluoroscopy time than infrapatellar nails (80.8 seconds versus 122.1 seconds, $p = 0.003$). Positioning the knee in the semi-extended position allows easier access for fluoroscopy and less radiation exposure for the patient.

Table 1. Demographic data on patients who underwent tibial intramedullary fixation via a suprapatellar and traditional infrapatellar approach.

Patient Data	Infrapatellar (n=24)	Suprapatellar (n=21)	P value
Gender (%)			
Male	11 (46)	15 (71)	0.082
Female	13 (54)	6 (29)	
Age (Years)	37.6	38.5	0.839
Follow up (Months)	25.2	8.0	<0.001
BMI	26.4	26.5	0.975
Mechanism of Injury (%)			
Fall	14 (58)	6 (29)	0.150
MVC	5 (21)	9 (43)	
Sports	4 (17)	3 (14)	
GSW	1 (4)	3 (14)	

Table 2. Oxford knee score, reduction, operative time, and intraoperative fluoroscopy of patients.

Results (Standard Deviation)	Infrapatellar (n=24)	Suprapatellar (n=21)	P value
Oxford Knee Score	40.1 (8.8)	36.2 (11.9)	0.221
Operative Time (minutes)	145 (43)	147 (41)	0.884
Fluoroscopy time (seconds)	122.1 (41.6)	80.8 (36.7)	0.003
Coronal plane reduction (degrees)	3.17 (1.99)	2.52 (1.94)	0.280
Sagittal plane reduction (degrees)	4.58 (2.86)	2.90 (2.57)	0.044
Rotation (cortical widths)	0.25 (0.32)	0.31 (0.42)	0.599

While acknowledging the retrospective nature of this study, it does have several strengths. Our sample size met the pre-study power analysis to determine a clinically important difference in the Oxford Knee Score. The investigator administering the telephone survey was blinded to the approach. It is also the first clinical study comparing outcomes of suprapatellar and infrapatellar nails. Rate of follow-up, however, was a weakness of this study. We lost 37 patients (45%) to follow-up, presumably as a result of the telephone numbers noted in the hospital records having changed since surgery.

Our retrospective cohort identified no difference in knee pain between a suprapatellar approach and traditional infrapatellar nailing for diaphyseal tibia fractures. Suprapatellar nails require less fluoroscopy time and may show improved radiographic reduction in the sagittal plane. While further study is needed, the suprapatellar entry portal appears to be a safe alternative for tibial nailing when using the appropriate instrumentation.

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Anterior Hip Dislocation Five Months After Hip Arthroscopy: A Case Report and Review of the Literature

[1]Daniel C. Austin, BA
[2]John G. Horneff III, MD
[2]John D. Kelly IV, MD

[1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

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

Introduction

Hip arthroscopy has increased in frequency over 300% between 2004 and 2009, as it has become an important technique used most often to treat diagnoses of labral tears or femoroacetabular impingement.[1-2] The procedure is most commonly performed in young adults aged 20-39 years and has been found to be an effective intervention for getting athletes back to their sport.[1,3] An important consideration in young active patients is the complication rate associated with a procedure. Notably, hip arthroscopy has been observed to be a low-risk intervention.[4] The hip arthroscopy complication rate has been reported to be 7.5% for minor complications, such as iatrogenic chondrolabral injury or transient neuropraxia, and 0.58% for major events, including post-operative dislocation, pulmonary embolus, and death.[2]

Dislocation has proven to be an exceedingly rare complication of hip arthroscopy with a systematic analysis documenting only four dislocation events out of 6,134 cases.[2] Although rare, these dislocation events, along with cadaveric studies, have highlighted the role of the iliofemoral ligament in anterior subluxation and overall hip stability.[5-6] On the whole, these observations have encouraged arthroscopists to minimize capsulotomies and repair the ligaments upon completion.[5,7-9] The previous reports of post-arthroscopy hip dislocation have occurred in the postoperative time period ranging from the recovery room to up to two months postoperatively after falling.[10-11] We report on a case of atraumatic dislocation that occurred in a high-level collegiate track and field athlete while jumping five months after hip arthroscopy. To our knowledge, this case represents the most remote dislocation event ever reported following arthroscopy and describes a novel mechanism of post-operative subluxation in athletes.

Corresponding author:
John G. Horneff III, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
John.Horneff@uphs.upenn.edu

Case Report

A 19 year-old collegiate high-jumper presented to our Sports Medicine Clinic with chronic right hip and groin pain along with a clicking and catching sensation associated with hip movement. Her exam was notable for a positive impingement sign and decreased right hip internal rotation. An MRI of her right hip showed labral fraying, a Cam lesion, and a questionable Pincer anomaly. Given the patient's symptoms and findings on imaging, hip arthroscopy was recommended.

The patient was taken to the operating room, and the hip joint was first accessed through a standard anterolateral portal. A routine anterior portal was then created, and a modest "T" capsulotomy was performed along the femoral neck to gain access to the femoral head. A "wave sign" was visible within the acetabulum, confirming the diagnosis of Cam impingement. No other impingement lesions within the acetabulum or labrum were visualized except slight labral fraying, which was addressed with debridement before traction was released. Next, a conservative femoral neck resection was performed based upon the limited amount of impingement visualized. Finally, the psoas tendon was partially released because of the patient's history of anterior "snapping." The capsule was not closed. All instrumentation was then removed, and the portals were closed with sutures in standard fashion.

The patient recovered well in the immediate postoperative period and was cleared to return to full activity at the twelve week postoperative visit. She returned to competition as a high and long jumper without incident. At 21 weeks after surgery, the patient returned to the office with a complaint of sudden anterior groin pain when jumping. On exam she had full range of motion and no sign of impingement. She was diagnosed with a hip flexor strain and urged to warm up thoroughly before activities. The following week, 22 weeks post-operatively, the patient felt a sudden excruciating pain when jumping. She was taken to the emergency room where she was found to have an anterior hip dislocation (Figure 1), and the joint was successfully closed reduced.

After this incident, the patient underwent an MRI arthrogram of her right hip. No capsular tear was visible upon dye injection, and the

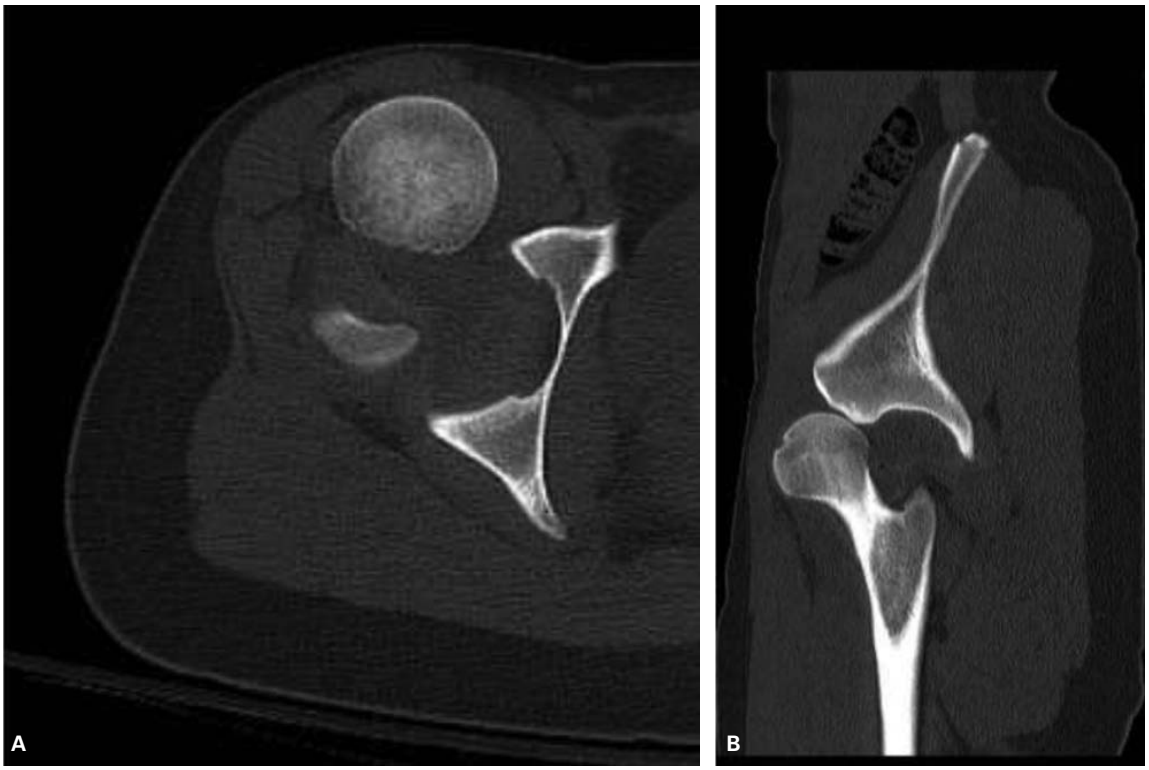

Figure 1. Axial (A) and sagittal (B) CT cuts of anterior dislocation.

decision was made to treat the patient conservatively with no additional surgery at this time. She "red-shirted" her track and field season and focused on rehabilitating her hip. The patient was last seen approximately ten months post-operatively, four months after her dislocation, and was doing well without pain or activity limitations.

Prior Reports and Relevant Literature

Though a rare complication of hip arthroscopy, postoperative dislocation is an important consideration for orthopaedic surgeons. Previous case reports regarding dislocation after arthroscopy highlighted dislocations that occurred earlier in the recovery period compared to our patient. Such reports have noted dislocations as soon as in the recovery room up to two months postoperatively after minor trauma.[10-13] Multiple causes of instability have been implicated, including excessive resection of the anterior acetabular rim, over-resection of the labrum in a patient with hip dysplasia, capsulotomy without repair in a ligamentously-lax patient, or a multifactorial etiology.[10-13] Ranawat *et al* reported a case most closely resembling our own as a woman who underwent hip arthroscopy for right hip pain and "popping."[11] The patient was noted to have a labral tear with a Cam lesion and subsequently underwent labral repair, Cam lesion resection, and capsular plication that included the iliofemoral ligament. Two months after her operation, the patient sustained a fall down a short flight of stairs, resulting in an anterior hip dislocation that was closed reduced in the emergency room and treated with ten weeks of physical therapy and crutch use. She found no relief and eventually underwent a repeat arthroscopy, which noted a tear in the anterior capsule and iliofemoral ligament that had previously been repaired. The authors discussed the importance of the iliofemoral ligament and how violation of the structure in anterior capsulectomy, although commonly performed by arthroscopists for exposure, is detrimental to hip stability and should be repaired and protected in the postoperative rehabilitation protocol.[11] The crucial role of the iliofemoral ligament in preventing anterior translation, and in hip stability overall, has been shown in anatomic cadaver studies.[5-6] Many other recent studies have highlighted the importance of capsular repair and urge all arthroscopists to consider a repair at the end of the case.[5,7-9]

Discussion

The important role of both dynamic and static stabilizers of the hip in post-arthroscopy patients has been described thoroughly in the literature.[10,13] While the hip capsule of the patient in this case appears to have healed completely, as shown by the lack dye extravasation in her MR arthrogram, a sutured closure of the capsule may have provided a more stable, less lax construct better able to prevent translation of the femoral head. Capsule management is a critical component in hip arthroscopy as the surgeon needs to provide adequate visualization to ensure an adequate resection while minimizing the capsulotomy to maintain stability.[14] This case strongly supports the recent trend in the literature to perform capsular repair, notably that of the iliofemoral ligament.

However, we believe the identification of a partial psoas tendon release as a cause of instability has not yet been investigated. The iliopsoas tendon is the common tendon connecting the psoas and iliacus muscles arising from their respective origins of the transverse processes of T12 to L5 and

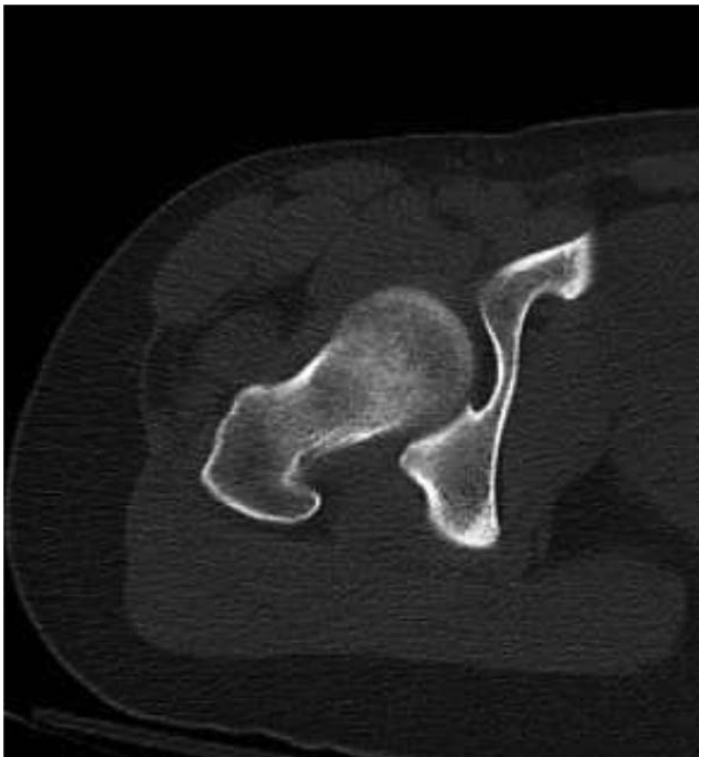

Figure 2. Axial CT cut of reduced hip displaying anteversion.

iliac fossa to the lesser trochanter.[9] As the hip is extended, the iliopsoas tendon moves medially and lies in close proximity to the anterior joint capsule.[14] Although it is an active hip flexor, the iliopsoas tendon produces its greatest passive tension across the joint when the hip is in extension.[15] We believe that the partial psoas release in this case, in the setting of an anteverted acetabulum, could have been another cause of hip joint instability. As can be seen in the post-subluxation imaging (Figure 2), the patient has an anteverted femoral neck measuring approximately 30 degrees. We postulate that psoas release should be avoided in patients with significant anteversion, as it may be an under-appreciated dynamic stabilizer of the hip when this anatomy is present.

Conclusion

The atraumatic dislocation experienced by our patient five months post-operatively, is over twice as long as any previously reported dislocation and raises awareness about the long-term effects that hip arthroscopy can have on hip joint stability. Furthermore, this case encourages surgeons to be particularly cautious with allowing jumping athletes to return to sport. The biomechanics of successful long jumpers, triple jumpers, and high jumpers all require the athlete to plant their foot and extend their hip significantly at takeoff. This mechanism likely played a critical role in the anterior dislocation seen in our patient. The fact that the patient experienced pain with jumping in the week prior to the dislocation also makes the point that groin pain with jumping after hip arthroscopy could be indicative of capsular stretching or damage and should alert the patient and treating physician that healing has not fully occurred. We believe that the capsulotomy without repair, along with femoral anteversion and a partial psoas release, played a major role, creating enough hip instability that the patient was able to dislocate atraumatically while at track practice. The experience with this patient has encouraged us to agree with current literature guiding arthroscopists to minimize capsulotomies, repair the capsule before closure, and encourage a gradual rehabilitation protocol to full activity.

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U·P·O·J

Intraoperative Use of Rib-to-Pelvis Traction to Correct Pelvic Obliquity in the Neuromuscular Spine

[1]Martin J. Morrison III, MD
[2]John M. Flynn, MD

[1]Department of Orthopaedic Surgery, Loma Linda University School of Medicine, Loma Linda, CA

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

Introduction

The goal of posterior spinal fusion in neuromuscular scoliosis is to obtain a balanced trunk as well as accommodative, pressure-free seating on a level pelvis. Development of pelvic obliquity or involvement of the pelvis in the scoliotic curve can cause difficulties with seating, costopelvic impingement, and worsening pulmonary function, ultimately leading to difficulty with caregiving, decubitus ulcers, or other comorbidities. Over time, flexible deformities become more rigid, making correction of the pelvic obliquity more difficult. Correcting pelvic obliquity can be challenging in this patient population due to poor bone quality.[1] Unit rod instrumentation has traditionally controlled pelvic obliquity well.[2] While third-generation instrumentation is technically difficult with extension to the pelvis, previous results were less than encouraging.[3] More recently, use of third-generation instrumentation has shown improved results.[4] Anteroposterior surgery has recently fallen out of favor due to patient comorbidities and comparable success and decreased complications of posterior surgery.[5] Ideally, indirect correction performed before instrumentation can decrease risk of failure at either the bone-implant interface or failure of the implant itself. Many types of traction techniques have previously been implemented in order to achieve this correction prior to instrumentation. Methods have included preoperative halo-gravity traction,[6,7] intraoperative halo-femoral traction,[8-10] halo-pelvic traction,[11-13] and temporary rods from vertebral body to vertebral body.[14,15]

Methods

We present a case of a 13 year-old female with GMFCS Level V spastic quadriplegic cerebral palsy. She had been followed in the spine clinic and was observed to have an 83° left lumbar scoliosis with severe apical rotation and significant pelvic obliquity (Figure 1). Preoperative bending films over a bolster showed reasonable flexibility in the lumbar curve but persistent pelvic obliquity. At our institution, we have implemented sacral alar iliac (SAI) screws as the preferred pelvic instrumentation technique for fusions to the pelvis. As previously described, they are in line with the spinal construct, allowing easy connection to the segmental instrumentation. They are usually long and larger in diameter, providing stronger fixation. They are recessed under the posterior superior iliac spine so as to not be prominent. They also have a decreased infection risk, and they utilize a solid column of bone for stout fixation.[16,17] Also, we use intraoperative navigation with the O-Arm® Surgical Imaging with StealthStation® Navigation (Medtronic Navigation, Inc., Louisville, CO).

During preoperative planning, we considered cantilever reduction using unit rod fixation versus screw and rod construction, which often uses derotational maneuvers to correct coronal and sagittal imbalance. The senior author's results after transition to screw and rod constructs left us searching for an improved method for correcting pelvic obliquity that was previously handled well by the unit rod. Our intraoperative setup was intended to optimize

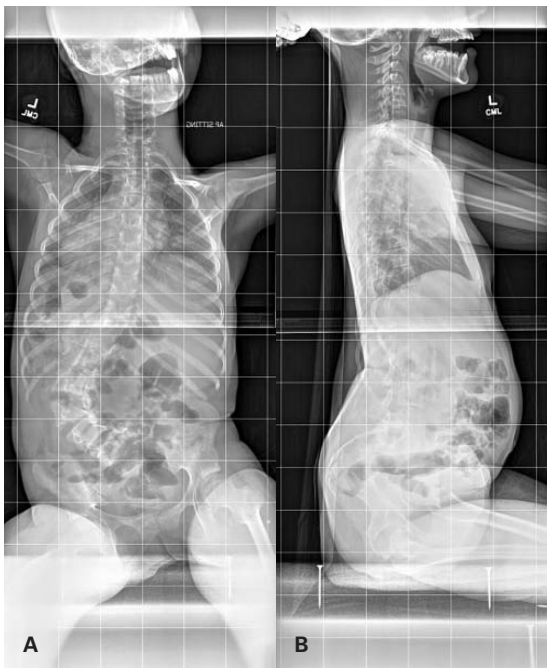

Figure 1. Preoperative posterior-anterior (A) and lateral (B) radiographs.

Corresponding author:
Martin J. Morrison III, MD
Department of Orthopaedic Surgery
Loma Linda University School of Medicine
11406 Loma Linda Drive, Suite 218
Loma Linda, CA 92354
martymorrisoniii@yahoo.com

safe navigation of screw placement while allowing for the application of traction to correct the patient's pelvic obliquity. The patient was positioned prone on the Mizuhosi Spinal Surgery Top (Mizuho OSI, Union City, CA) table in the knee-chest position with both knees in 90° of flexion using the assistance of a leg sling. A standard subperiosteal posterior approach was performed with confirmatory imaging to assess the correct levels for fusion. O-Arm® navigation was used, and three "spins" were obtained off of two arrays, according to our standard protocol.

After acquiring navigational data, all pedicle screws and both SAI screws were safely placed. At this point, a temporary distraction rod was placed on the right (concave) side of the lumbar deformity, corresponding to the high side of the pelvic obliquity. It was constructed from the seventh rib to the pelvis using the vertical expandable prosthetic titanium rib (VEPTR®, DePuy Synthes Spine, West Chester, PA) system components: rib hook, 90° pelvic S-hook, S-hook rod (with the S-hook removed and the rod cut) and two parallel connectors (Figure 2). Minimal lateral dissection was needed to place the construct consistent with placement of a rib-to-pelvis VEPTR®. The seventh rib was exposed through a small incision in the fascia, and the rib hook was placed. The right posterior pelvic brim was exposed through a separate fascial incision, and the S-hook was seated on the pelvis. A subfascial tunnel was created to connect the rib hook to the pelvic S-hook using two parallel connectors and two rod segments (Figure 3). A series of stepwise corrections were performed using a distractor to reduce the pelvic obliquity under fluoroscopic imaging and intraoperative neuromonitoring. A half-ring was used to obtain additional distraction. The construct was locked in position in order to take advantage of the viscoelastic properties of the spine. After safe correction, attention was turned back to the spine for soft tissue releases and rod contouring. With the pelvic obliquity corrected, cantilever rod placement was performed first on the left, then on the right side. After setting the rods, traction was released from the temporary distraction rod. No collapse was noted as the rods maintained the correction. The integrity of the bone-screw interface was examined at each level and noted to be intact.

Results

After placement of both rods and completion of the correction, the temporary rib-to-pelvis distraction was released. All bone-screw interfaces were inspected and deemed to be intact. Fluoroscopic imaging confirmed maintenance of screw positions and a level pelvis. All neuromonitoring signals, including somatosensory evoked potentials (SSEP) and motor evoked potentials (MEP), were unchanged from baseline. Postoperative radiographs (Figure 4) revealed significant improvement of the scoliosis, complete correction of pelvic obliquity, no evidence of pneumothorax or rib fractures, and no changes at the site of the pelvic S-hook.

Discussion

Difficult spinal deformities challenge us to utilize a host of reduction and instrumentation techniques. In particular, patients with neuromuscular scoliosis are often less medically optimized, making staged procedures more difficult.[5] The ultimate goal in this patient population is to safely perform an instrumented fusion with a balanced trunk and pelvis with minimal morbidity along with long-term goals of improved quality of life for the patient, family members, and other caretakers. Residual deformity and imbalance compromise these goals.

While previous use of the unit rod allowed for increased correction of pelvic obliquity due to the nature of its construct, there are several drawbacks. It is a technically demanding procedure, it has a fixed angle to the pelvis, and it necessitates the use of segmental sublaminar wires that require entering the canal at multiple levels. Mechanical failure can also occur either intraoperatively, due to cut out from poor bone quality, or postoperatively, due to loosening. Transition to segmental rod use has evolved from hooks and wires to hybrid constructs that use hooks, wires, and pedicle screws, and finally to predominantly all-screw constructs. The benefits of pedicle screws have been well described, including 3-column fixation and improved axial correction.[18-20] In cases when pelvic fixation is required, options include iliac screws, sacral (S1) screw fixation, or both. Recently, popularization of SAI screw fixation has led to novel pelvic fixation.

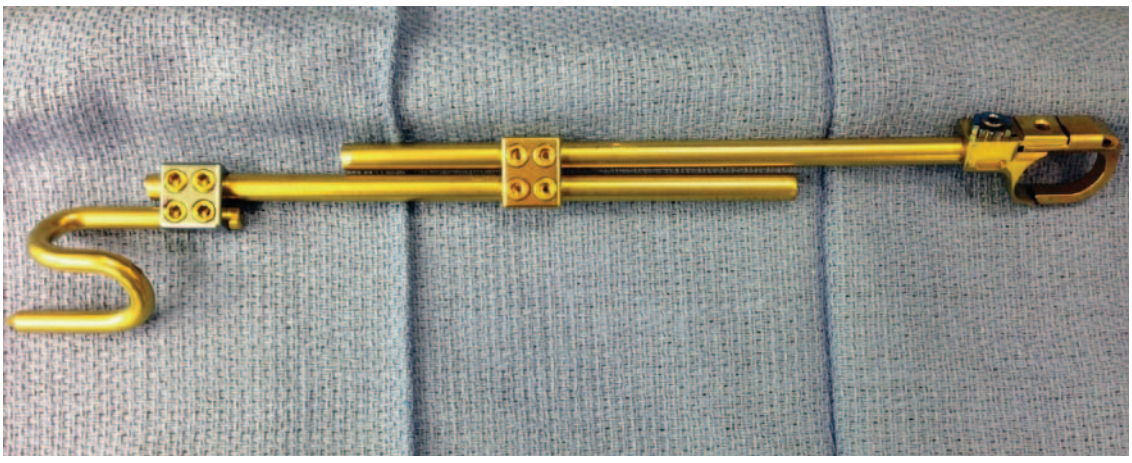

Figure 2. Construct used for the temporary intraoperative rib-to-pelvis traction.

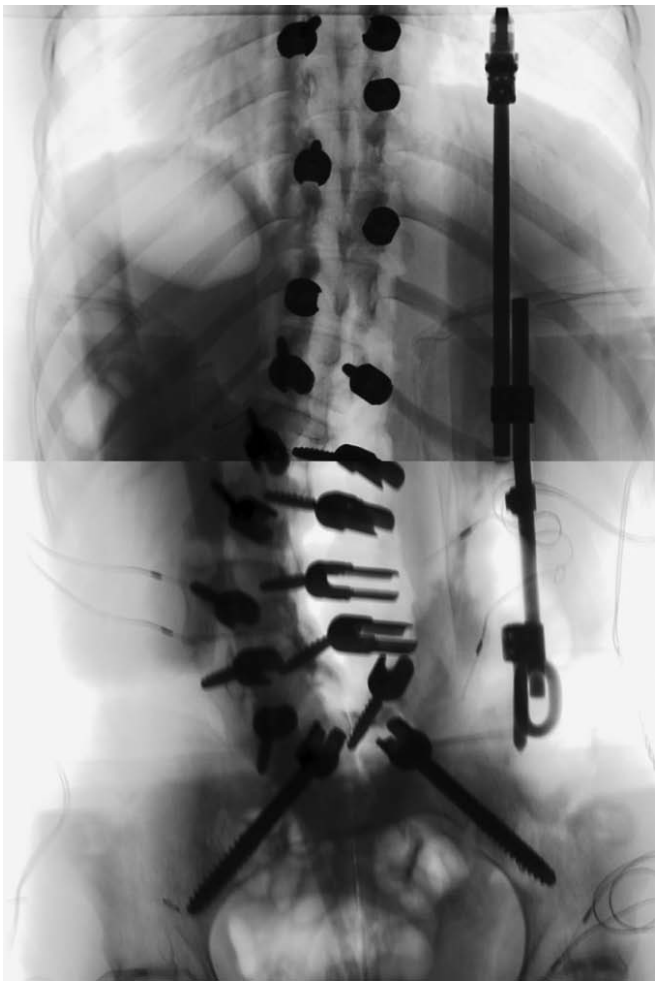

Figure 3. Intraoperative posterior-anterior (PA) radiograph with rib-to-pelvis distraction in place with level pelvis

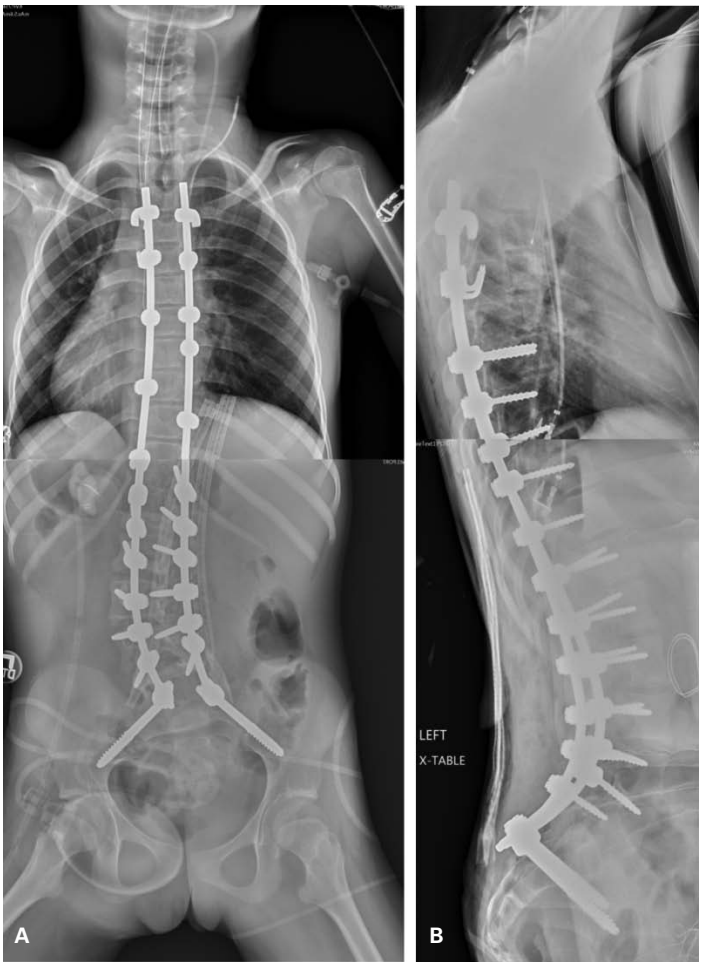

Figure 4. Postoperative posterior-anterior (A) and lateral (B).

In our case, we were able to rely on the VEPTR® to correct our pelvic obliquity safely in a single setting without having to rely on the screws when the potential for bone-screw interface failure is significant in patients with poor bone quality. Also, having our temporary distraction away from the midline afforded us multiple benefits: 1) the moment arm of correction was more powerful than having to correct the pelvic obliquity near the midline, 2) we were able to instrument the entire spine while the distraction rod continued to work as it was not obstructing our operative field, 3) the temporary distraction was entirely within the operative field and controlled by the surgeon, 4) none of our final implants utilized an area occupied by the temporary rib-to-pelvis rod so as not to compromise any fixation points, and 5) the temporary distraction could also take advantage of the viscoelastic properties of the spine and be left in, if needed, for a staged procedure.

Conclusion

Intraoperative rib-to-pelvis temporary distraction can be safely performed to correct pelvic obliquity in the neuromuscular spine in a single setting and should be considered in the challenging neuromuscular patient.

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U·P·O·J

Arthroscopic-Assisted Reduction and Buttress Fixation of Tibial Plateau Fracture Using a Bioabsorbable Interference Screw

[1]Pramod B. Voleti, MD
[2]Surena Namdari, MD, MSc
[1]John D. Kelly IV, MD

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

[2]Department of Orthopaedic Surgery, Washington University, St. Louis, MO

Introduction

Arthroscopic-assisted fixation of tibial plateau fractures is not a novel concept. Studies have demonstrated equivalent and sometimes superior outcomes compared to open techniques in appropriately selected patients. Most arthroscopic-assisted techniques have relied on percutaneous screw or open plate and screw placement to achieve fixation.[1-3] For isolated depression-type tibial plateau fractures, we describe a technique that eliminates the need for percutaneous screw placement using an image intensifier and relies on arthroscopic visualization of reduction and a bioabsorbable implant to achieve buttress fixation of the fracture fragment.

Technique

The technique of arthroscopic-assisted fixation of pure depression-type tibial plateau fractures (Figure 1) has been previously described. Generally, these techniques require percutaneous or even open placement of screws to achieve fixation. This modified technique is an option for fracture patterns that are contained and amenable to less extensive soft tissue dissection.

A high contralateral portal is created, an arthroscope is positioned within the joint, and the plateau fracture is identified. Gravity inflow or a fluid pump on a low setting is utilized. This is preferred to minimize the potential problems associated with fluid extravasation and elevated compartment pressures. The lipohemarthrosis is drained, and any osteochondral fragments are removed. An anterior cruciate ligament (ACL) guide is used to drill a tunnel to the subchondral bone opposite the fracture fragment. A reamer is placed over the guide wire and the tibial cortex is circumferentially reamed. A tamp is then used to raise the depressed fragment. If the depression is posterior, the posterior cortex is 'hugged' with the elevator to ensure adequate reduction. Additional bone graft or

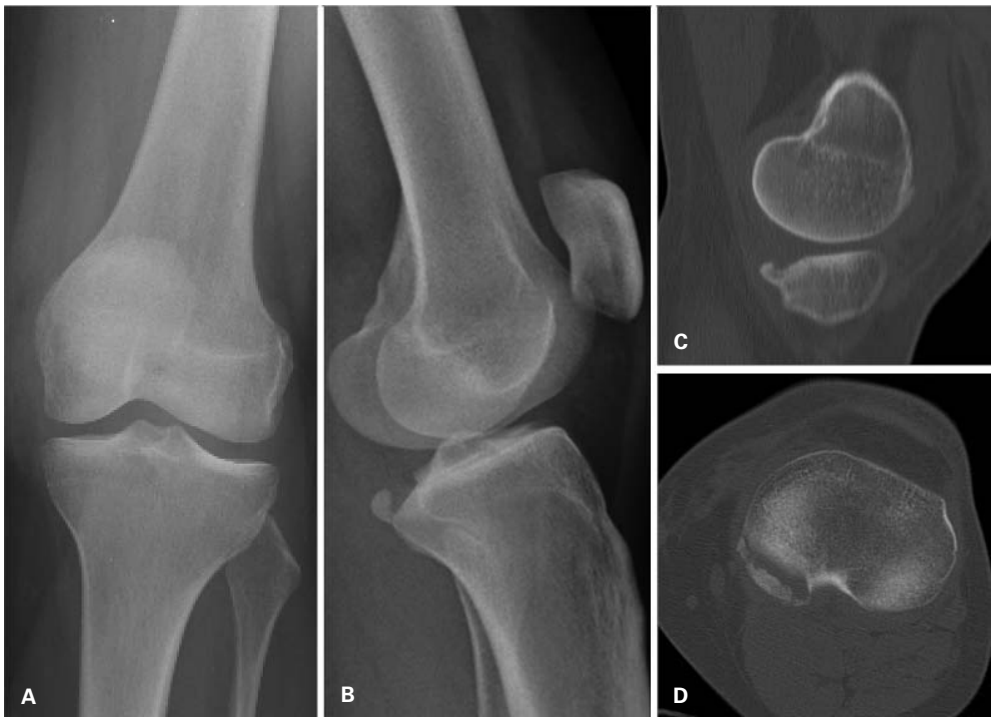

Figure 1. Anteroposterior (A) and lateral (B) plain radiographs and sagittal (C) and axial (D) computed tomography scan cuts demonstrating a pure depression-type posterior tibial plateau fracture in a 33-year-old female.

Corresponding author:
Pramod B. Voleti, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Building
Philadelphia, PA 19104, USA
Pramod.Voleti@uphs.upenn.edu

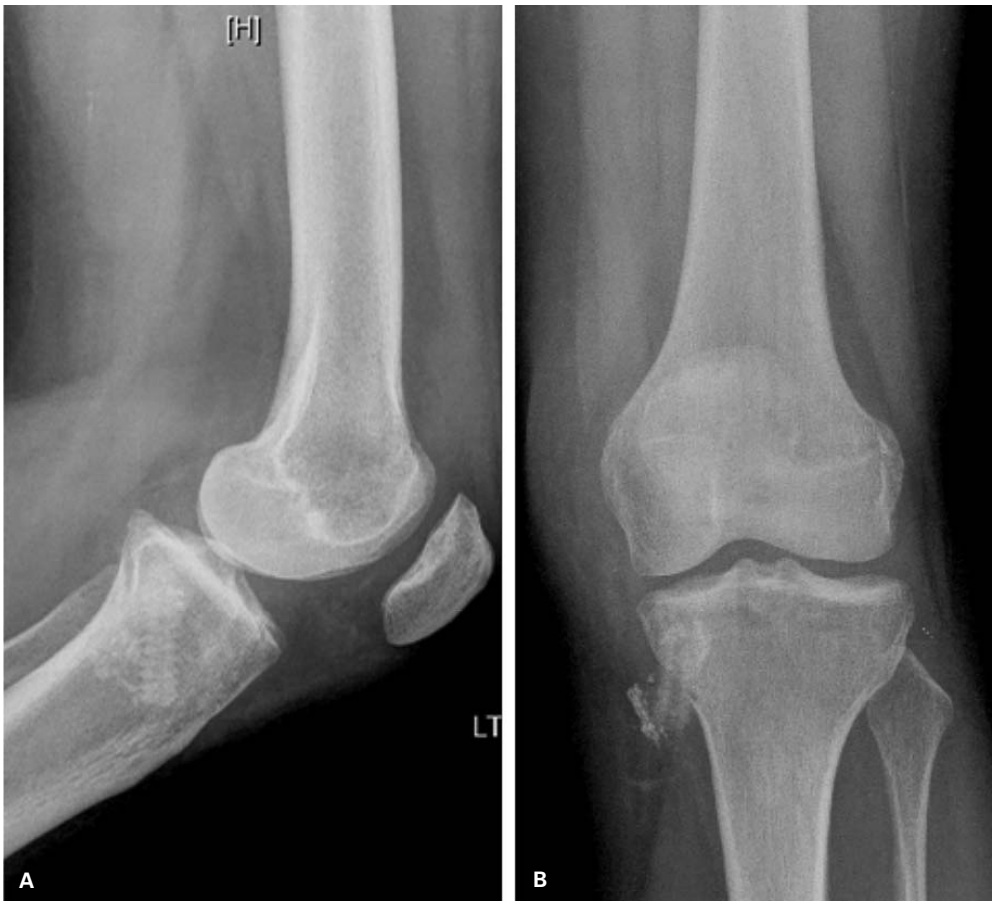

Figure 2. Anteroposterior (A) and lateral (B) plain radiographs of the knee performed after arthroscopic-assisted reduction and buttress fixation using a bioabsorbable interference screw.

filler may be placed through the tunnel if necessary. The reduction is visualized and confirmed using the arthroscope. A bioabsorbable screw of appropriate length and diameter is advanced through the tibial tunnel (Figure 2). Reduction and fixation are subsequently confirmed with arthroscopic visualization.

We generally begin continuous passive motion and early range of motion immediately postoperatively. Weight-bearing is delayed for approximately six weeks or until radiographic evidence of healing is demonstrated.

Discussion

Pure depression fractures of the tibial plateau present an opportunity for surgical treatment that restores the articular surface without extensive soft-tissue dissection. Multiple authors have described arthroscopic management of tibial plateau fractures using percutaneous, cannulated interference screws under fluoroscopic guidance with good outcomes.[4-6] Lubowitz et al. have previously described a similar technique for arthroscopic reduction and interference screw fixation of compression fractures of the tibial plateau.[7]

By utilizing arthroscopic guidance, fluoroscopy is eliminated and definitive reduction is visualized. Additionally, commonly used instruments in ACL reconstruction allow for a technique that should be readily executed by many orthopaedic surgeons. A bioabsorbable implant eliminates concern for future hardware-related complications and provides a more biologically inert mode of fixation. Bioabsorbable screws have been used for treatment of physeal and epiphyseal fractures of the distal tibia in children and shown to have no increase in operative time, nonunion rate, number of unplanned secondary surgeries, or other complications compared with metallic screws.[8] Authors have previously demonstrated no significant difference in the results of knee joint stability or knee joint functional outcome between bioabsorbable and metallic interference screws after ACL reconstruction,[9, 10] and we would expect both implants to fare well with this technique. Importantly, there is a concern that once the bioabsorbable screw undergoes resorption, the area of reactive tissue left by the screw in the tibial bone tunnel may lead to a stress riser and vulnerability of the tibial plateau.[11] Patient-selection remains the most important variable in the success of this surgical technique. Bicondylar fractures, uncontained fractures, and fractures with fragments that cannot be adequately buttressed by a single bioabsorbable screw are more appropriate for open or traditional arthroscopic-assisted techniques. Depressed articular segments surrounded by intact cortices are ideal for this technique.

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Balanced Cranial Suspension for Intraoperative Correction of Cervical Kyphosis

[1]Michael T. Talerico, MD
[2]Venus Vakhshori, BS, BA
[1]Andrew H. Milby, MD
[1]Adam T. Griska, MD
[1]Harvey E. Smith, MD
[1]Vincent M. Arlet, MD

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

[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Introduction

Cervical spinal deformity may result in significant neurologic and physical impairment, either in the form of pain, myelopathic symptoms, or chin-on-chest deformity. The relative intolerance of the cervical spinal cord to manipulation renders any correction of cervical spinal alignment inherently dangerous. As such, any reduction or correction maneuvers must be performed in as gradual and controlled a manner as is possible. Classically, posterior correction of cervical spinal deformity relies upon the use of osteotomies and instrumentation to maintain correction. It is often necessary to have a member of the surgical team manipulate the Mayfield headrest in order to achieve the desired correction once osteotomies have been performed. We present a technique that may be of use in the correction of cervical spinal deformity to decrease the risk of intraoperative neurologic injury. Herein we describe the application and potential benefits of balanced cranial suspension via halo traction in cases of cervical kyphotic deformity correction.

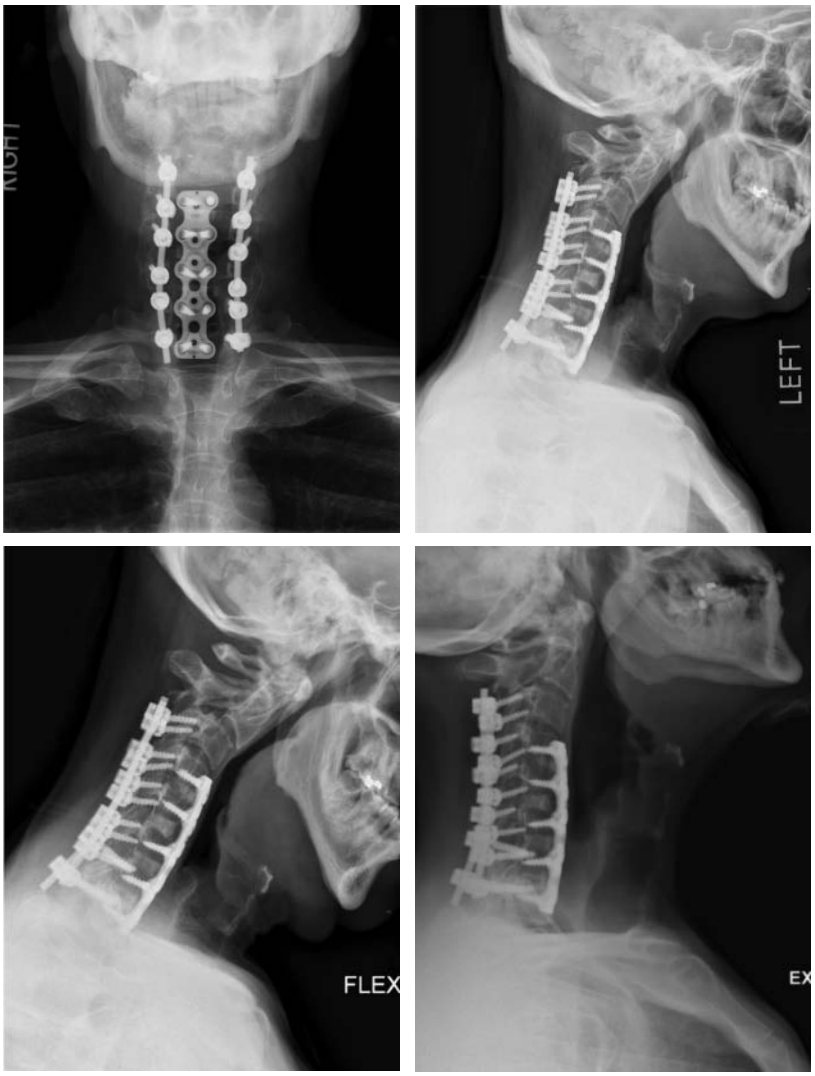

Figure 1. Antero-posterior and lateral plain radiographs in neutral, flexion, and extension of the cervical spine of a 41 year-old male who presented with severe axial neck pain and the inability to hold his head upright. The patient had previously undergone anterior-posterior cervical fusion for cervical spondylotic myelopathy. Prior surgery involved extensive laminectomy cranially to C3 with disruption of the posterior ligaments at C2-3. Junctional kyphosis with anterolisthesis of C2 on C3 is present cranial to the prior fusion construct.

Corresponding author:
Vincent M. Arlet, MD
Director, Penn Orthopaedic Spine Center
Professor of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
vincent.arlet@uphs.upenn.edu

Indications

Cervical kyphosis may be the result of a number of etiologic factors. Fixed chin-on-chest deformities may be seen with progressive ankylosing spondylitis, resulting in an inability to maintain horizontal gaze and significant impairment of activities of daily living.[1,2] Relatively inflexible kyphosis may also be seen with advanced spondylosis, ossification of the posterior longitudinal ligament, or disseminated idiopathic skeletal hyperostosis.[3] Flexible deformity is more likely in the setting of systemic myopathy, either primary or secondary to other systemic processes or medication toxicities, and may be associated with position-sensitive neurologic symptoms.[4] Another important cause of progressive, flexible deformity is injury to the posterior ligamentous complex, either from prior trauma, or iatrogenic following cervical laminectomy without stabilization.[5-9] While progressive kyphosis may eventually result in myelopathy due to anterior cord compression, patients may also complain of neck pain, the inability to hold their head up, dysphagia, arm pain, or low back pain secondary to compensatory lumbar hyperlordosis. All of these factors must be considered when planning a potential surgical intervention for correction of cervical sagittal alignment.

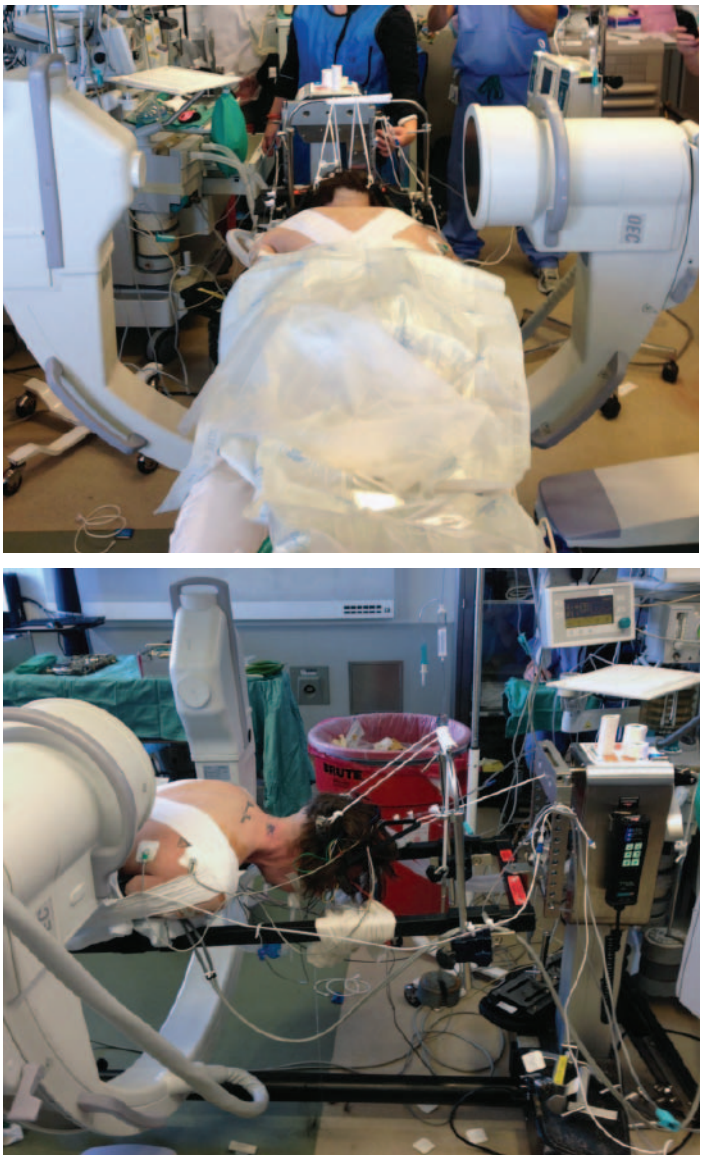

Figure 2. Axial and lateral photographs demonstrating patient positioning after induction of general anesthesia and halo placement with balanced cranial suspension in place. 15 lbs. of longitudinal traction and 10 lbs. of 45° suspensory traction are present.

Intraoperative stabilization of the head and neck must account for factors specific to the patient's pathoanatomy and accommodate for the potential need to reposition during the procedure. Stabilization for posterior cervical spinal procedures is typically achieved via use of a Mayfield headrest. This affords excellent stability of the head and neck during surgery, though intraoperative adjustment often requires that a member of the surgical team adjust the clamp in a non-sterile fashion. The Mayfield headrest also does not accommodate changing patient position due to Trendelenburg or reverse-Trendelenburg adjustments of the operating room table, or even the execution of posterior osteotomies, and may result in inadvertent traction if such adjustments are not properly anticipated. Traction via Gardner-Wells tongs allows for a more consistent level of longitudinal traction regardless of positioning, though at the expense of some rotational and translational stability. In addition, the level of longitudinal traction alone necessary to maintain head position may itself be dangerous for the spinal cord. Following completion of an osteotomy, longitudinal traction alone may induce translation of the cervical spine, and a single traction vector offers somewhat less flexibility with regard to purely translational intraoperative adjustments, if needed. Placement of a circumferential halo frame allows for the attachment of weights at multiple points, resulting in multiple traction and/or suspension vectors. Intraoperative alteration of head position is facilitated by direct manipulation of the head through halo and/or weight adjustments. In addition, gradual and sequential adjustments of the weights are less likely to require a member of the surgical team or to result in sudden position changes that could result in neurologic injury.

Surgical Technique

General anesthesia is induced by the anesthesia team with consideration given to the need for fiberoptic intubation and intraoperative neuromonitoring, if available. After induction, neuromonitoring leads are placed and baseline signals established prior to positioning. The halo ring is placed in the standard fashion. A minimum of six pins are recommended to achieve sufficient stability for traction placement. Ropes are attached to fixation points along the halo in order to produce the desired traction and suspension vectors. The patient is then positioned in accordance with the planned surgical approach, with special attention paid to perfusion pressure and the stability of neuromonitoring signals during and after positioning. It is useful to place a stockinette or other elastic material across the table below the level of the head to serve as backup restraint in the event of halo or traction failure. For flexible deformities, traction weights may gradually be added at the outset to produce the desired correction. This correction

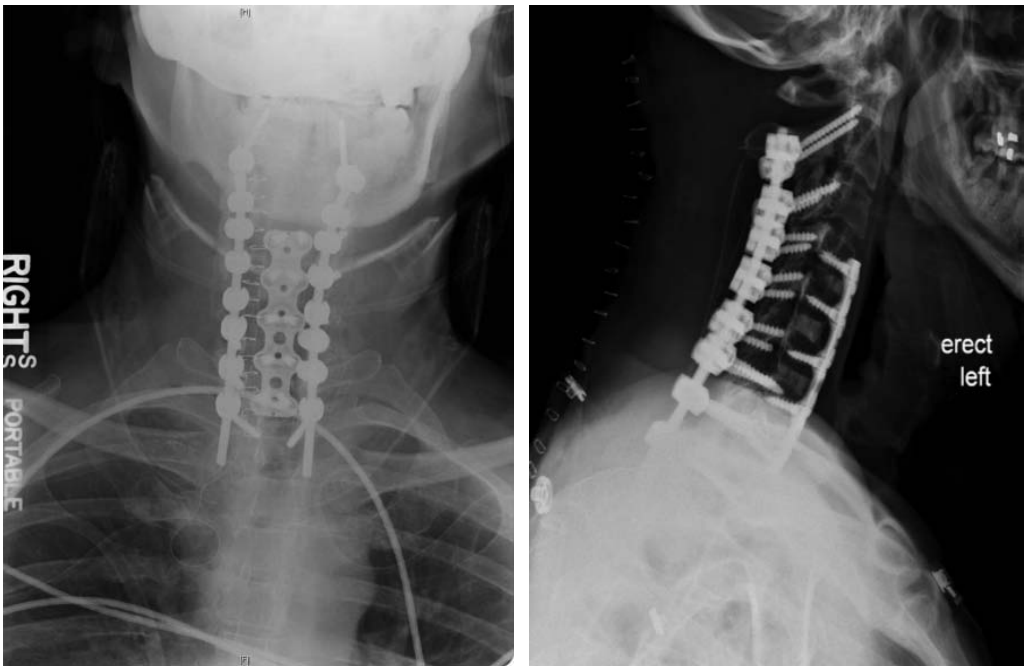

Figure 3. Postoperative antero-posterior and lateral plain radiographs following revision posterior decompression with deformity correction via posterior osteotomies at C2-3 and C3-4 and extension of fusion construct with pedicle screw placement at C2, C7-T2 demonstrating restoration of cervical sagittal alignment.

may be verified with C-arm fluoroscopy prior to incision. Fixed deformities or revision surgery may require osteotomy and/or instrumentation removal prior to achievement of correction. In such cases, the traction apparatus may still be used to maintain head position until flexibility is achieved, at which time it functions in a manner similar to that of a counterweight in a sash window allowing for controlled and gentle deformity correction. Prior to performing any reduction maneuver, it is important to perform a thorough decompression of any structures that have the potential to cause impingement once the desired alignment has been achieved.

After deformity correction, the definitive instrumentation may be placed and the fusion bed prepared with the use of either allograft or autograft as indicated. The halo may be left in place until satisfactory alignment and instrumentation placement are radiographically confirmed. The halo is then removed, the pin sites are dressed in the standard fashion, and a cervical orthosis is applied as dictated by the extent of correction and quality of fixation.

Discussion

Halo traction has an established role in the gradual preoperative correction of flexible spinal deformities prior to and during definitive surgical correction and fusion.[10-13] It is of special importance in cases of poor bone quality or where limited fixation options prevent the use of intraoperative correction maneuvers typically possible with pedicle screw fixation. Halo traction alone has also been successfully employed as definitive treatment of certain flexible cervical spinal deformities, albeit in limited numbers.[14,15]

The use of intraoperative vectored (i.e. non-longitudinal) traction has been previously described by Koreckij *et al* for use in thoracolumbar deformity correction with special attention paid to the optimum traction angle to reduce facial contact pressures during prolonged prone procedures.[16] In their series of 10 patients undergoing adolescent idiopathic scoliosis correction, 15 lbs of traction at an elevation angle of 45° was found to minimize facial contact pressures. As in our reported case (Figures 1-3), halo placement facilitates the combination of multiple traction vectors, allowing for both deformity correction and mitigation of the risks associated with lengthy prone positioning.

Conclusion

Correction of cervical spinal deformity presents significant treatment challenges. Careful preoperative planning, including patient positioning, neuromonitoring, and thorough preemptive decompression may help reduce the inherent risk of neurologic complications with intraoperative reduction. In addition, halo placement may allow for the use of balanced cranial suspension to assist in deformity correction, reduce the risks of prone positioning, and allow for controlled intraoperative repositioning. Further prospective study is needed to refine the indications for its use relative to other established means of patient positioning for cervical spinal procedures.

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Idiopathic Avulsion Fractures of the Lesser Trochanter in Pediatric Patients

[1,2]Christine M. Goodbody, BA
[1]Wudbhav N. Sankar, MD

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

[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Introduction

Lesser trochanter avulsion fractures are a rare injury in childhood. This injury has not recently been well-described in the literature, and standard of care and expected outcomes remain unclear. In adult populations, this fracture has been considered pathognomonic for metastatic oncologic disease.[1,2] More recently, it has been associated more broadly with chronic disease states, particularly endocrine and renal disorders which may impact bone health.[3] In pediatric patients, on the other hand, it is our clinical impression that these fractures occur in otherwise healthy, athletic children and adolescents without underlying disease. The purpose of this study is to describe the current presentation of this injury and to report our experience with these avulsion fractures in a larger series with more current data.

Methods

After obtaining approval from our institutional review board, we queried our outpatient database for ICD-9 codes consistent with a lesser trochanter fracture (820.20). Patients aged 0-18 years who presented to our institution between 2003 and 2013 with an avulsion fracture of the lesser trochanter were included in the study. Patients with underlying syndromic pathology were included in the initial review, but their epidemiologic and follow-up information was not included in the aggregate data of otherwise healthy patients. Diagnosis was confirmed for each potential case by radiographic evidence of lesser trochanter avulsion fracture and by supporting clinical documentation. We then performed a retrospective review of medical records to determine patient characteristics, injury mechanism, treatment methods, time of protected weight-bearing on crutches, time until return to full activity, and clinical outcomes. Injury radiographs were used to determine initial fracture displacement on an anteroposterior (AP) radiograph of the pelvis or hip.

Results

Between 2003 and 2013, we identified 36 documented lesser trochanter avulsion fractures. Of these, 35 were idiopathic, occurring in otherwise healthy individuals. One injury occurred in a 12 year old male with spastic quadriplegic cerebral palsy (ambulatory in a walker). Of the 35 otherwise healthy patients with this injury, 33 were male and 2 were female. The average age at time of presentation was 13.7 years, with a range of 9-17 years. Of note, all subjects were 12-17 years of age, with the exception of three 9 year-olds. Two of the 9 year-olds were obese males, and one was a normal weight female.

All injuries occurred during athletic activity. Nine (25.7%) were by contact or fall, and 26 (74.3%) were by non-contact mechanisms. Of the 26 injured by non-contact mechanisms, 24 (92.3%) occurred during vigorous running, sprinting or skating, and 2 (7.7%) occurred during a pivoting move. Of the contact/fall injuries, 4 were from tackles or hits, and 5 were from falls. The most common sports involved were basketball (9 patients, 25.7%) and football (8 patients, 22.9%) followed by baseball/softball (5 patients, 14.3%), hockey (3 patients, 8.6%), and soccer (1 patient, 2.9%). Other activities associated with injury were running/sprinting and jumping. Ten patients were documented as feeling a pop at the time of injury. One patient had an associated injury, an avulsion fracture of the contralateral anterior inferior iliac spine. Twenty-six patients had initial injury films available. On AP pelvic radiographs, average fracture displacement for these patients was 10.9 mm (range of 4.0-24.7 mm).

All patients were treated nonoperatively, with protected weight bearing (non weight-bearing or toe-touch weight-bearing) and crutches for an average of 5.6 weeks (range: 1 week 4 days – 9 weeks 2 days). All patients were then referred to physical therapy and instructed to return to full weight bearing as tolerated. Release to full activity occurred after an average of 12.1 weeks (range: 5 weeks 3 days – 19 weeks).

Two patients returned, one at 8 months and the other at 1 year post-injury, for evaluation of ipsilateral hip pain, but in both cases the cause of symptoms was determined to be unrelated to the original fracture. No long-term sequelae of

Corresponding author:
Wudbhav N. Sankar, MD
Assistant Professor of Orthopaedic Surgery
The Children's Hospital of Philadelphia
Division of Orthopaedic Surgery
34th and Civic Center Boulevard
Philadelphia, PA 19104
sankarw@email.chop.edu

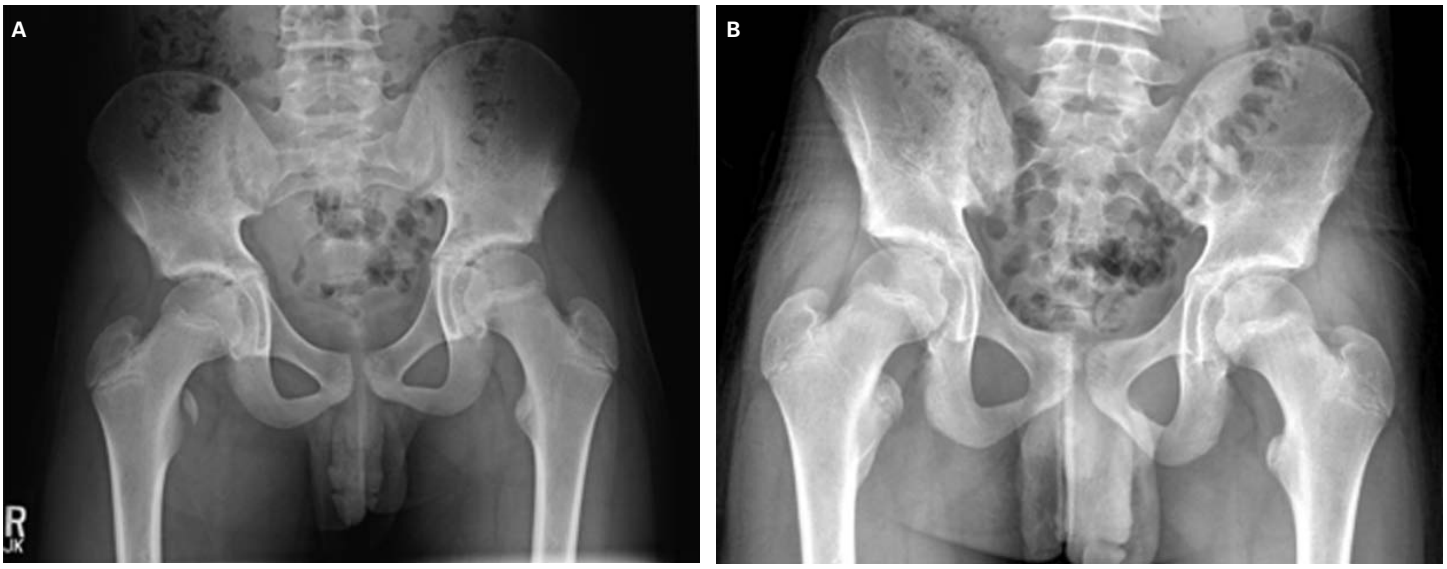

Figure 1. (A) AP pelvis Xray of a 12 year old male who presented with right groin pain of acute onset while sprinting during football. He was diagnosed with a right-sided avulsion fracture of the lesser trochanter. (B) He presented to clinic again 1 year later for an unrelated complaint, but was found to have excellent radiographic healing of his lesser trochanter avulsion fracture.

the avulsion fracture were documented in any patients (Figure 1A and 1B).

Discussion

To the best of our knowledge, the largest previous report of pediatric patients with lesser trochanter avulsion fractures is a 26 patient series published by Dimon in 1972.[5] In the four decades since this series was published, few updates have been reported, with most available data coming in the form of case reports and series of up to 3-4 patients.[4,6,7]

Similar to Dimon's study, we found that idiopathic avulsion fractures of the lesser trochanter occur in otherwise healthy adolescents, particularly males. This fracture is strongly associated with athletic activity in this population. Most patients were managed successfully with approximately 6 weeks of protected weight-bearing on crutches, followed by approximately 6 additional weeks of progressive weight-bearing and physical therapy. After this, gradual return to full activity can be expected.

A major limitation of our study was lack of follow-up. In most cases, patients were asked to follow-up only as needed once they achieved clinical healing and were released to athletics. The two patients that did return with symptoms in the ipsilateral hip were both found to have pain unrelated to the previous avulsion injury.

In spite of its limitations, our report is the largest series to date on isolated lesser trochanter fractures in adolescents. As such, this series provides important information for caregivers managing these injuries and potentially offers important information with which to counsel patients and their families.

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Core Decompression Surgery for Avascular Necrosis Can Delay Femoral Head Collapse in Patients with Sickle Cell Disease: A Case Report

Afamefuna Nduaguba, BA
Christine Goodbody, BA
Wudbhav N. Sankar, MD
Lawrence Wells, MD

Division of Orthopedic Surgery,
The Children's Hospital of Philadelphia,
Philadelphia, PA

Introduction

Avascular necrosis (AVN) of the femoral head is a common orthopaedic complication in patients with sickle cell disease (SCD). By age 35, approximately half of patients homozygous for the sickle cell gene mutation have AVN, with involvement of both hips in 40-91% of patients.[1] Without early intervention, the rate of femoral head collapse is high and often necessitates total hip arthroplasty (THA).[1]

Various treatment options exist for AVN, including physical therapy, pharmacotherapies, core decompression, and arthroplasty.[2]the possibility has been raised that bone marrow containing osteogenic precursors implanted into a necrotic lesion of the femoral head may be of benefit in the treatment of this condition. For this reason, we studied the implantation of autologous bone-marrow mononuclear cells in a necrotic lesion of the femoral head to determine the effect on the clinical symptoms and the stage and volume of osteonecrosis.METHODS:We studied thirteen patients (eighteen hips However, outcomes of most treatments have been varied,[3]and core decompression is a relatively safe and possibly effective option. To optimize core decompression further, we have tested a new technique involving thorough decompression of the osteonecrotic zone under endoscopic visualization (TDEV and as a result, there is no consensus on the best method to effectively prevent collapse and postpone the need for THA. Despite the lack of consensus, surgical core decompression has shown potential in the management of these cases. Core decompression with thorough debridement under endoscopic visualization followed by bone grafting and fixation with a nail/plate device produced encouraging results in a cohort of pediatric patients after a mean follow-up of 28 months, particularly for the treatment of lesions graded lower than Steinberg Stage IIIB.[3]and core decompression is a relatively safe and possibly effective option. To optimize core decompression further, we have tested a new technique involving thorough decompression of the osteonecrotic zone under endoscopic visualization (TDEV Meanwhile, a recent modification of core decompression involving autologous bone marrow mesenchymal stem transfer and multiple smaller drill holes resulted in statistically significant improvement in pain and hip survival compared to standard decompression in patients with Association Research Circulation Osseous (ARCO) Stage I/II hips in a recent randomized control trial.[4]

In this case report, we present two patients with SCD whose disease course was complicated by AVN for which they subsequently underwent decompression procedures. One patient underwent multiple core drilling decompression with iliac crest bone marrow grafting, and the other underwent the standard core single bore drilling and iliac crest bone grafting with pin stabilization. Both patients had significant improvement in symptoms and radiographic evidence of at least arrest of femoral head collapse at three years of follow-up.

Case Report

Case 1

A 12-year-old African-American male with hemoglobin SC variant SCD presented to our institution with a one-month history of progressive left-sided hip pain without any history of trauma or steroid use. On physical exam, he had normal gait but exhibited a mildly stiff left hip. Left hip range of motion was particularly notable for limited internal rotation in flexion at 20° and painful abduction to 35°. This was in contrast to a painless right hip with range of motion within normal limits.

Antero-posterior (AP) and frog lateral images of the left hip revealed femoral head flattening, confirmed by subsequent magnetic resonance imaging (MRI) (Figure 1) as osteonecrosis of the left hip with evidence of subchondral fracture, graded as Steinberg IIIb. His right hip was normal. Given advanced osteonecrosis on imaging and severity of his hip pain stiffness, the decision was made for a multiple drill hole core decompression and grafting with iliac crest bone marrow mesenchymal stem cells. The patient underwent the procedure as previously described by Gangji *et al*[2] to try to stimulate growth and healing of his osteonecrotic lesion.

Corresponding author:
Lawrence Wells, MD
Division of Orthopaedic Surgery
The Children's Hospital of Philadelphia
3401 Civic Center Blvd
Philadelphia, PA 19104
wellsl@email.chop.edu

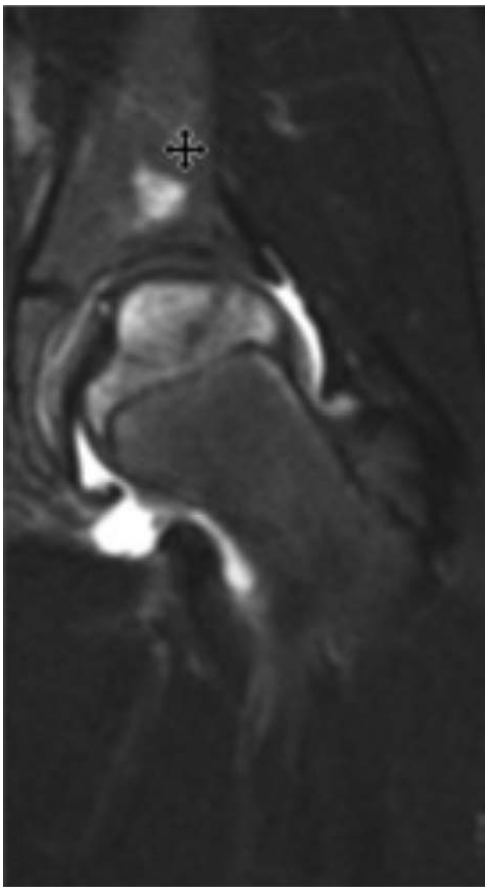

Figure 1. Preoperative MRI of left hip showing avascular necrosis in a 12-year-old male.

His immediate post-operative course was unremarkable. The patient began physical therapy at six weeks and continued to have improved range of motion. At twelve weeks, he had improved abduction to 45°. Index radiographs at eight and twelve-week intervals continued to show stable osteonecrosis. Follow-up Xrays (Figure 2) have shown a halt in progression of femoral head irregularities and improvement of the femoral head contour.

Case 2

A 9-year-old African-American female with history of SCD and asthma presented to our institution with left hip pain. At initial presentation, she had a three-month history of intermittent left hip pain and a progressive limp on the left side. There was no inciting trauma or injury. She had a history of sickle cell crises requiring inpatient admissions despite a medication regimen that included hydroxyurea and prednisone. Her initial exam was significant for a severely stiff left hip with flexion limited to 70°, abduction to 25°, external rotation of 5°, and internal rotation of 5°. This was in contrast to an asymptomatic right hip.

AP and frog lateral images revealed advanced osteonecrosis of the left hip (Figure 3a) confirmed by MRI, which further showed evidence of subchondral fracture. The left hip was graded as Steinberg IIIC. Early signs of osteonecrosis with bone marrow edema were evident in her right hip as well, although it was clinically stable.

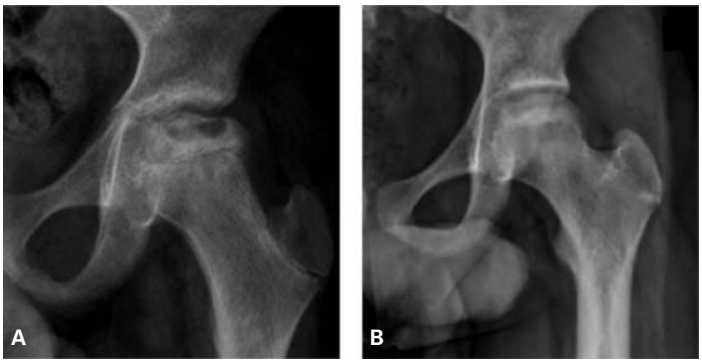

Figure 2. (A) 3 weeks postoperative AP image after decompression of left hip, and (B) follow-up AP of left hip 3 years after surgery showing minimal changes in femoral head contour.

Given the patient's age, degree of femoral head collapse and decreasing hip mobility, she was treated with core decompression, iliac crest bone grafting, and stabilization with a compression hip screw as previously described by Wells *et al.*[3] She did very well in the immediate postoperative period and had significant improvements in hip stiffness. A 0.5cm leg length discrepancy was noted at her 1.5-year follow-up visit, which was addressed with a shoe lift. At her most recent 5-year post-operative visit, a slight improvement in femoral head contour was noted (Figure 3b). Her physical exam at this visit demonstrated increased hip motion with improvement in flexion to 95°, abduction to 50°, adduction to 30°, external rotation to 40°, and internal rotation to 30°. There was no pain with range of motion.

Discussion

Treatment of advanced AVN with subchondral collapse is very challenging with various treatment options showing mixed results. We present two cases of adolescent African-American patients with advanced AVN, both of the left femoral head, who underwent successful decompression procedures: one with multiple drill hole decompression and iliac bone marrow grafting, and the other with a single drill core decompression, bone grafting, and stabilization with hip screw. The first patient was doing very well at his most recent 3-year follow up, and the latter was followed for five years with excellent improvement. Both have full, painless range of motion of both hips, and their radiographs show stable disease with improvement of femoral head contour.

Core decompression has become the most common way of preventing or prolonging the time to femoral head collapse in AVN, yet very few rigorous studies have validated long-term outcomes.[5] More specifically, for SCD patients, the studies that do exist demonstrate very conflicting results. Neumayr *et al*, in a prospective study, reported equal efficacy of physical therapy alone compared to decompression surgery, while Mukisi-Mukaza *et al*, in a more recent prospective study, demonstrated delayed need for arthroplasty with early decompression.[1,6] Both studies had a three-year follow-

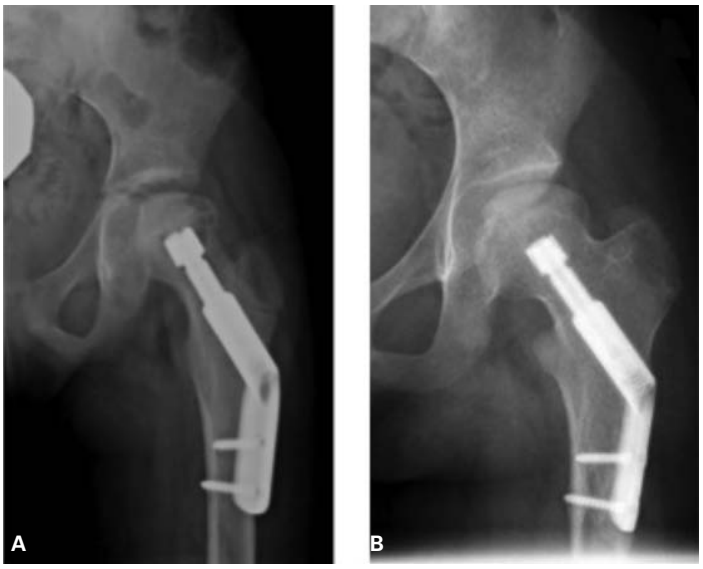

Figure 3. (A) Postoperative AP image of left hip in a 9 year-old female after core decompression, iliac crest bone grafting, and stabilization with a compression hip screw for AVN, and (B) AP Xray at 5 year follow-up visit showing no progression of AVN.

up period. In our own experience of treating AVN in SCD patients, limited weight bearing, physical therapy, and other non-operative treatments do not compare favorably to surgery.

Complicating the treatment picture are the numerous available core decompression procedure modifications, which include standard core decompression, multiple smaller drillings, and grafting with either autologous bone or mesenchymal bone marrow stem cells. While various studies of these procedure modifications have shown promising results in patients with AVN, no specific reports have addressed therapeutic benefits specifically in patients with SCD. Although this case report is only of two patients, the results are very encouraging. Both procedures were successful in preventing catastrophic collapse of the femoral head, improving gait, restoring motion, and alleviating pain in both patients. Both patients have radiographic evidence showing halting of disease progression for at least three years with no further femoral head collapse. Both standard core decompression with iliac crest bone grafting and pin stabilization, and multiple core decompression with iliac crest bone marrow grafting appear to be effective in prolonging femoral head collapse in SCD patients.

The few studies that compared multiple drill hole core decompression to conventional methods all claim improved outcomes, decreased fracture rate, lower rates of collapse, and longer time before collapse with the multiple drill hole method,[4,7,8] with Kim and associates demonstrating that the multiple drill hole technique for SCD had a lower rate of collapse (14.3%) than the conventional method (45%).[8] Bone marrow instillation in several small studies appears to be superior when added to core decompression.[2,4] To the best of our knowledge, no studies have compared standard bone grafting to marrow grafting. Thus it appears that, individually, core decompression with multiple drill holes and bone marrow mesenchymal stem cell graft confers a hip survival advantage to affected patients. Perhaps when both techniques are used in concert, greater benefits may be expected. Further studies are needed to compare methods of treating osteonecrosis in the sickle cell population, especially regarding bone marrow mesenchymal stem cell versus whole bone graft, as well as outcomes of standard decompression compared to multiple drill hole decompression.

Conclusion

Patients treated with either multiple drill hole decompression and iliac bone marrow grafting or single drill core decompression, bone grafting, and stabilization with a hip screw fare better than patients treated non-operatively. We feel that earlier disease detection will result in improved outcomes and longer preservation of the diseased femoral head. We recommend and encourage routine radiographic screening in patients with sickle cell anemia who are at high risk for osteonecrosis.

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Operative Technique: Arthroscopic Repair of Massive Rotator Cuff Tears

Michael H. McGraw, MD
John D. Kelly IV, MD

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

Introduction

Rotator cuff tears are a common cause of pain and disability.[1, 2] With modern advances in arthroscopy and arthroscopic techniques, most rotator cuff tears can now be repaired arthroscopically, with several authors reporting successful results.[3-6] However, the optimal management of massive rotator cuff tears is controversial and evolving.[7] In general, a massive rotator cuff tear (MRCT) is defined as a tear in which the major tear diameter is greater than 5 cm or tears that involve more than one tendon.[8] Despite the imposing retraction, most massive tears can be reduced to their native configuration once the tear configuration is recognized. Burkhart *et al* have classified massive cuff tears into one of three categories: crescent shaped, U-shaped, and L- shaped.[9] Crescent shaped tears are mobile and reduce easily to the anatomic footprint without excessive tension. U-shaped tears extend medially with the apex of the tear at the level of the glenoid. L-shaped tears are massive rotator cuff tears with a longitudinal component along the fibers of the rotator cuff as well as a transverse component along the cuff insertion.

Arthroscopic repair of massive rotator cuff tears presents a challenge to the orthopaedic shoulder surgeon due to tendon retraction, adhesions, and poor tissue quality making tension free repair difficult. Several arthroscopic techniques have been reported with the goal of gaining adequate tendon mobility, including margin convergence, interval slides, as well as release of fibrous bursal tissue and adhesions.[9, 10] Several open options are available to treat this condition, including tendon transfer, the use of allograft and synthetic grafts, arthrodesis, hemiarthroplasty, and reverse total shoulder arthroplasty (RTSA).[11-13] However, there is currently no consensus on the appropriate surgical treatment of massive irreparable tears when non-operative management fails.

There has been a recent broadening of the indications for RTSA for the treatment of patients with massive rotator cuff tears but without arthritis. We urge caution to surgeons performing RTSA for this indication, as the clinical outcome after arthroscopic repair is favorable for most cases with minimal risk, and RTSA may have a high complication rate.[13, 14] Additionally, arthroscopic repair does not preclude or complicate arthroplasty if needed in the future. So the question remains: why are many abandoning arthroscopic repair of massive rotator cuff tears for reverse total shoulder arthroplasty? Here, we review the rationale, preoperative evaluation, and indications for arthroscopic repair, and provide a detailed discussion of our surgical technique and post-operative care.

Preoperative Evaluation and Indications

Massive rotator cuff tears present in different clinical situations: acute traumatic, acute on chronic, and chronic atraumatic. Acute traumatic tears tend to occur in young active individuals, while chronic atraumatic tears occur in elderly patients and by far are most common. Muscle atrophy is typically not seen in acute traumatic tears, whereas atrophy is usually present in patients with chronic atraumatic tears. Patients with acute on chronic tears either present with an acute exacerbation in pain in the presence of a chronic symptomatic tear or with new onset shoulder pain in the presence of a chronic asymptomatic tear.

A detailed physical examination is paramount in determining the status of the rotator cuff and can typically provide insight into the size of the tear. Physical examination of the patient with a suspected MRCT should include thorough visual inspection of the shoulder girdle musculature paying particular attention to the presence of atrophy, any anterior-superior subluxation, and prominence of the humeral head. A MRCT occasionally can be detected as a palpable defect in the supraspinatus tendon at the anterolateral aspect of the shoulder. Loss of external rotation strength in the adducted arm indicates infraspinatus insufficiency. A positive belly press or bear hug test signifies a subscapularis defect, with the "lift off" sign associated with larger retracted tears. A "hornblower sign" denotes the presence of a teres minor lesion.

Corresponding author:
Michael H. McGraw, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein Pavilion
Philadelphia, PA 19104
Michael.McGraw@uphs.upenn.edu

Cervical spondylosis and radiculopathy can cause shoulder pain that mimics rotator cuff pathology; therefore, a complete cervical spine examination is warranted. The combination of a detailed history and thorough physical examination often provides sufficient information to establish a diagnosis of MRCT.

All patients should be evaluated with preoperative imaging including Xray and MRI. A complete radiographic evaluation of the shoulder includes anteroposterior, anteroposterior in both internal and external rotation, axillary lateral, and outlet views. Radiographs are particularly helpful in demonstrating the osseous changes associated with massive rotator cuff tears. Elevation of the humeral head relative to the glenoid and narrowing of the acromiohumeral space are findings consistent with long-standing rotator cuff pathology. Studies have reported that an acromiohumeral space <7 mm is consistent with a rotator cuff tear, and that a space <5 mm indicates a massive tear. MRI is highly accurate and demonstrates detailed anatomic information of the rotator cuff.[15] The size, presence of fatty infiltration, and retraction of the rotator cuff muscles can be easily identified, thus allowing determination of the chronicity of the tear, guiding surgical decision-making, and providing prognostic insight which can be relayed to the patient. The Goutallier classification is the standard means of assessing cuff integrity.[16] Many investigators advise against cuff repair with Goutallier grade greater than two. However, Burkhart has reported excellent results in patients presenting with Goutallier grade four (more fat than cuff).[17]

Patients with a history and physical examination findings of pain and/or weakness with the presence of a massive rotator cuff tear on MRI are excellent candidates for arthroscopic rotator cuff repair provided there is some remaining "force couple," or ability to initiate abduction. Pseudoparalysis, once considered a contraindication for cuff repair, has been found to be amenable to repair, provided the abduction deficit has not been present for longer than six months.[18]

Surgical Technique

Pre-operatively, a scalene block is placed to aid with post-operative pain. Examination under anesthesia is performed to assess shoulder range of motion and stability. The patient is placed in the lateral decubitus position. The extremity is placed in ten pounds of traction with the shoulder held at 45° of abduction and 15° of forward flexion. A posterior portal is made in the standard fashion with the portal established slightly lateral to the convexity of the humeral head. Massive cuff tears are evident once the joint in entered. Gentle mobilization of the cuff off the labrum is commenced at this point. Subscapularis tears, complete with the attached "comma sign" (Figure 1) are repaired at this time. Subscapularis repair is critical as restoration of the comma tissue (coracohumeral and superior glenohumeral ligaments) will enhance the superior cuff repair. Retracted infraspinatus tears can be sewn to comma tissue once the subacromial space is entered (Figure 2). If superior migration of the humeral head is appreciable, an inferior capsular release is performed to minimize strain on the repair.

The camera is then placed in the subacromial space through the posterior portal and a thorough bursectomy is performed via a lateral working portal. The portals should be placed low enough such that the cannulas are parallel with the rotator cuff tendons. A second lateral portal can be established for large tears in order to obtain a "50-yard line view" of the tear. Thermal ablation is used to excavate the rotator cuff to the scapular spine while viewing laterally. An acromioplasty is performed, making sure to remove the anterior-inferior hook

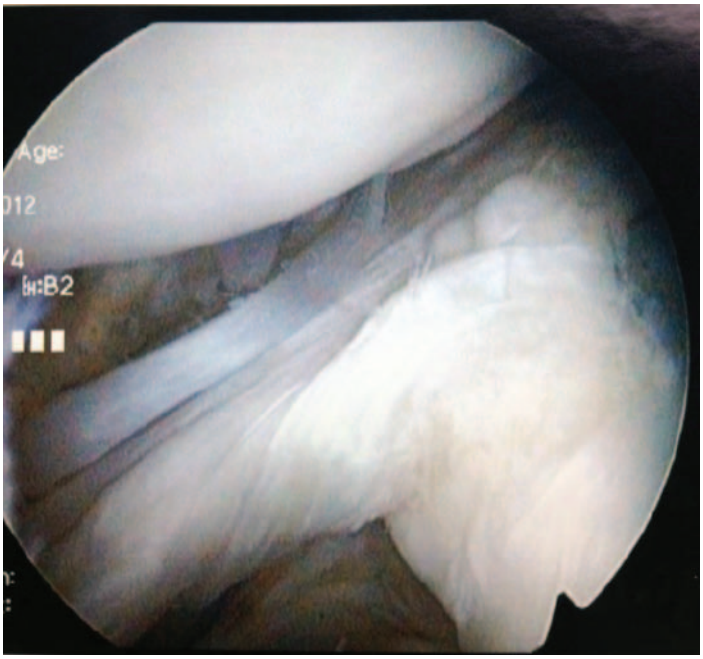

Figure 1. The comma sign, an indication of a subscapularis tear.

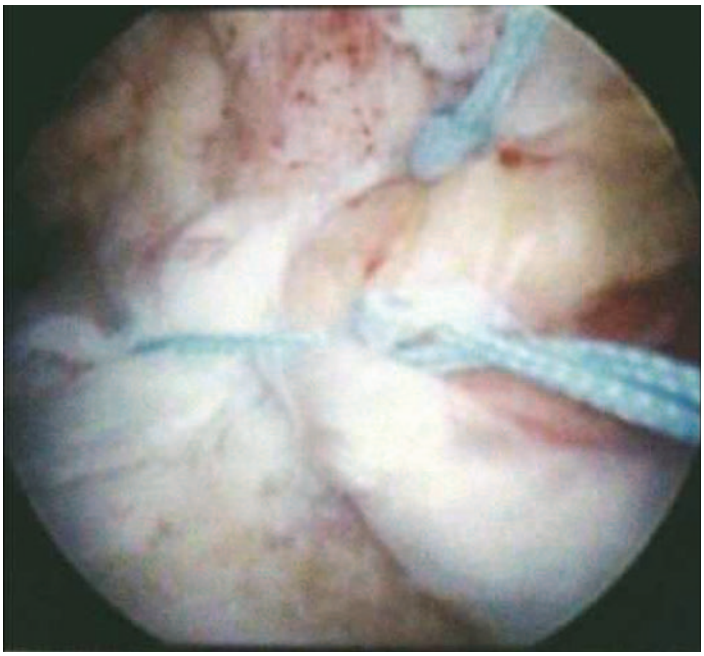

Figure 2. The infraspinatus is sewn to the comma tissue.

while protecting the coracoacromial ligament. The senior author prefers to perform a Mumford procedure in most cases as the procedure is quick, and acromioclavicular joint arthritis is usually present.

The coracohumeral ligament is then released if the subscapularis tendon is not involved. This maneuver increases the lateral mobility of the supraspinatus and infraspinatus tendons. Traction sutures are placed in opposing cuff edges in order to facilitate approximation. The biceps tendon is then visualized and addressed. The biceps tendon is usually frayed or subluxed medially if a tear of the subscapularis tendon is present. Generally, a tenodesis is performed in patients younger than 60. In patients over the age of 60, a biceps tenotomy is usually preferred.

The tear is visualized and a tear pattern is determined. The mobile limb of the tear indicates the pattern of tear extension. Crescent shaped tears have symmetric retraction. U-shaped tears have anterior and posterior limbs that are equally mobile. L-shaped tears and reverse L-shaped tears have a mobile anterior and posterior limb respectively. The cuff tears are repaired using margin convergence. This technique involves placing side-to-side sutures in the tear which shifts the adjacent tissue into the cuff defect. This technique shortens the medial-lateral dimension as the free margin "converges" toward the tuberosity. This results in decreased strain in the rotator cuff margin (Figure 3).

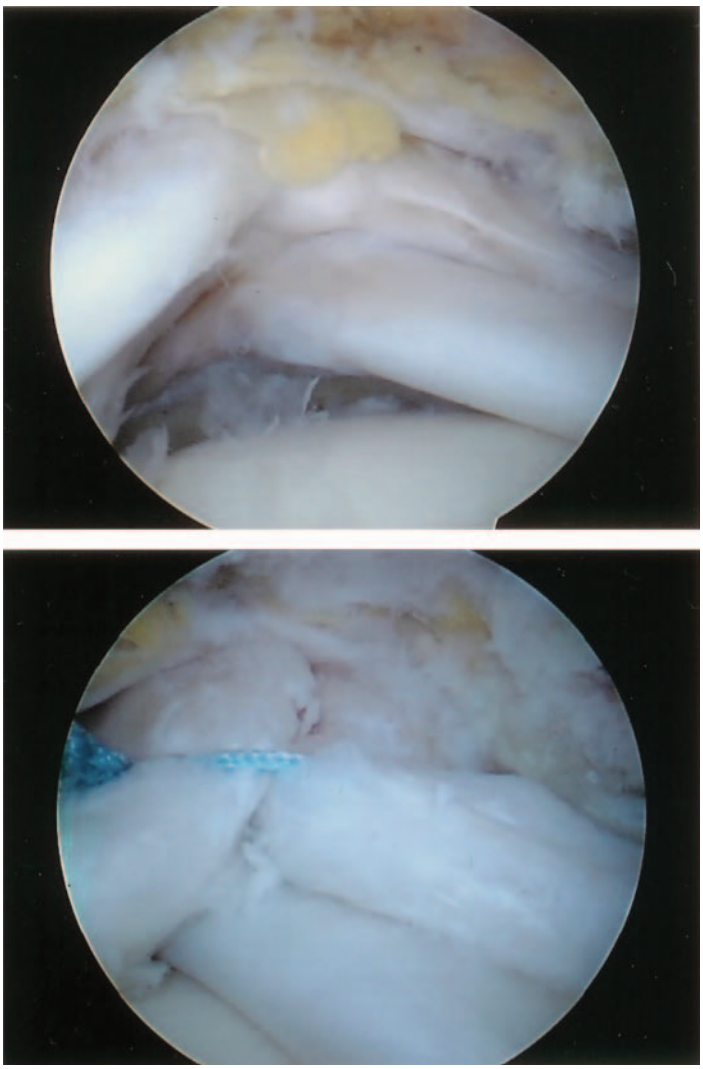

Figure 3. Margin convergence shifts tissue toward the cuff margin.

If the cuff cannot be fully mobilized to its footprint without over-tensioning the repair, then partial repair is performed. "Rip stop" sutures are employed in cases of very weak tissue. The senior author favors "tape" type suture as reinforcement. A single row of anchors is used to reattach the tendons to the footprint. Care is taken to minimize tension across the repair. Double row configurations are not indicated as they do not effect a proper "reduction" of the tear pattern. Secondly, undue tension disturbs biology and is to be avoided. If full coverage is not achieved, an awl is used to punch holes into the tuberosity in order to enhance biology. More recently, the senior author has augmented deficient tissue with dermal allograft secured with 'four corner" arthroscopic fixation.

Postoperative Care

Patients are kept in an abduction pillow for six to eight weeks, depending on the tissue quality. Only elbow and wrist motion is permitted. Active elevation is discouraged for at least six weeks. Physiotherapy commences approximately at week seven, and strengthening is avoided until 12-14 weeks.

Discussion

There are several advantages to performing arthroscopic repair of massive rotator cuff tears. Arthroscopic repair of massive tears can provide pain relief, help the patient regain function, and halt or delay the onset of arthropathy. Additionally, arthroscopic repair is relatively safe with low complication rates when compared to other open surgical options such as RTSAs.[9] Denard *et al* reported that arthroscopic repair of MRCTs with advanced mobilization techniques can lead to reversal of preoperative pseudoparalysis in 90% of patients who have not had previous surgery. These results were achieved with low complication rates.[18] Good to excellent outcomes have been reported even in patients who do not maintain cuff integrity after arthroscopic rotator cuff repair.[19,20]

There has recently been increased interest in the role of RTSA in the treatment of massive rotator cuff tears. There may be a population of patients for whom this is a reasonable option, including patients with rotator cuff arthropathy and a high riding humeral head. However, RTSA is not without risk. Studies have reported as high as a 68% complication rate after RTSA.[21-23] The most common complications include neurologic injury, periprosthetic fracture, hematoma, infection, scapular notching, dislocation, mechanical baseplate failure, and acromial fracture.[14]

Conclusion

Arthroscopic rotator cuff repair is a viable surgical option for management of massive rotator cuff tears. It provides pain relief and improves function with or without the maintenance of structural integrity. It also poses minimal

risk and does not preclude further intervention if necessary. Reverse total shoulder arthroplasty for the management of massive cuff tears is also an option but is associated with significant complication rates and should be reserved for advanced cuff tear arthropathy. Shoulder surgeons should still have arthroscopic repair as a treatment modality in their armamentarium when tackling massive rotator cuff tears.

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Displaced Inferior Ramus Fractures as a Marker for Pelvic Instability

P. Maxwell Courtney, MD
Ryan M. Taylor, MD
John Scolaro, MD
Derek J. Donegan, MD
Samir Mehta, MD

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

Background

Isolated anterior or posterior pelvic ring injuries rarely occur due to the ring structure of the bony pelvis. While much attention is focused on disruption of the sacrum or sacroiliac joint, the anterior ring is often neglected. Fractures of the pubic rami are not benign injuries, causing functional impairment, disability, and the utilization of substantial healthcare resources.[1] The purpose of this retrospective study was to determine whether displaced inferior pubic ramus fractures are a marker of posterior ring instability. Scheyerer *et al* described a case series of patients with a pubic ramus fracture and found that 96.8% of patients had a posterior ring injury on computed tomography (CT) scan.[2] The prevalence of posterior ring disruption and pelvic instability in the presence of a displaced inferior pubic ramus fracture has yet to be addressed in the literature.

While inferior ramus fractures in isolation are treated nonoperatively in the majority of cases, much controversy surrounds the need for fixation for Young and Burgess lateral compression type I (AO/OTA type 61-B) injuries. Lefaivre *et al* looked at these fractures, which have a high incidence of posterior ring injury but are considered stable, and found that with CT evaluation the severity of posterior ring injury represented a higher degree of instability than initially thought[3]. Previous studies have evaluated the disruption of the posterior pelvic ring with injury of the public symphysis,[4] but the correlation with displaced inferior ramus injuries has not been fully evaluated. The authors hypothesize that patients with displaced inferior ramus fractures on plain radiograph have a high incidence of unstable posterior ring injuries which warrants further careful clinical and radiographic evaluation.

Methods

Using International Classification of Diseases, 9th edition (ICD-9) codes, the authors identified 493 patients with any fracture of the pelvis at a single Level I trauma center from 2007 to 2011. Institutional review board approval was obtained for this study. Of this group, 155

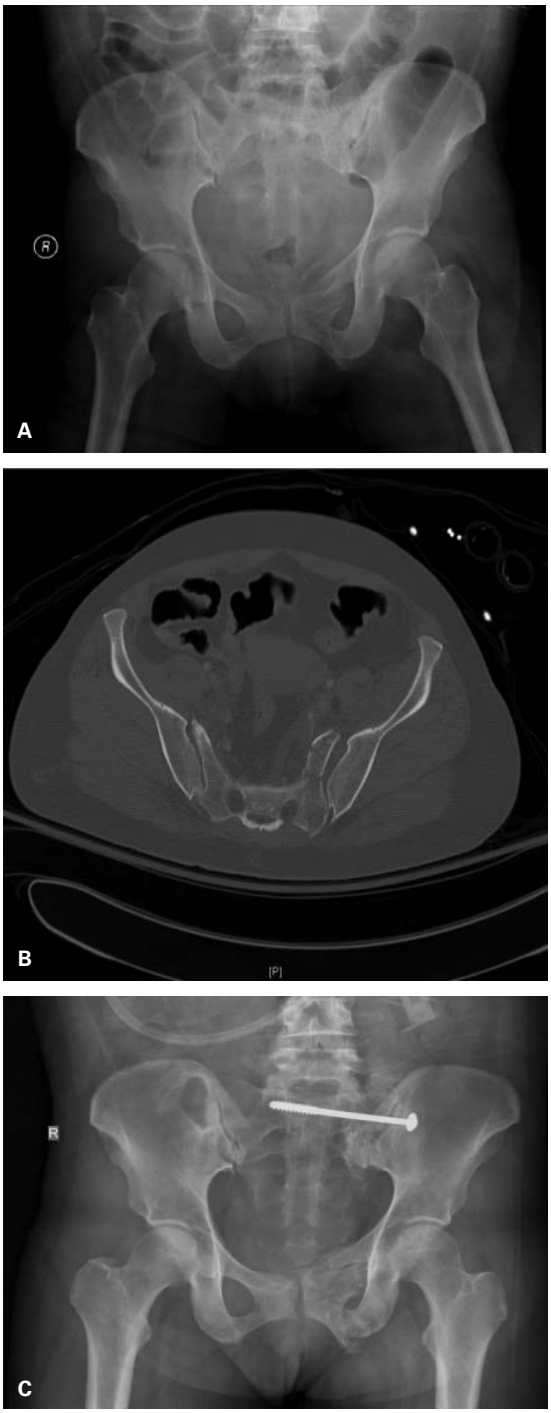

Figure 1. Pelvic radiograph (A) and CT scan (B) of a 49 year old female after a motor vehicle crash showing a displaced left inferior ramus fracture, superior ramus fracture, and a posterior ring injury which was treated with a sacroiliac screw (C).

Corresponding author:
P. Maxwell Courtney, MD
Department of Orthopaedic Surgery
University of Pennsylvania
3400 Spruce Street,
2 Silverstein
Philadelphia, PA 19104
Paul.Courtney@uphs.upenn.edu

Table 1. Summary of patient data with displaced inferior ramus fractures.

Gender	Number (%)
Male	44 (47)
Female	49 (53)
Age	**Number (%)**
18-30	25 (27)
31-45	27 (29)
46-60	35 (38)
> age 60	6 (6)
Mechanism	**Number (%)**
Fall	27 (29)
Motor vehicle accident	43 (46)
Pedestrian struck by vehicle	13 (14)
Other	7 (8)
Associated Injuries	**Number (%)**
Superior ramus fracture	71 (76)
Bilateral inferior ramus fracture	12 (13)
Posterior ring injury	63 (68)
Surgical fixation of posterior ring	37 (40)
Unstable posterior ring injury	38 (41)

patients were found to have a displaced inferior ramus fracture on pelvic plain radiograph. Patients under age 18, those with a concurrent acetabular fracture, or without a CT scan were excluded. Ninety-three patients met the inclusion criteria. Complete pelvic radiographs and computed tomography (CT) scans were then evaluated for additional pelvic ring injuries.

The inferior ramus fracture was classified anatomically as parasymphyseal or shaft. We defined a posterior ring injury as a fracture of the sacrum, any displacement of the sacroiliac joint, or fracture of the ilium with extension into the sacroiliac joint. The AO/OTA classification of the pelvic ring injury was noted by two of the authors. Patients requiring operative fixation of the posterior ring or those with AO/OTA type C injury who expired prior to fixation were deemed to have an unstable injury. The data was analyzed using the chi-square test to determine associations with posterior ring injury and instability. A logistic regression analysis was performed to identify any potential correlation with age and posterior ring disruption. A p-value of 0.05 was used to determine statistical significance.

Results

Of our original 155 patient series with a displaced inferior ramus fracure, 60 patients (39%) were found to have an acetabular fracture. We looked closer at the 93 patients with isolated ring injuries, where 71 patients had a superior ramus fracture and 12 patients had bilateral inferior ramus fractures. There were 44 men and 49 women with an average age of 44 (range 18-64) at the time of injury. No statistically significant correlation was found between age and incidence of posterior ring injury or pelvic instability. The most common mechanism of injury was a motor vehicle accident in 43 patients, followed by a fall in 27 patients.

Sixty-three (68%) patients were found to have a posterior ring injury on additional radiographs and CT scan, with 60% of these injuries being unstable. Patients with concurrent superior ramus fractures were statistically more likely to have a posterior ring injury ($p<0.001$) and an unstable pelvis ($p=0.013$). Those with bilateral displaced inferior ramus fractures had a higher rate of posterior ring injury which approached statistical significance ($p=0.057$). Of those with a displaced unilateral inferior ramus fracture, parasymphyseal involvement was associated with higher incidence of posterior ring injury ($p=0.047$) and pelvic instability ($p=0.028$).

Discussion

Injury to the bony pelvis has previously been described by the mechanism of injury and the degree of instability which results. Tile described pelvic injuries as stable, rotationally unstable but vertically unstable, or rotationally and vertically unstable.[5] Young and Burgess further described pelvic injuries by the mechanism of injury: lateral compression (LC), anteroposterior compression (APC), vertical shear (VS) fractures, and those with a combined mechanism (CM).[6] Both systems base the degree of instability of the pelvic ring on the location of the fracture and relate radiographic findings to the direction of the force which created such an injury. Fractures to the anterior pelvic ring can occur infrequently in isolation and are often associated with disruption of the ring in another location. In isolation, these fractures are considered rotationally and vertically stable (Tile A) and are treated non-operatively in the majority of cases. Disruption of both the anterior and posterior ring often results in instability requiring operative fixation.

While the anterior ring is often a neglected entity in pelvic trauma, it can be a marker for additional injuries of the ring. The authors hypothesized that displaced inferior ramus fractures are a marker for instability of the pelvic ring. Sixty-three of the 93 patients in our case series had an injury to the posterior ring, 37 required surgical stabilization of the posterior ring, and one sustained a fatal AO/OTA type C pelvic ring injury. The high incidence of an unstable posterior ring injury should prompt all clinicians evaluating pelvic trauma to closely scrutinize all patients with an inferior ramus fracture for further injuries to the pelvic ring. When looking at the subset of unilateral inferior ramus fractures, parasymphyseal involvement was more likely to have a posterior ring injury and pelvic instability than inferior ramus shaft fractures. These parasymphyseal patterns are more likely to act as a Young and Burgess APC injury.

Both the Tile and Young and Burgess systems rely on three plain films of the pelvic ring and were not created with the consideration of CT imaging. In a single retrospective study,

Table 2. Additional radiographic findings with incidence of posterior ring injuries and instability.

	Posterior Ring Injury	P value	Unstable Injury	P value
Superior ramus fracture	56 (79)	< 0.001	34 (48)	0.013
Bilateral inferior ramus fracture	11 (92)	0.057	7 (58)	0.186
Unilateral inferior ramus fracture				
Parasymphyseal	20 (80)	0.047	14 (56)	0.028
Shaft/Root	32 (57)		17 (30)	

37 of 53 patients with any pubic ramus fracture were found to have evidence of a posterior ring injury on CT,[7] but none of those patients underwent operative treatment. The authors did not recommend routine use of CT scanning for patients with isolated ramus fractures. Our data contradict this study, as 41% of all patients in our series with displaced inferior ramus fractures required surgical fixation. We, therefore, recommend CT scans in all patients with a displaced inferior ramus fracture found on plain radiographs.

While acknowledging the retrospective nature of the study, we present the first case series of patients with displaced inferior ramus fractures to determine the incidence of posterior ring injury and pelvic instability. There exists considerable debate whether AO/OTA type B fractures are inherently stable or unstable, and in practice, it is difficult to determine which of these fracture patterns are truly unstable. As our marker for instability, we used the clinical judgment of two fellowship-trained orthopaedic traumatologists at our institution if they chose to pursue surgical stabilization of the posterior ring. Concurrent acetabular fractures are a confounding variable of pelvic stability and were excluded from the study.

Conclusion

Patients with displaced inferior pubic ramus fractures warrant a detailed examination of their posterior ring to identify instability, particularly in those with associated superior ramus fractures, bilateral inferior ramus fractures, and parasymphyseal injuries.

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Alternative Protocol for Heterotopic Ossification Prophylaxis in Posterior Approaches for Acetabulum Fractures

Deren T. Bagsby, MD
Karl Shively, MD
Brian H. Mullis, MD

Department of Orthopaedic Surgery,
Indiana University School of Medicine,
Indianapolis, IN

Introduction

Heterotopic ossification (HO) is a well-known potential complication that can adversely affect patient outcomes by decreasing functional range of motion.[1,2] There are multiple known patient and injury-related factors associated with HO formation, including male sex, hip dislocation, certain fracture patterns, head injury, extensive burns, and a delay in surgical fixation.[1-6] However, it has also been shown that certain exposure types, such as the Kocher-Langenbeck or extensile approaches, increase the risk of postoperative HO formation. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce the risk of HO, but these drugs carry potential risks, which include long bone nonunion, GI symptoms, and hemorrhage.[1,3] Additionally to date, NSAID prophylaxis has only been examined in the context of single agent therapy. The purpose of this retrospective pilot study was to evaluate a novel dual NSAID protocol to determine if this protocol was an acceptable alternative to the traditional use of indomethacin in preventing HO following open fixation of acetabulum fractures through a posterior approach, while minimizing complications traditionally associated with NSAID usage.

Methods

A retrospective review of patients treated by two fellowship-trained orthopaedic traumatologists (KS, BHM) at a Level One trauma center from September 2006, through July 2011, was performed, following IRB approval. Sixty-nine patients were identified with acetabulum fractures that were treated by internal fixation. This study included 44 of these patients who were done through a posterior approach and had a minimum of six months of follow-up. Thirty of these 44 patients received an NSAID protocol of ketorolac, 30mg intravenous every 6 hours for 3 days, followed by naproxen, 500mg twice a day for 6 weeks. The remaining patients received no prophylaxis. Given the retrospective nature of this study, the reason for this is unknown. HO severity was evaluated using the Brooker classification. Grading of the radiographs was done by an independent reviewer, who was not involved in the care of these patients and was blinded to the treatment groups. To ensure a homogenous study population, all patients were evaluated for other potential risk factors for HO formation, including age at the time of injury, time delay of operative intervention, head and burn injuries, and hip dislocation or other associated high-risk fractures. Statistical analysis was performed for comparison of treatment and no treatment groups. Wilcoxon rank sum tests, Pearson chi-square tests, and Mantel-Haenszel chi-square tests were used to compare the two groups for differences in continuous, non-ordered categorical and ordered categorical responses, respectively.

Results

There were no significant differences in operative side, gender, presence of head injuries, or presence of associated high-risk fractures between our two groups (Table 1). Additionally, there was no difference between age ($p=0.88$), follow-up time in months ($p=0.25$), operating surgeon ($p=0.39$), surgical approach ($p=0.25$), or fracture type ($p=0.11$) (Table 2). There was a statistically significant reduction in HO rates in the treatment group seen in the individual Brooker classes ($p=0.004$) and the absolute presence of HO ($p=0.0275$), shown in Table 3. Treatment was associated with an absolute risk reduction of 33.81% and a relative risk reduction of 60% compared with those who did not get prophylaxis. Importantly, no severe (Brooker grade 3 or 4) HO was seen in the treatment group. Post-hoc power analysis demonstrated power of 0.9 and effect size of 0.5 with 44 patients.There was no increased risk for complications such as renal failure ($p=0.49$), GI bleeding ($p=0.48$), nonunion ($p=0.48$), repeat operation ($p=0.16$), or nerve palsy ($p=0.39$).

Discussion

Debate continues over which method of HO prophylaxis is best or whether any should be given routinely. NSAIDS provide a cheap and convenient method of prophylaxis while avoiding potential risks of radiation. Treatment

Corresponding author:
Deren T. Bagsby, MD
Department of Orthopaedic Surgery
Indiana University School of Medicine
541 Clinical Drive, Suite 600
Indianapolis, IN 46202-5111
dbagsby@iupui.edu

Table 1. Data for treatment and control groups.

		Treatment	Control	p
Side	Left	15 (50%)	8 (57%)	0.66
	Right	15 (50%)	6 (43%)	
Gender	Male	8 (27%)	3 (21%)	0.71
	Female	22 (73%)	11 (79%)	
Head Injury	Present	3 (10%)	1 (7%)	0.76
	Absent	27 (90%)	13 (93%)	
Other Fractures	Present	13 (43%)	6 (43%)	0.98
	Absent	17 (57%)	8 (57%)	

Table 2. Acetabular fracture types in treatment and control groups.

	Treatment	Control
Associated Both Column	2 (7%)	0 (0%)
Posterior T-type/Anterior Column	0 (0%)	1 (7%)
Posterior Column	1 (3%)	1 (7%)
Posterior Wall	12 (40%)	4 (29%)
Transverse/Posterior Wall	12 (40%)	3 (21%)
T-type	1 (3%)	4 (29%)
Transverse	0 (0%)	1 (7%)
Posterior Column/Posterior Wall	1 (3%)	0 (0%)
Posterior Wall/Posterior Column	1 (3%)	0 (0%)

Table 3. Brooker Classification of HO for patients in the treatment and control groups.

Class	Treatment	Control
0	23 (77%)	6 (43%)
1	4 (13%)	2 (14%)
2	3 (10%)	3 (21%)
3	0 (0%)	1 (7%)
4	0 (0%)	2 (14%)

as short as three weeks has been shown to be effective, but treatment beyond six weeks postoperatively has also been recommended in some studies.[7] Unfortunately NSAIDs carry multiple drawbacks, including reduced patient compliance and ulcer formation, possibly leading to GI bleeds.[8,9] This is particularly concerning in patients already on anticoagulation. Additionally, NSAIDs can increase the risk of bony nonunion after fixation. With our two agent combination protocol, we were able to show a reduction in the overall presence of ossification and reduced prevalence at each Brooker grade. Interestingly, there was no severe HO (grade 3 or 4) seen in our treatment group. Furthermore, our protocol was associated with no increased incidence of GI bleeding, renal failure, or fracture nonunion. The primary limitation of this study was its small sample size and retrospective design comparing our prophylactic regimen against no treatment. In addition, our control group averaged a two day delay before operative fixation, which can also be associated with HO.

Overall, our pilot study suggests that the use of intravenous NSAIDs (ketorolac) for 3 days postoperatively followed by 6 weeks of naproxen appears to be a safe and possibly efficacious method of preventing HO following posterior approaches for acetabulum fractures. This study serves to demonstrate the safety and potential efficacy of our protocol in HO prophylaxis. Further work will involve a prospective, randomized double-blind comparison of our protocol to standard indomethacin and radiation protocols.

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EOS Imaging: Insight Into This Emerging Musculoskeletal Imaging System

Emmanouil Grigoriou, MD
Saba Pasha, PhD
John P. Dormans, MD

Division of Orthopaedic Surgery,
The Children's Hospital of Philadelphia,
Philadelphia, PA

Introduction

EOS 2D/3D imaging system (EOS imaging, Paris, France) is a multidimensional Xray imaging system that is able to acquire high quality images in two perpendicular planes with less radiation than standard imaging techniques.[1] EOS is currently used clinically in scoliosis and lower extremity deformities (leg length discrepancy, angulation deformities, *etc*). Although technically very promising, the available clinical data from the EOS imaging system are still limited, and its clinical benefits are under further investigation.

Background

EOS (EOS imaging, Paris, France) is a biplane, weight bearing, whole-body digital Xray imaging system that uses slot-scanning (an ultrasensitive Xray detection technology) as opposed to conic projection. The EOS system can produce images of comparable or better quality than computed radiography (CR) and digital radiography (DR) with 6-9 times less radiation dose and shorter examination time.[2,3] EOS image quality has been reported to be comparable or superior to film Xray imaging and CR. Two perpendicular Xray tubes and associated slot scanning detectors move simultaneously down the entire height of the patient up to 175 cm, or any desired subset of this length, and capture both frontal and lateral images simultaneously. Digital images are immediately available on the acquisition workstation and can be directly transferred to the picture archiving and communications system (PACS) (Figure 1). A whole body scan takes approximately 20 seconds and a spine scan approximately 4-6 seconds.[1,4] Patients must be able to stand or sit, and for spine Xrays specifically, they should be developmentally mature and physically able to hold their breath on command. In addition, the enclosed design of the EOS machine places a limit on the patient's size (Figure 2).

The main application of EOS is for pathology with a rotational component, which changes under load, and pathology that requires frequent and chronic follow-ups that pose a radiation exposure concern.[1,2,4] As a result, EOS imaging's main clinical indication is scoliosis/kyphoscoliosis, but it is also being used in lower extremity deformity and length discrepancy.

Methods for clinical diagnosis, evaluation, treatment planning, and follow-up monitoring of spine deformities are being continuously examined and reevaluated with numerous alternative techniques proposed throughout the years. The most commonly used Cobb angle method, the basis of scoliosis evaluation and treatment, relies on AP and lateral Xrays. Many have argued that this two-dimensional method oversimplifies and erroneously interprets a three-dimensional deformity.[5] EOS addresses the two main issues of traditional scoliosis imaging with methods of CR and DR: the dependence of the degree of curvature on the plane of radiographic projection and the concern for radiation exposure due to frequent and chronic radiographic follow-up of these patients.[5,6] The full-length EOS images eliminate the need for manual or digital stitching when there is an interest to study the relative spino-pelvic alignment in scoliosis.[1,4] Additionally, EOS addresses another major issue, the accuracy of the Cobb angle for the evaluation and monitoring of kyphoscoliotic deformities, by providing additional information on the axial rotation (Figure 3). The Ster-EOS 2D/3D software provides a quick method to generate a personalized 3D reconstruction of the spine and quantitatively deliver the rotational components of the spinal vertebrae to the PACS.[1,6] The 3D reconstruction procedure is semi-manual; hence, its accuracy depends on the user expertise. Three-dimensional reconstruction of the spine has not been developed for patients younger than 7 years old or for pathologies such as supernumerary vertebrae, congenital deformities, and spondylolisthesis. Three-dimensional reconstruction is not meant to detect bone fracture, osteophytes, fibrocartilage calluses, nor significant changes in the geometry of the bone. The 3D reconstruction of the lower extremities is still not available for patients younger than 15 years old. The 3D reconstructions of the cervical spine, ribcage and upper extremities are not still developed in this software.[1]

EOS system is an up-and-coming technology. Several 3D parameters of the spine and lower extremities are still being validated. Despite

Corresponding author:
John P. Dormans, MD
Division of Orthopaedic Surgery
The Children's Hospital of Philadelphia
3400 Civic Center Boulevard,
Philadelphia, PA 19104, USA
dormans@email.chop.edu

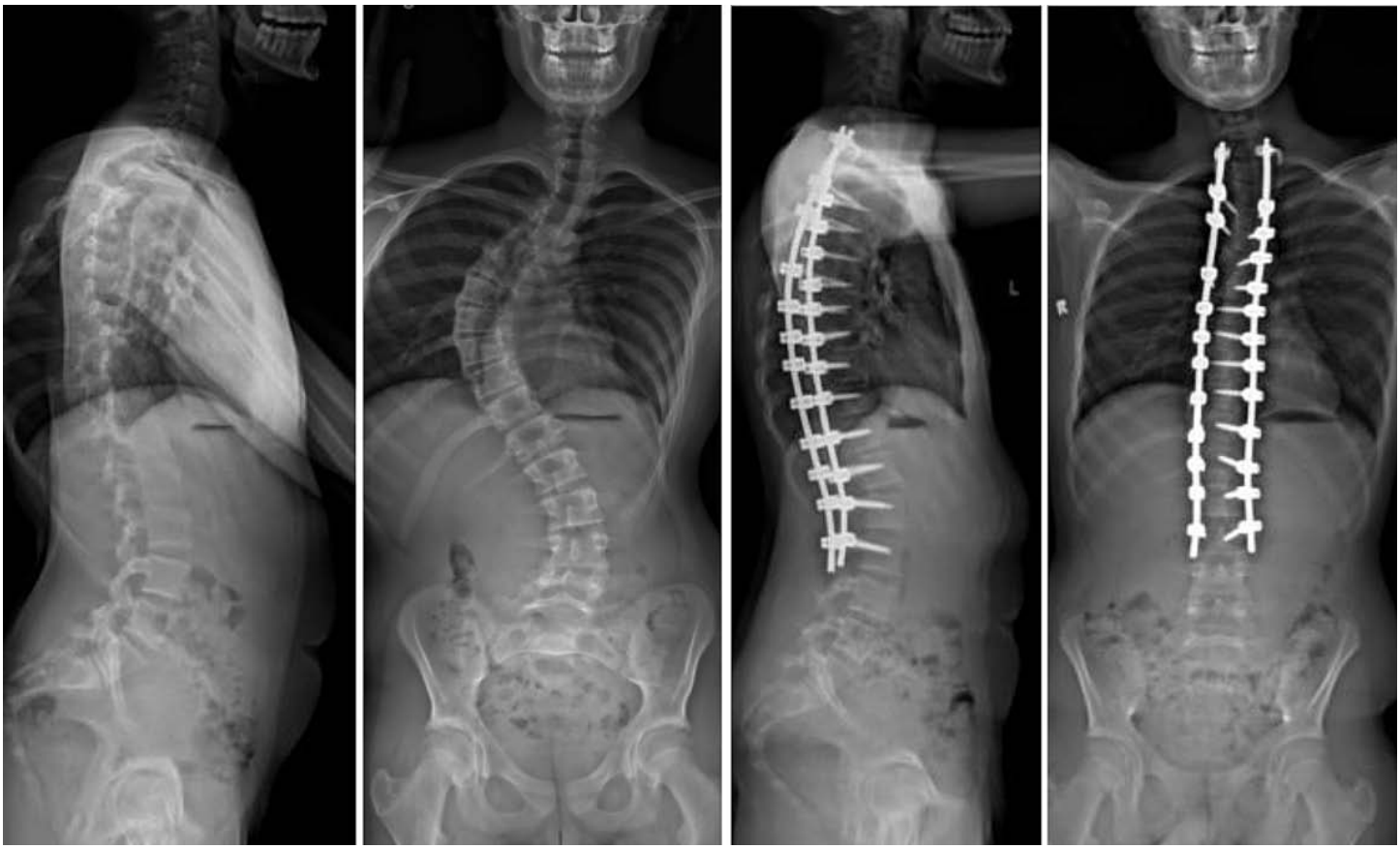

Figure 1. Preoperative (on the left) and postoperative (on the right) LAT and AP EOS spine views of a 70 degrees right thoracic adolescent idiopathic scoliosis treated with posterior spinal fusion with instrumentation of T1-L2 levels.

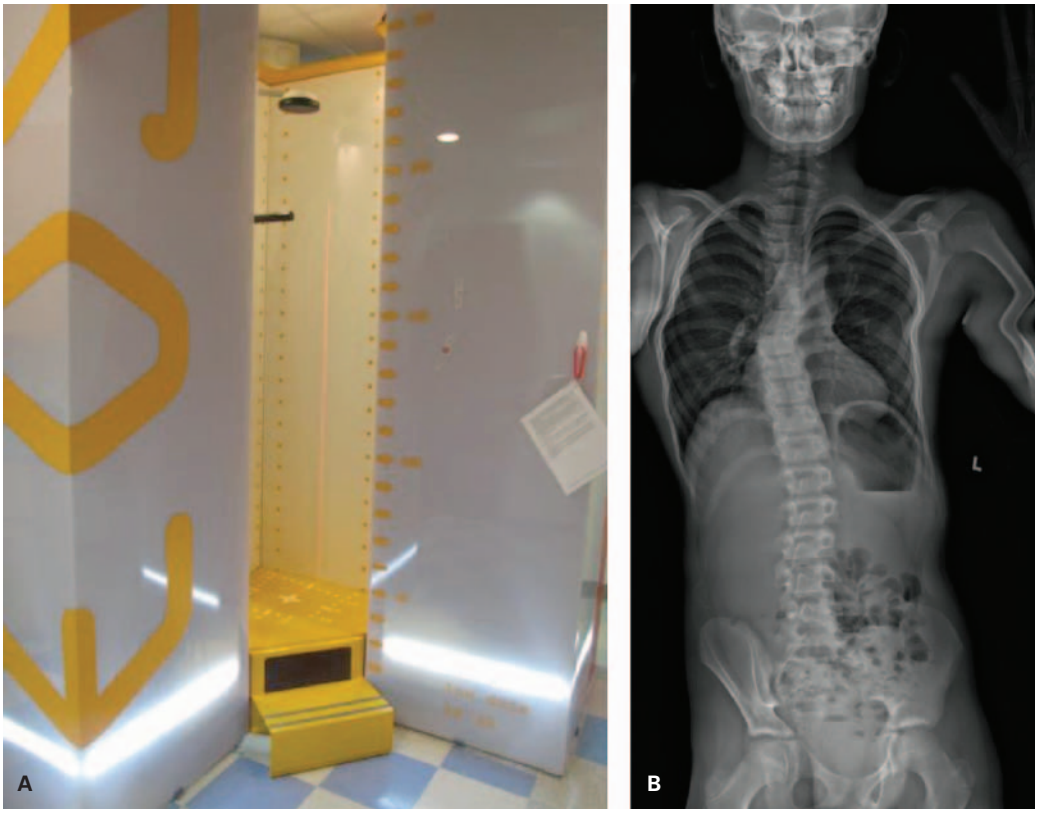

Figure 2. (A) EOS imaging system machine. (B) Artifacts due to patient motion during a spine scan.

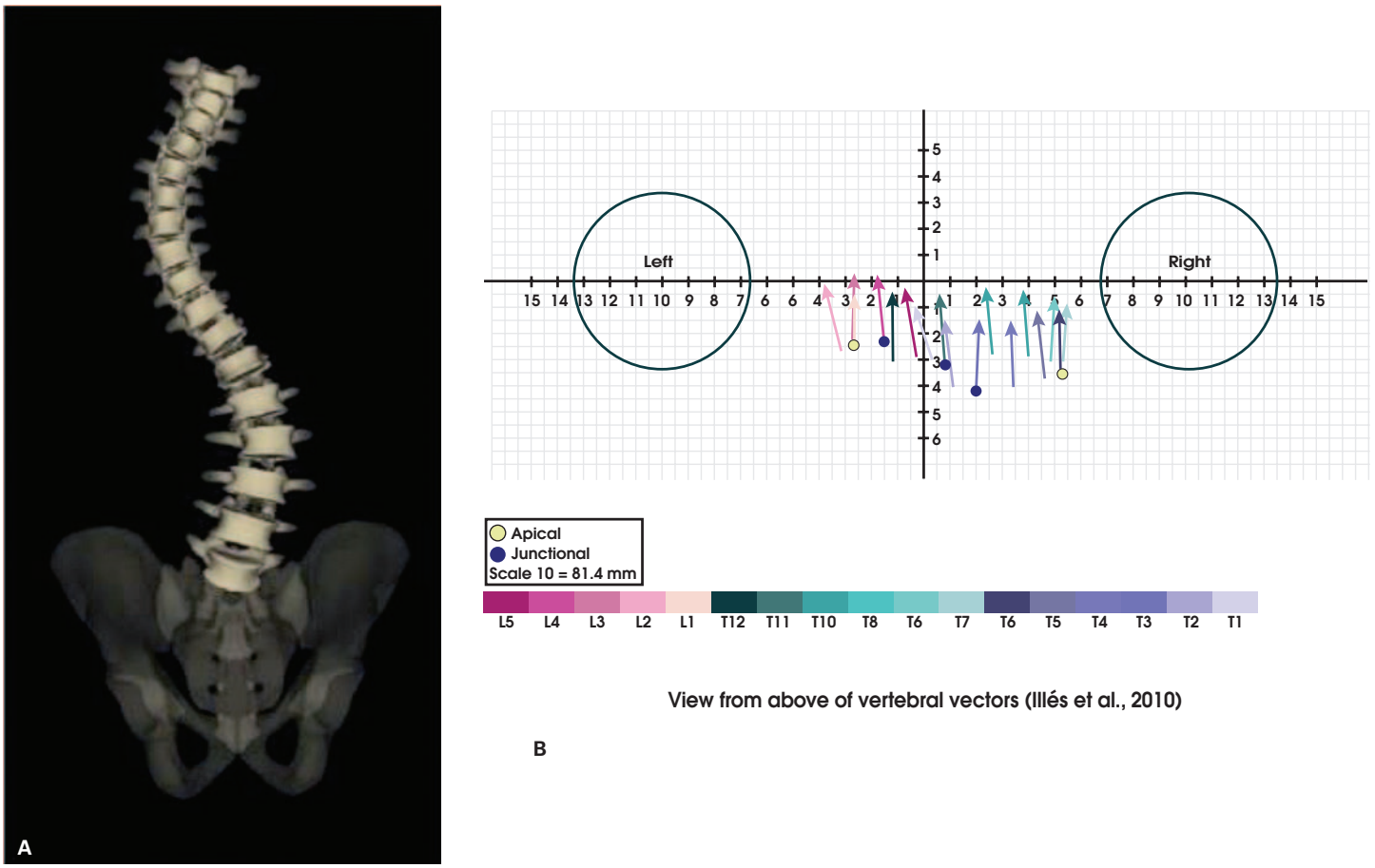

Figure 3. (A) EOS-generated 3D reconstruction of the spine of a patient with adolescent idiopathic scoliosis (AP view). (B) EOS-generated diagrams of vertebrae axial rotations shown by vertebral vectors (with respect to the femoral heads, top view).

the very promising features of the EOS imaging system the application of the 3D components of the skeletal deformities in the patient's clinical care is yet to be investigated and quantified.[2]

Question

What are the main advantages and disadvantages of the new EOS imaging system?

- Advantages:
  1. Low radiation
  2. Quick test (20 seconds for an adult full-body scan)
  3. Provides information on axial rotation
  4. More accurate representation of the deformity/spinal balance (plane of radiographic projection, weight bearing images)
  5. Less expensive than CT 3-D reconstruction for preoperative planning
  6. Full body imaging without the need for digital stitching/manual joining of images
- Disadvantages:
  1. Limited clinically validated outcomes
  2. Limited use in non-ambulatory patients and developmentally immature
  3. Not widely available
  4. Expensive equipment
  5. Narrow range of indications and applicability outside of the aforementioned uses

How can the EOS imaging system and 3D morphological parameters affect orthopedic clinical practice?

- 3D parameters permit visualization and evaluation of the true shape of the skeletal deformity. Quantitative parameters from the 3D reconstructions permit close monitoring of the progression of the deformity and surgical outcome.
- The full body Xray images allow more accurate assessment of progression of skeletal deformities and detection of abnormalities associated with a specific pathology.

Discussion

The main question that arises whenever a new device or method is introduced is if it can prove its superiority to existing methods or the standard of care. The main challenge associated with EOS is further clinical research to investigate and potentially prove whether the nature and quality of the produced images are better than the traditional imaging modalities and if the measured decline in radiation exposure translates to improved health outcomes of orthopaedic patients. Further research is needed to investigate its cost-effectiveness related to these potential health benefits.[3]

In conclusion, EOS 2D/3D imaging system is a very promising method that addresses several limitations of the current diagnostic means for various musculoskeletal disorders. However, at this time, EOS has limited clinical data and its ability to improve patient outcomes needs further investigation.[2,3] It is imperative that the orthopaedic community embraces the potential of this new imaging system and formally investigates its clinical effectiveness in patient management and long-term health outcomes.

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For Patients With Impingement Syndrome, is the Acromion Innocent?

[1]Shawn Bifano, BS
[2]Kevin B. Freedman, MD, MSCE
[3]Joseph Bernstein, MD
[2]Fotios Tjoumakaris, MD

[1]Thomas Jefferson Medical College, Philadelphia, PA

[2]Rothman Institute, Philadelphia, PA

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

Introduction

Subacromial impingement syndrome is one of the most common causes of shoulder pain.[1] When nonoperative measures fail to reduce the pain, patients may benefit from surgical decompression. When surgery is selected, the physician must consider the following question: what is the better procedure to perform: an acromioplasty (resection of bone) or bursectomy (resection of soft tissue)?

To help answer this question, we surveyed 500 experts in sports medicine, members of the American Medical Society for Sports Medicine and the American Orthopaedic Society for Sports Medicine and asked them if they agree with the statement, "In a patient with impingement syndrome of the shoulder to be treated surgically, 'the acromion is innocent' and unless there is a focal spur, no bone has to be removed."[2] Respondents were asked to register agreement or disagreement with that statement according to a seven point, centered and symmetrical scale ranging from, "The statement is false" (one point) to, "The statement is true" (seven points). For this particular statement, the mean score was 3.7, signifying that experts were more inclined to answer, "This statement may be true/false; 50-50." The mean score was higher for orthopaedic surgeons (4.4) than other correspondents (3.6). The distribution of the responses is shown in Table 1.

The purpose of this article is to review the role of the acromion in subacromial impingement syndrome, to share what the literature has to say about this topic, and lastly to attempt to interpret the expert responses in context.

Question

The etiology of subacromial impingement syndrome is not known with certainty. Some researchers believe that subacromial impingement syndrome is caused primarily by extrinsic (mechanical) compression,[3,4] whereas others believe that the syndrome is caused primarily by intrinsic tendon degeneration, with subacromial abutment of bone against the cuff being simply a manifestation of tendon dysfunction.[5,6] Because the etiology is unclear, there is no clearly preferred remedy. Surgeons advising patients who have failed nonoperative treatment can reasonably recommend an acromioplasty (resection of bone), bursectomy (resection of soft tissue only), or combined acromioplasty/bursectomy (resection of bone and soft tissue). Both bone and soft tissue operations can be justified on theoretical grounds.

The so-called extrinsic hypothesis of impingement syndrome hypothesizes that the impingement of the shoulder is due to downward pressure from the acromion pressing on the rotator cuff. This is the theory implicitly espoused by the name *impingement*, which comes from a Latin word *impingo* meaning "to force upon or press upon."[7] It has been suggested that prolonged impingement of the rotator cuff by the acromion will damage the surface of the cuff and eventually lead to a complete tear of the rotator cuff.[8] Accordingly, Neer's landmark paper in 1972 advised that impingement syndrome should be treated via anterior acromioplasty.[8]

Along those lines, morphological variations in the acromion and its effect on the rotator cuff were described by Bigliani *et al*.[9] They classified

Table 1. Distribution of responses to the statement "In a patient with impingement syndrome of the shoulder to be treated surgically, 'the acromion is innocent' and unless there is a focal spur, no bone has to be removed."

Percentage of respondents	indicating "The statement is false"	13%
Percentage of respondents	indicating "The statement is very likely to be false"	19%
Percentage of respondents	indicating "The statement is probably false"	16%
Percentage of respondents	indicating "The statement may be true/false; 50-50"	15%
Percentage of respondents	indicating "The statement is probably true"	14%
Percentage of respondents	indicating "The statement is very likely to be true"	15%
Percentage of respondents	indicating "The statement is true"	8%

Corresponding author:
Kevin B. Freedman, MD
Rothman Institute
Medical Arts Pavilion, Suite 200
825 Old Lancaster Avenue
Bryn Mawr, PA 19010
Kevin.freedman@rothmaninstitute.com

acromial morphology into three types: type I (flat), type II (curved), and type III (hooked). Hooked acromions were thought to be associated with a higher incidence of rotator cuff impingement and rotator cuff tears, an association that offers indirect evidence that the acromion is the primary abnormality in subacromial impingement.[9,10]

An alternative theory posits that intrinsic degeneration is the root cause of symptoms in patients with impingement. According to this theory, poor perfusion (due to hypovascularity) is the inciting factor,[5,6] and with it, the damage inflicted by repetitive use is not matched by necessary repair. It is only when the supraspinatus has degenerated and weakened to the point that it is no longer able to center the humeral head in the glenoid that the subacromial space narrows. That is, the cuff pressing against the undersurface of the acromion is an effect, not a cause of the disease. By that theory, physical impingement is a secondary phenomenon. If the intrinsic theory is correct, the appropriate procedure for impingement is to remove only the bursa (tissue known to be richly supplied by free nerve endings),[11] leaving the bone well enough alone.

The question then remains: which theory is correct? And in turn, assuming some surgery is needed, which procedure provides the most benefit? To those who argue that extrinsic compression is the cause, removing part of the acromion should most effectively rid the patient of symptoms. On the other hand, if the problem is caused by intrinsic factors, bursectomy alone should be equally effective and will prevent the complications that may result from unneeded interventions.

Existing Literature

Although subacromial impingement syndrome is the most common cause of shoulder pain, and although there is controversy surrounding the cause (and hence the more appropriate treatment), there is little data directly comparing acromioplasty to bursectomy alone. A thorough literature search reveals only one study directly comparing bursectomy to acromioplasty. Henkus *et al*[12] directly compared the results of bursectomy to acromioplasty in 57 patients suffering from impingement syndrome without a rotator cuff tear who failed conservative treatment. The investigators included patient age, gender, body mass index, type of acromion, and preclinical baseline clinical scores in the demographics. The Simple Shoulder Test score improved by 3.6 for patients treated by bursectomy alone and by 4.4 for patients treated with acromioplasty. The mean Constant score had a mean improvement of 13.9 for bursectomy alone as compared to a mean improved score of 18.5 for acromioplasty. Since patients with different acromions were not randomized into two different groups, a multivariate analysis was used to determine the effect of the procedure on each type of acromion. Type III acromions scored on average 12.6 points less in final Constant score[13] compared to type I acromions, whereas there were no differences between the type of acromion and the procedure performed in relation to improvement of clinical scores. The authors concluded from the data that the severity of symptoms at baseline and acromion type are better predictors of outcome than the procedure performed. Overall, there were no statistically significant differences between acromioplasty and bursectomy alone.

Donigan and Wolf completed a systematic review of the literature to determine if bursectomy or acromioplasty is better for impingement syndrome.[14] Only the aforementioned study[12] met the inclusion criteria and directly compared the outcomes of acromioplasty to bursectomy alone. The other studies they reviewed were case series demonstrating improved outcomes from acromioplasty, but there was no comparison to bursectomy alone. From this, Donigan and Wolf concluded that the surgical management of impingement syndrome "is an area that would benefit from prospective, randomized controlled studies using validated outcomes."

There are several studies evaluating the outcomes of acromioplasty for the treatment of subacromial impingement syndrome using open versus arthroscopic techniques;[16-19] both procedures show clinical improvement with surgery with no significant differences in overall outcome. Surgery may be the appropriate step in patients who fail a trial of nonsurgical treatment for impingement syndrome. Neer described an open acromioplasty in 1972, which has since become the gold standard open procedure.[8] He stated that the anterior portion of the acromion rubbing on the supraspinatus tendon needed to be removed. The primary goals of the open acromioplasty are to relieve pain and to prevent wear and degeneration of the rotator cuff and biceps tendon. Chin *et al*[15] reported the long-term outcomes in a 25-year follow-up to be 88% positive patient satisfaction. Comparisons were made to the opposite shoulder in this older patient group. There was a mean difference between the opposite shoulder and the operative shoulder in the Simple Shoulder Test with a score of 0.4,[13] with scores of 8.9 for the operative side and 9.3 for the opposite side.[15]

The literate is sparse regarding the outcome of bursectomy alone for the treatment of subacromial impingement syndrome. Budoff *et al*[20] conducted a retrospective study of 60 patients who underwent arthroscopic debridement without acromioplasty. The average follow-up was 114 months when they determined UCLA[13] score, Simple Shoulder test score,[13] residual pain, and ability to return to recreational activities. According to the UCLA score, there were 31 (50%) excellent and 18 (29%) good results. Of the 49 patients who decided to continue recreational activities, 28 (50%) could do so with no difficulties and 10 (20%) could continue. Budoff *et al* concluded that bursectomy and debridement alone provides effective treatment for subacromial impingement.[20]

There are, of course, some putative disadvantages to performing acromioplasty and coracoacromial ligament resection, as this operation disrupts the coracoacromial arch. Lazarus *et al*[21] showed the coracoacromial arch to be an important barrier to the subluxation of the humeral head in the anterosuperior direction. This has been suggested as a cause for rotator cuff pathology by Hsu *et al*.[22] For this reason alone, some surgeons believe a bursectomy is a better procedure.[9,10] In addition, it has been shown that disruption of the coracoacromial arch can lead to anterosuperior instability in patients with massive rotator cuff insufficiency.[23]

There have also been studies comparing the outcome of rotator cuff repair with and without acromioplasty. Gartsman and O'Connor[24] performed a prospective, randomized study with one-year follow-up comparing arthroscopic rotator cuff repair with and without acromioplasty for full-thickness tears of the supraspinatus tendon. The ASES score[13] was determined for both groups preoperatively and postoperatively. No statistical difference was shown between the ASES scores postoperatively for patients with and without acromioplasty.[24] It can be concluded from the data that an acromioplasty does not improve outcomes following arthroscopic rotator cuff repair. This study, albeit indirectly, lends credence to the belief that the rotator cuff is the source of pain in these patients and not painful impingement against the acromion.

In 2005, McCallister *et al*[25] found no difference with and without acromioplasty for full thickness tears in the supraspinatus with open rotator cuff repair in their prospective study. Results also showed that one-tendon tears of the supraspinatus had better outcomes in comparison to two-tendon and three-tendon tears of the rotator cuff,[25] once again showing that severity of symptoms might be a better predictor of outcome than whether or not bursectomy alone or acromioplasty is performed.

Expert Opinion

The mean score for "In a patient with impingement syndrome of the shoulder to be treated surgically, 'the acromion is innocent' and unless there is a focal spur, no bone has to be removed" was 3.7, which aligns most closely with the response "This statement may be true/false; 50/50." It is noteworthy that 32% of expert respondents rejected the statement; 13% selected "The statement is false" with an additional 19% answering "The statement is very likely to be false." On the other hand, 23% of the experts were supportive; 8% were certain that the acromion should be left alone, with an additional 15% voting "The statement is very likely to be true." That is, there was strong support for both extremes. This broad distribution of responses indicates that this statement is controversial. By that measure, the responses can be read as a call for more research to be completed or disseminated before a uniform standard of care can be adopted.

Future Research

The question, "When a patient with impingement syndrome of the shoulder fails nonoperative management and submits to surgery, should the procedure be an acromioplasty or simple bursectomy?" is a question unusually well-suited to analysis using the prospective, double-blinded, randomized trial approach.

Prospective, double-blinded, randomized trials in surgery are rare for many reasons. It is hard to blind patients who have had surgery to what was done, and it is often hard to justify randomizing patients, as there is often some consensus, justified or not, that one treatment is superior. These objections may not apply to the case of impingement syndrome. With an arthroscopic approach, patients can truly be blinded to what was done. Also, the counseling physician can genuinely assert that there are theoretical benefits to both approaches, yet the superiority of one over the other is not known. The only justification we can suggest for not doing this study is that the costs (and hassles) of the study may not justify the clinical benefits of discovering which treatment is better. On the whole, because such a trial could also help answer some fundamental questions regarding the etiology of the condition, with implications for nonoperative management as well, such a trial should be done. Furthermore, there is a bigger and better question to be addressed, namely, should *any* surgery be employed for impingement syndrome? To answer that question, a placebo arm wound need to be added to the trial, and such a trial is indeed burdened by traditional objections.

Conclusion

The expert panel was ambivalent in its support of the statement, "In a patient with impingement syndrome of the shoulder to be treated surgically, 'the acromion is innocent' and unless there is a focal spur, no bone has to be removed." Likewise, the medical literature does not provide a definitive answer. There are very few studies directly addressing the question posed. Until such data are available, either approach (resecting bone or not) would be justified.

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Overuse Following a Large Rotator Cuff Tear Alters Trabecular Bone Architecture but Not Glenoid Curvature in a Rat Model

Michael W. Hast, PhD
Sarah Yannascoli, MD
George W. Fryhofer
Wei-Ju Tseng
Allison Altman, PhD
X. Sherry Liu, PhD
Louis J. Soslowsky, PhD

University of Pennsylvania,
Philadelphia, PA, USA

Introduction

Rotator cuff tears are common shoulder injuries that cause significant pain and often require surgical intervention and physical therapy. Reestablishment of normal shoulder kinematics is often difficult and relies on balancing the active muscle forces and passive contact forces between the glenoid and the humeral head.[1] Previous studies have determined that damage to the rotator cuff tendons leads to alterations of subchondral mineralization patterns at the glenoid joint surface[2,3] with significant regional changes in articular cartilage thickness.[4] However, the influence of repetitive loading following a large rotator cuff tear on the glenoid surface geometry or underlying bony architecture has not been determined. Therefore, the purpose of this study was to utilize an established rat model[5] to analyze changes in the geometry of the glenoid articular cartilage and trabecular bone structure when a rat undergoes a supraspinatus and infraspinatus tear and is subsequently required to overuse the injured shoulder. We hypothesized that the presence of a rotator cuff tear will not affect the geometry of cartilage or underlying bony architecture in rats that are allowed to return to cage activity; however, repetitive overuse following the rotator cuff tear will result in significant changes of the geometry of articular cartilage surface and alterations in bony architecture.

Methods

Experimental Design and Sample Preparation

Twenty-three Sprague-Dawley rats were used in this study (IACUC approved). Four rats were used as controls (CTL) and the remaining animals were subjected to a 2 week training period followed by 4 weeks of overuse treadmill activity to create a tendinopathic condition as described.[5] A unilateral detachment of the supraspinatus and infraspinatus tendons was then surgically created to model an acute on chronic injury. Following surgery, animals were returned to cage activity (CA; n=10) or progressively returned to treadmill overuse (OV; n=9). All rats were sacrificed 8 weeks after surgery and frozen at −20°C until testing.

Micro-CT Analysis

Following sacrifice, the left glenoid of each rat was carefully dissected free of all soft-tissue attachments and potted in a custom acrylic cylinder secured with polymethyl-methacrylate, leaving the glenoid fossa exposed. The glenoid cartilage was stained with Lugol's solution and each specimen was aligned such that the superior glenoid was parallel to the floor within a μCT system (VivaCT 40, Scanco Medical, 10.5 μm voxel size). μCT scan volumes were determined by choosing a point at the nadir of glenoid concavity and analyzing 100 slices above and below (for a total of 200 slices) the level of the subchondral bone. A rectangle was drawn to fit the glenoid at the nadir of concavity and sectioned into four equal quadrants for analysis of the anterosuperior (AS), anteroinferior (AI), posterosuperior (PS), and posteroinferior (PI) glenoid regions. Trabecular analysis was then completed for each of the 4 regions (AS, AI, PS, PI) individually, and as a whole (Total). Variables of interest include bone volume fraction (BV/TV), tissue mineral density (TMD), trabecular number (Tb.N), trabecular thickness (Tb.Th), and structural model index (SMI).

Glenoid Surface Geometry

ITK-SNAP[6] and MeshLab[7] were used to create three-dimensional (3D) surface representations of the glenoid cartilage from μCT data. The 3D models were split into two separate surfaces to represent the bony and articular cartilage surfaces of the glenoid. A boolean function was employed in Meshlab to remove faces with normals that exceeded predetermined convexity inflection limits. The resulting bony and articular geometries were transformed into interpolated surfaces, and spheres were fit to the concave surfaces representing the four quadrants (AS, AI, PS, PI) and the entire glenoid (Total).

Statistics

Statistical differences were evaluated with an ANOVA followed by planned comparisons between groups (CTL vs CA and CA vs OV to test study hypotheses) using two-tailed t-tests with significance set at $p<0.05$ and trends set at $p<0.10$.

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mike.hast@gmail.com

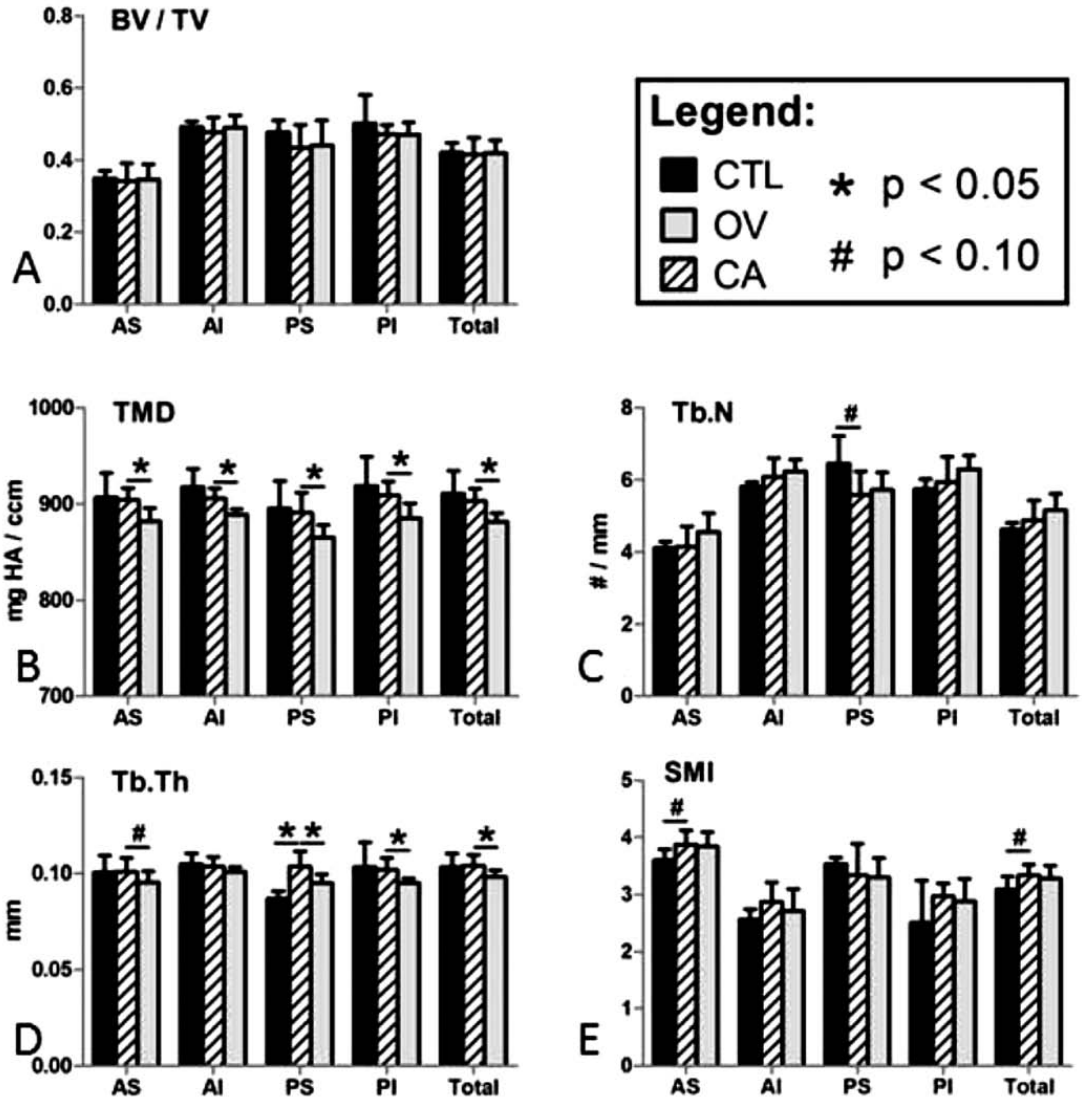

Figure 1. Trabecular analysis for bone colume fraction (A), tissue mineral density (B), trabecular number (C), trabecular thickness (D) and structureal model index (E) in four quadrants of the glenoid (AS, AI, PS, PI) and as a whole (Total). Decreases in Tb.Th and TMD may indicate the degeneration of bone due to overuse after injury.

Results

Trabecular Bone Measurements

BV/TV (Figure 1A) and TMD (Figure 1B) of the trabecular bone stock in the glenoid were not affected by the presence of a rotator cuff tear. However, a decrease (trend) in Tb.N (Figure 1C) and an increase (significant) in Tb.Th (Figure 1D) in the PS region was seen. CA Rats also exhibited an increase (trend) in SMI in the AS region and in the overall bone volume (Figure 1E). The addition of overuse loading did not change BV/TV (Figure 1A), Tb.N. (Figure 1C), or SMI (Figure 1E). Significant decreases in TMD (Figure 1B) and Tb.Th (Figure 1D) were measured in rats that returned to overuse following injury.

Geometric Measurements

Surprisingly, there were no significant differences between groups for radii of curvature for the glenoid bone or cartilage surfaces (Figure 2).

Discussion

The results confirm our hypothesis that repetitive loading following rotator cuff rupture results in altered architectural properties of trabecular bone. Recent studies have related microstructural changes in trabecular bone to bone mineral density measurements as a surrogate for the "loading history" of the glenoid.[2] In the current study, μCT analysis has improved our ability to understand the adaptations of glenoid bone in response to rotator cuff tears and its response to subsequent rehabilitation protocols. Specifically, when comparing CTL to CA, it is notable that the PS region was the only area in which a decreasing trend in Tb.N was measured. Interestingly increases in Tb.Th were measured in the same region, which may be indicative of a compensatory mechanism taking place to account for losses in Tb.N.This change in bony architecture may be a result of the CA rats favoring the injured limb, and therefore decreasing the frequency and magnitude of ground reaction force vectors passing through this region. When

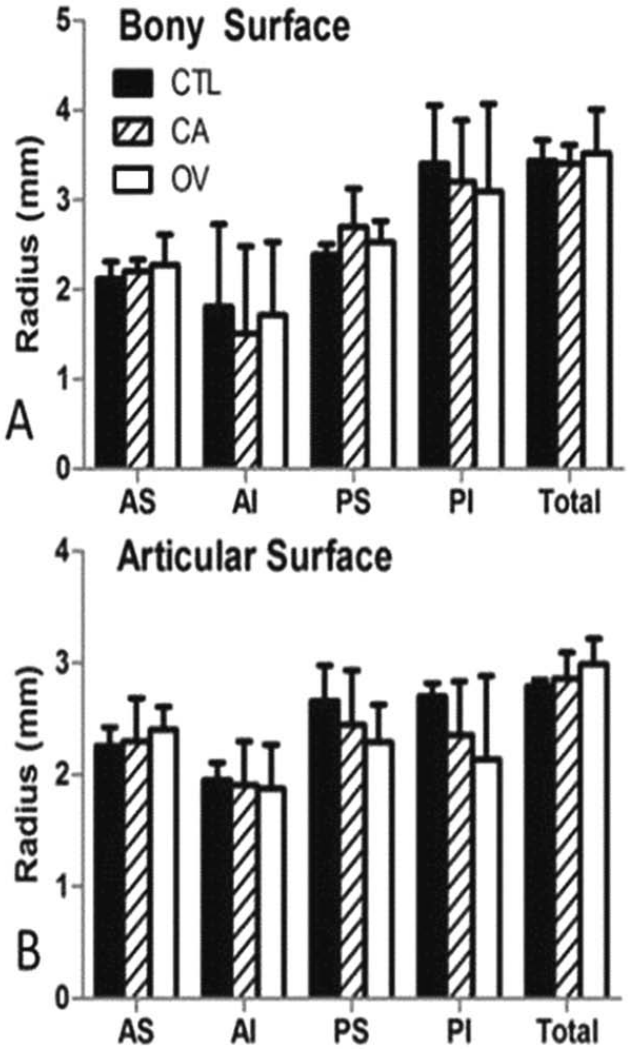

Figure 2. Sphere-fitting the concave regions of the bony (A) and articular cartilage (B) surfaces for four quadrants of the glenoid (AS, AI, PS, PI) and as a whole (Total). No changes were seen in bony or articular surface geometry as a result of injury or overuse.

comparing CA to OV, quantitative assessment of trabecular structures shows decreases in Tb.Th paired with decreases in TMD. This phenomenon is indicative of an undesirable loss of mechanical strength of the bone structure in the OV rats, though this is yet to be confirmed by direct testing.

The results of this study did not support our hypothesis that overuse after injury would alter the geometry of the glenoid. We successfully fit spheres to surfaces representing the glenoid bone and articular cartilage, and no alterations in the radius of the bone or the articular cartilage were observed. While the overall shape of the bone and cartilage surfaces are unaffected by repetitive overuse, changes are clearly occurring in the underlying trabecular bone stock.

Significance

Our study demonstrates that a return to activity after a large rotator cuff tear may be detrimental to the mechanical properties of the underlying trabecular microstructure, but the return to overuse did not have a significant effect on the glenoid surface curvature. This study has increased our knowledge of the effects of loading on the shoulder joint following a rotator cuff tear, but the longitudinal implications of such a scenario remains unclear. Follow-up *in vivo* studies that include mechanical testing at varied time points throughout a longer term will be necessary.

Acknowledgments

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Collagen V Null Mice Have Decreased ACL Mechanical Properties and Altered Fibril Morphology

[1]Brianne K. Connizzo
[1]Benjamin R. Freedman
[2]Mei Sun
[2]David E. Birk
[1]Louis J. Soslowsky, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]University of South Florida College of Medicine, Tampa, FL, USA

Introduction

Classic (type I) Ehlers-Danlos Syndrome (EDS) is a rare genetic disease associated with mutations in collagen V.[1] The most common mutations result in a single null COL5A1 allele and haploinsufficiency. Patients with classic EDS exhibit connective tissue hyperelasticity and laxity, suggesting a key role for collagen V in soft tissue function. While collagen V is a quantitatively minor (~2%) component of collagen fibrils in tendons and ligaments, modulation of its expression has dramatic phenotypic effects, indicating critical regulatory roles.[2] In addition, collagen V has been linked to injury,[3] performance deficiencies,[4] Achilles tendinopathy,[5] and anterior cruciate ligament (ACL) rupture.[6] The ACL is the most commonly injured ligament of the knee, with approximately 80,000 surgical repairs per year, resulting in an estimated cost of over one billion dollars.[7] Understanding the structure-function relationships in the ACL could provide valuable insight into mechanisms of matrix maintenance, as well as joint laxity, injury and repair. Therefore, the purpose of this study was to investigate the regulatory roles of collagen V on the mechanical properties and fibril morphology of the mouse ACL using collagen V haploinsufficient and null mouse models. We hypothesized that mechanical properties would be reduced, fibril diameter would be increased, and fibril density would be decreased compared to wild type ligaments when collagen V is reduced or absent in ACLs.

Methods

Mice from two genotypes, Col5a1+/+ (Wild Type, n=19) and a tendon/ligament-specific conditional knockout, ScxCre+Col5a1−/− (Col5a1 KO, n=10) were sacrificed at P60 (IACUC approved).[8] Hind limbs were detached and dissected free of soft tissue leaving only the knee joint intact. Surrounding ligaments, menisci, and soft tissue were carefully removed to expose the ACL and then surrounding soft tissue was carefully trimmed, leaving only the femur-ACL-tibia complex intact. Under a microscope, the ACL was imaged in the coronal and sagittal planes for area measurement. Verhoeff's stain was applied to both insertions of the ACL for optical strain tracking. The femur and tibia were affixed at 60 degrees of flexion in custom fixtures using PMMA (Figure 1). The ACLs were mechanically tested with a standard protocol consisting of preconditioning, stress relaxation and a constant ramp to failure. Cross-sectional area was calculated assuming an ellipsoidal shape from microscope images. Local strain was measured optically and mechanical parameters were calculated using custom software. ACLs from 4 additional mice at P30 of each genotype were analyzed for fibril morphology at 80 kV using transmission electron microscopy.[9] Images were captured at 60,000X and transferred to RM Biometrics-Bioquant software. Fibril diameter analyses were performed using a region of interest (ROI) from images across the central portion of the ACLs. Fibril diameters were determined along the minor axis of the fibril profile. Fibril density was defined as the total number of fibrils within the ROI. Statistics. Comparisons were made using Student's t-tests with significance set at $p<0.05$ and a trend defined at $p<0.10$.

Results

Cross-sectional area was not different between the control and the knockout ACLs (Figure 2A). Maximum load, stiffness, modulus (significant, Figure 2B-D), maximum stress (trend, not shown), and percent relaxation (trend, not shown) were decreased in the knockout group. In addition, the

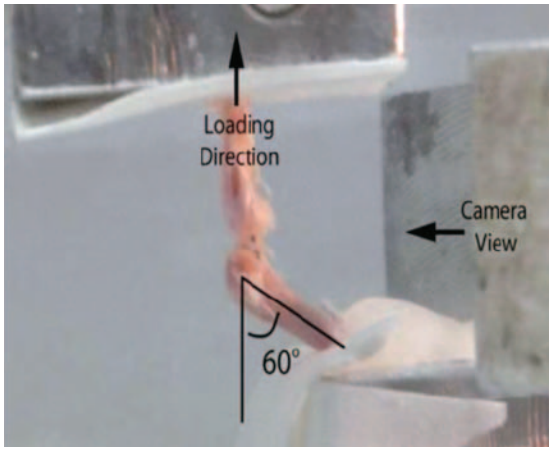

Figure 1. Mechanical testing setup of the tibia-ACL-femur complex.

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connizzo@seas.upenn.edu

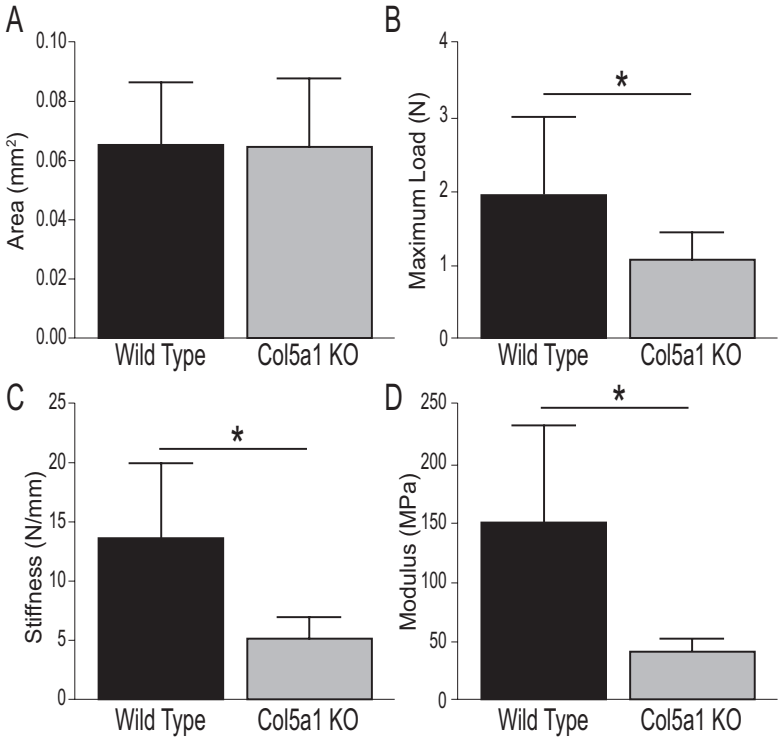

Figure 2. (A) There were no differences in cross-sectional area between groups. (B) Maximum load was decreased when comparing the knockouts to the wild type. (E) Stiffness and (F) modulus were both also decreased in the knockout group when compared to the wild type group. Results are presented as mean ± standard deviation with *p<0.05.

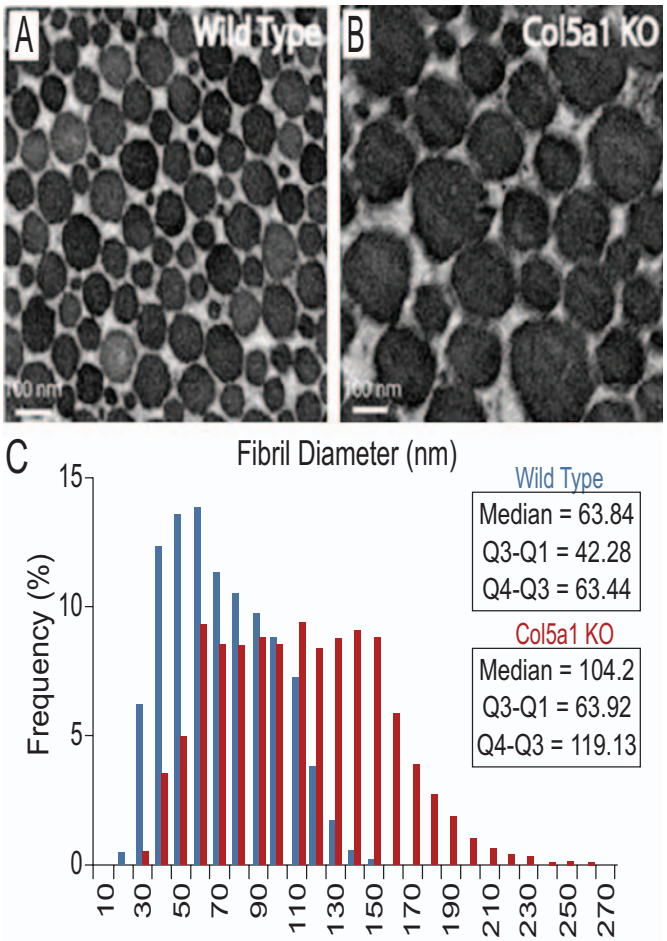

Figure 3. Representative images of fibril morphology in (A) wild type and (B) knockout ACLs confirm quantitative measurements. (C) Fibril diameter distributions shifted towards a broader profile with more larger diameter fibrils. There was a significant increase in fibril diameter in the knockout group when compared to the control group.

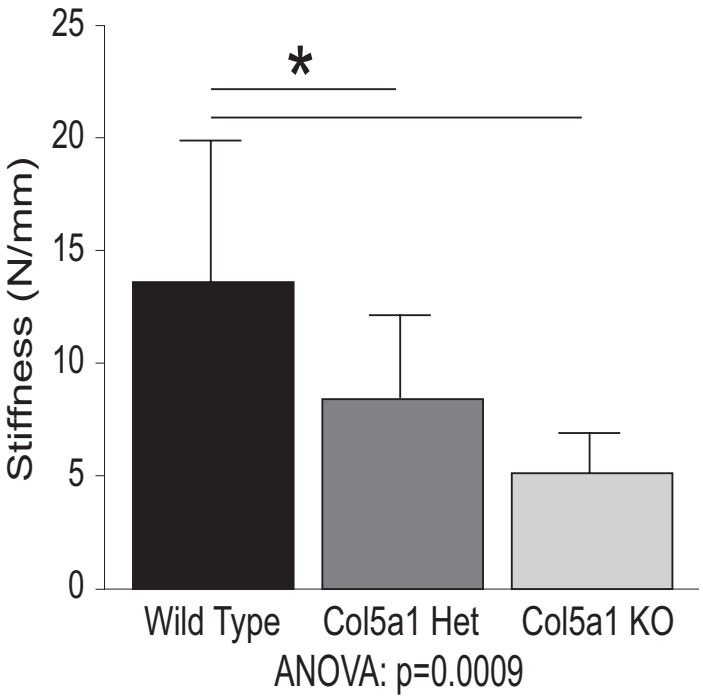

Figure 4. Stiffness was decreased in heterozygous and knockout ACLs. Other mechanical parameters had similar trends in the data.

distribution of fibril diameters was shifted towards increased larger diameter fibrils and a broader profile (Figure 3) in the knockout group. Fibril diameters were significantly larger and fibril density was significantly decreased in the knockout ACLs (not shown).

Discussion

Despite being a quantitatively minor component of the extracellular matrix, removal of collagen V resulted in severely decreased mechanical properties and altered fibril morphology, confirming that collagen V plays a critical role in the ACL. While these mechanical and structural results are consistent with previous work in the FDL,[10] the mechanical changes in the ACL were much more dramatic than the changes in the FDL,[10] suggesting that collagen V may play a larger role in the ACL. Since the ACL acts primarily as a joint stabilizer during knee movement, collagen V could play a key role in tissue laxity or elasticity. In the mouse model of EDS (Col5a1 heterozygous mouse), ACL mechanical evaluation showed that reduction of collagen V decreases ACL stiffness (and other mechanical parameters) in a dose-dependent manner (Figure 4), suggesting that some EDS-related joint laxity may be attributed to the functional deficiencies in the stabilizing soft tissues. Further investigation is necessary to elucidate other functional alterations in collagen V deficient tendons such as their viscoelastic and fatigue responses. In addition, investigation into the role of collagen V during injury, healing, and aging could aid in determining specific mechanisms by which collagen V regulates fibrillar structure and function.

Significance

This study demonstrated that collagen V plays a crucial role in the structure and function of the ACL. More broadly, this study confirms altered structure and function of joint stabilizing components that suggest further research in collagen V deficient tendons and ligaments, such as in EDS, is necessary.

Acknowledgments

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Evaluating Changes in Tendon Crimp with Fatigue Loading as an Ex Vivo Structural Assessment of Tendon Damage

Benjamin R. Freedman
Andrey Zuskov
Joseph J. Sarver, PhD
Mark R. Buckley
Akash Kumar
Louis J. Soslowsky, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Since many tendons operate at high and repeated loads, fatigue-induced damage is a likely contributing factor for tendon rupture. Previous studies have used various imaging modalities to study the accumulation and progression of fatigue-induced damage.[1,2] However, such methods have not been used to evaluate load and region dependence simultaneously on the entire tissue, and, in addition, can be costly and time consuming. We have developed a novel, ex vivo imaging method to study fascicle-level crimp using polarized light imaging. This technique has been used to directly measure tendon crimp (e.g., to assess the dynamics of collagen uncrimping and lateral contraction, and the effect of ionic concentration),[3] but has not yet been applied to the evaluation of structural damage via fatigue loading. Therefore, the objective of this study was to measure regionally-dependent, fatigue-induced changes in crimp frequency in the mouse patellar tendon using polarized light imaging. We hypothesized that crimp properties would show regional differences, increase with fatigue damage, and correlate with mechanical properties assessed during fatigue loading.

Methods

Ten patellar tendons from 10 C57BL/6 mice at P120 were used (IACUC approved). Following tissue harvest, surrounding musculature was removed and the patella-patellar tendon-tibia unit was carefully prepared for mechanical testing. Cross-sectional area was measured using a laser device.[4] Tendons were fatigue tested using a sinusoidal waveform, oscillating at 1Hz, between 2 and 4N (~30-75% of ultimate failure load) (Figure 1A), while being imaged with a crossed polarizer system.[3] After preconditioning, images were captured at 3 loads (0.1, 0.5, and 2.0 N) (Figure 1B), at 10, 25 and 50 cycles, and every subsequent 100 loading cycles. These 3 loads were chosen to approximate the toe, transition, and linear portions of the patellar tendon force-displacement curve (Figure 1B).

To quantify tendon crimp (Figure 1C), a region of interest (ROI) of visible tendon crimp was chosen. Since it was expected that crimp properties would show regional dependence,[5] two specific ROIs were chosen (tendon center (N=10) and lateral portions (N=9)) for analysis in this study. These same ROIs were used for the analysis of all images throughout

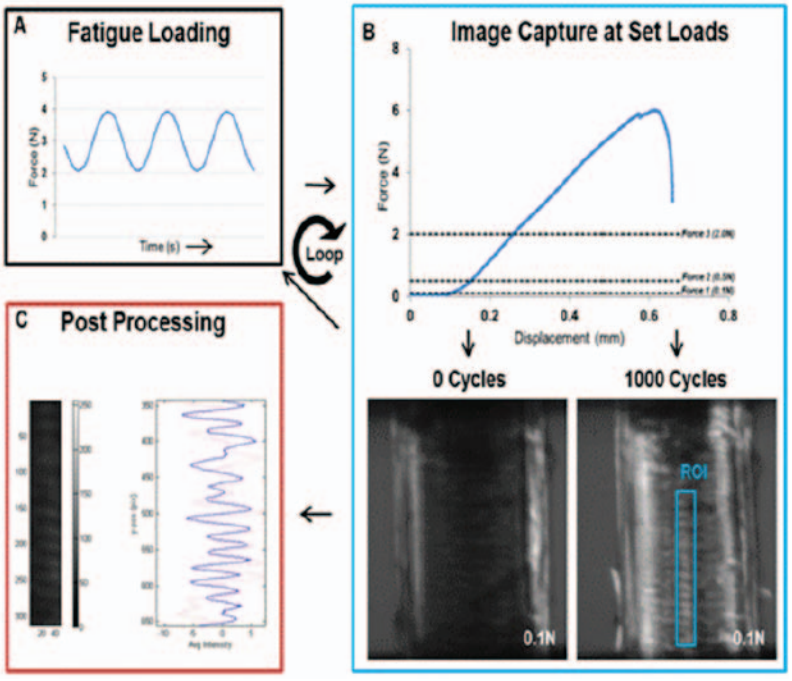

Figure 1. Mechanical testing and imaging capture flow chart: (A) Tendons were fatigue loaded between 2 and 4N with a sinusoidal waeform. (B) After 10, 25, 50, and 100 cycle intervals of fatigue loading, images were captured at threee loads (0.1, 0.5, and 2.0N) to quantify tendon crimp properties. This process was repeated until tendon failure or tendons reached 7500 cycles. (C) ROIs were low pass filtered to enhance the visibility of light and dark bands and intensities were averaged across the ROI width (red dashed line) before being highpass filtered (blue line). From these spectra, the crimp frequency (F_{cr}) and cumulative spectral power (CSP) were computed.

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freedman.br@gmail.com

the fatigue life from mechanical testing of the particular specimen. A Gaussian low-pass filter was applied to the image within the ROI to enhance the visibility of light and dark bands (Figure 1C) using a custom MATLAB program.[3] Next, intensity values were averaged across the ROI width to give an intensity profile as a function of the vertical axis of the region that was then high-pass filtered. The spectral power was determined using the Fast Fourier Transform (FFT), which in turn was integrated to determine the cumulative spectral power (CSP). Finally, the crimp frequency (Fcr) was determined by taking the frequency at mean spectral power. Throughout specimen fatigue life, the CSP was evaluated at the Fcr to provide a measure of average crimp amplitude. All post-processing procedures were completed for all images acquired throughout specimen mechanical fatigue testing. Repeated measures ANOVAs followed by paired T-tests with Bonferroni corrections ($p<0.05$) were used to evaluate the effects of the change in CSP and Fcr (ΔCSP and ΔFcr) following fatigue loading. Single linear regressions were evaluated to determine if mechanical fatigue properties (peak cyclic strain, tangent stiffness, hysteresis, modulus, and damage (defined previously[6] as the ratio of displacement from gauge length at a set threshold to the tissue displacement and displacement at a set threshold after the first cycle of fatigue loading)) were correlated to ΔCSP or ΔFcr.

Results

As hypothesized, fatigue loading resulted in increased regional dependent crimp property differences. In particular, the lateral region of the tendon demonstrated a larger increase in ΔCSP after 10, 100, and 1000 cycles of fatigue life at both 0.1N and 0.5N than the center region ($p<0.001$), but not at 2.0N (Figure 2). ΔFcr only demonstrated regional differences after 1000 cycles at 0.1N and after 100 and 1000 cycles at 0.5N ($p<0.01$) (Figure 3). Both the center and lateral regions of the tendon showed a dramatic increase in ΔCSP with fatigue loading and at all loads evaluated (Figure 2) ($p<0.006$). ΔFcr decreased with fatigue loading at both 0.1N and 0.5N, but only in the center region (Figure 3) ($p<0.001$). In the center region, ΔCSP was moderately correlated ($r= 0.68$-0.75 ($p<0.001$)) to tendon mechanical damage at all loads. In the lateral region, ΔCSP was moderately to strongly correlated ($r=0.68$-0.86

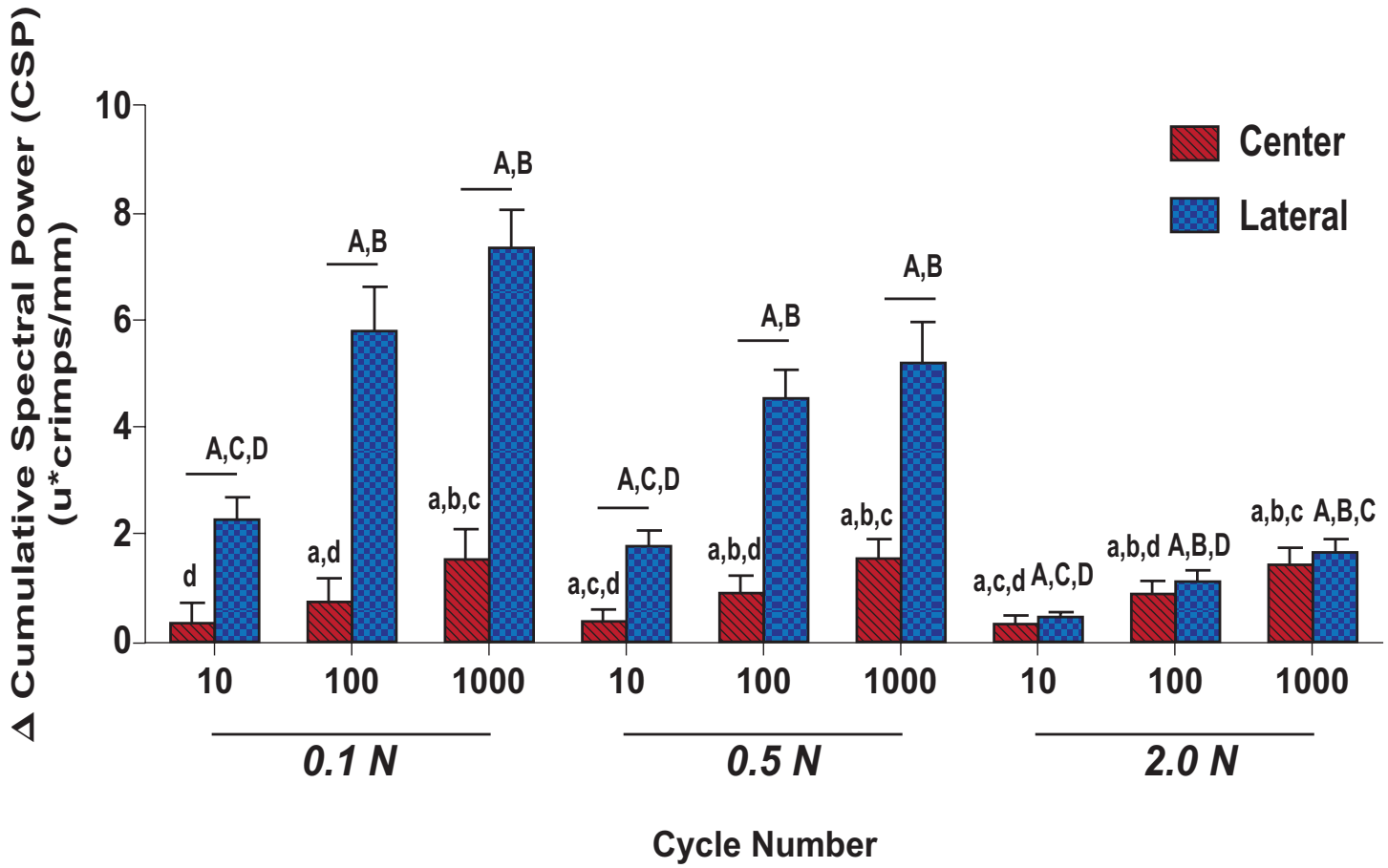

Figure 2. Δ cumulative spectral power (ΔCSP) increased with fatigue loading when assessed at three different loads (0.1, 0.5 and 2.0N) representative of the toe, transition and linear portions of the force-displacement mechanical testing curve. Bars indicate significant paired differences between the center and lateral ROIs for a tendon after 10, 100 or 1000 cycles of fatigue loading "u" indicates and intensity unit ranging between 1 and 256, "a, b, c, d" indicate significant differences in the center ROI when compared to 0,10, 100 and 1000 cycles respectively. "A, B, C, D" indicate significant differences in the lateral ROI when compared to 0, 10, 100, and 1000 cycles, respectively.

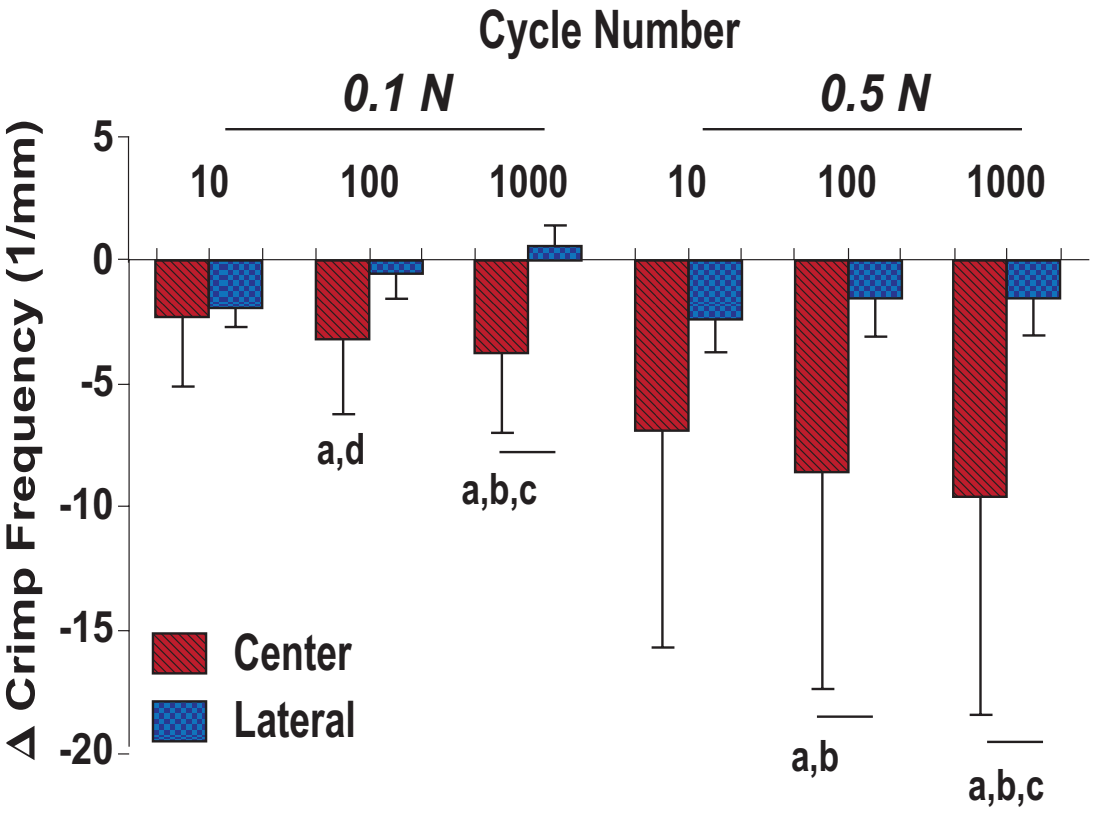

Figure 3. Δ Crimp frequency (ΔF_{cr}) decreased with fatigue loading when assessed at two different loads (0.1 and 0.5n) representative of the toe and transition potons of the force-displacement mechanical testing curve. Bars indicate significant paired differences between the center and lateral ROIs for a tendon after 10, 100, or 1000 cycles of fatigue loading. "a, b, c, d" indicate significant differences in the center ROI when compared to 0, 10, 100, and 1000 cycles, respectively. ΔF_{cr} was not significantly different in the lateral ROI when compared at 0, 10, 100 and 1000 cycles, respectively.

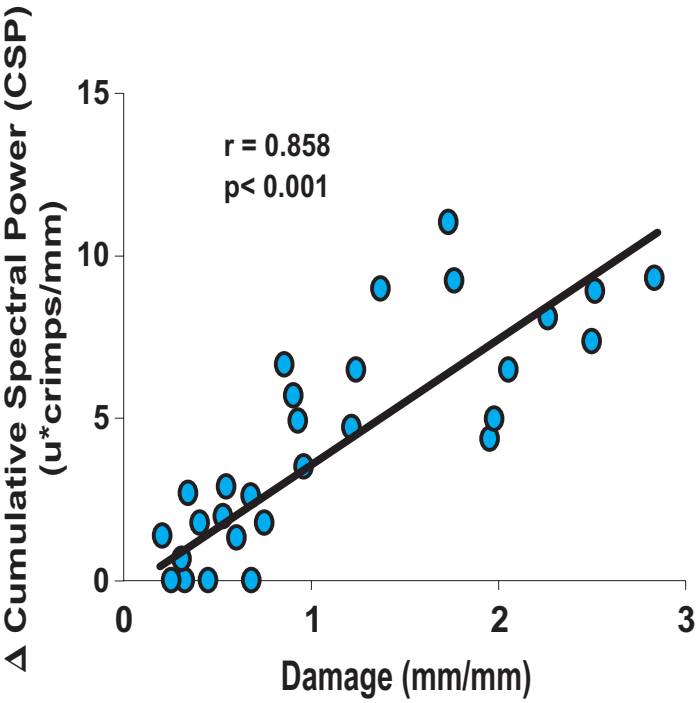

Figure 4. Tendon damage (defined as the ratio of displacement from gauge length at a set threshold to the tissue displacement and displacement at a set threshold after the first cycle of fatgue loading) was strongly correlated to the change in cumulative spectral power (ΔCSP) at 0.1N as assessed at 0, 10, 100 and 1000 cycles of fatigue life. This same relationship held at both higher loads (0.5N and 2.0N). "u" indicates an intensity unit ranging between 1 and 256.

($p<0.001$) (Figure 4)) to tendon mechanical damage at all loads. In addition, ΔFcr was moderately correlated to tendon dynamic modulus, but only at 0.5N ($r= -0.55, p<0.001$).

Discussion

This study characterized patellar tendon crimp and mechanical properties during fatigue loading. The decrease in Fcr observed after fatigue loading may indicate the initial increase in stiffness observed during fatigue testing.[7] The ΔCSP showed region specific changes as it increased with induction of fatigue loading, but region specific differences were muted at high loads. This supports the concept that crimp remains a primary factor at lower loads in the toe/transition regions of mechanical loading, but this response may be altered with the induction of fatigue loading. Furthermore, the regional difference in uncrimping across the tendon width, supports the observation that the structural response of collagen fibrils to loading is non-uniform.[5] Although the specific structural mechanisms leading to failure were not investigated, recent studies have suggested that repeated subrupture loading results in fibril kinks that occur at distinct spacing intervals at the nanostructural level.[2,8] Such changes in nanostructure have been shown to primarily occur early during repeated loading,[2] which was also observed in this study for ΔCSP. The strong relationship between ΔCSP and damage with fatigue loading as assessed at multiple loads through mechanical testing demonstrated both the utility of damage[7] as a parameter for

modeling the response of patellar tendon fatigue loading and ΔCSP as a contributing factor to the mechanism governing the progression of tendon damage. Interestingly, in some lateral regions, the patterns of crimp frequency mirrored increases in cyclic peak strain with fatigue loading. This suggests that localized regions of tissue may be experiencing a failure response that may not have been detected with the current method. Thus, future work will investigate crimp parameters at several regions throughout the tendon width to elucidate the specific locations of failure. Such changes may also be incorporated into structural fit fiber recruitment models to study cases of tendon damage.[9]

Significance

Knowledge of tendon structural and mechanical properties throughout fatigue loading remains critical in elucidating the mechanics of subrupture damage accumulation and ultimate failure. Such information may lead to improved diagnostic imaging methods based on tissue-level structural measures to assess injured and healing tendons, which may ultimately improve patient monitoring and recovery.

Acknowledgments

This study was supported by the NSF GRFP and NIH/NIAMS. We thank Michael Hast, PhD for discussion.

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Scapular Dyskinesis is Detrimental to Shoulder Tendon Properties and Joint Mechanics in a Rat Model

Katherine E. Reuther
Stephen J. Thomas, PhD, ATC
Jennica J. Tucker
Sarah M. Yannascoli, MD
Adam C. Caro, DVM
Rameen P. Vafa
Andrew F. Kuntz, MD
Louis J. Soslowsky, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Shoulder injuries including rotator cuff and biceps tendinitis are common clinical conditions and are a significant source of pain and dysfunction.These tendinopathic conditions are frequently seen in the presence of abnormal scapulothoracic joint kinematics.[1,2,3] Specifically, altered scapular motion and position (termed scapular dyskinesis) has been observed in 68-100% of patients with shoulder injuries,including shoulder impingement.[1] However, the cause and effect relationships these mechanical alterations have on the shoulder joint are unknown and therefore, it is unclear whether abnormal scapulothoracic joint kinematics contributes to (or instead compensates for) these disorders. Therefore, the objectives of this study were to examine the effect of scapular dyskinesis on the initiation and progression of pathological changes in the rotator cuff and biceps tendon and to define the mechanical processes that lead to these changes.We hypothesized that scapular dyskinesis will: H1) alter joint function and passive joint mechanics and H2) permanently diminish supraspinatus and biceps tendon mechanical properties.

Methods

A rat model of scapular dyskinesis was developed and 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. 60 adult male Sprague-Dawley rats (400-450 grams) were randomized into two groups: nerve transection (SD) or sham nerve transection (Control).All rats were sacrificed at 4 or 8 weeks after transection and frozen at −20°C. Forelimb gait and ground reaction forces were quantified over time in all animals using an instrumented walkway.[4] Data was collected one day prior to nerve transection to obtain baseline values and then collected at days 3, 7, 14, 28, 42, and 56 post-surgery. Ground reaction force data, including medial/lateral (ML), propulsion, braking, and vertical forces were collected for each walk. Parameters were normalized to the animal's body weight.

Passive shoulder joint range of motion and stiffness were measured over time using a custom instrument and methodology.[5] Parameters were normalized to baseline. Measurements were taken one day prior to nerve transection, and at days 14, 28, and 56 days post-surgery. Briefly, under anesthesia, the arm was secured into the rotating clamp at 90° of elbow flexion and 90° of glenohumeral forward flexion. The scapula was manually stabilized in order to isolate glenohumeral motion.The arm was then rotated through the full range of internal and external rotation three times. Range of motion was determined using data from all three cycles. A bilinear fit was applied to calculate joint stiffness in the toe and linear regions for both internal and external rotation.

At the time of testing, the animals were thawed and the scapula and humerus were dissected with the biceps and supraspinatus tendons intact. Stain lines, for local optical strain measurement, were placed on the supraspinatus and biceps tendons. Cross sectional area was measured using a custom laser device. To determine biomechanical properties, tensile testing was performed as follows: preload to 0.08 N, preconditioning (10 cycles of 0.1-0.5 N at a rate of 1% strain/s), stress relaxation to 4% (biceps) or 5% (supraspinatus) strain at a rate of 5% strain/s for 600s, and ramp to failure at 0.3% strain/s. Stress was calculated as force divided by initial area, and 2D Lagrangian optical strain was determined from stain line displacements measured using custom texture tracking software.

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. Significance was set at $p<0.05$.

Results

Gross observational examination demonstrated clear alterations in scapular movements, consistent with scapular "winging."

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katie.reuther@gmail.com

Additionally, joint function was significantly altered in the SD group (Figure 1). Specifically, ML force was significantly altered at early time points (5 and 7 days post-transection), with the SD group demonstrating less of a laterally directed force than control (Figure 1A). No differences between groups were observed in braking force (Figure 1B). However, propulsion force was significantly increased and vertical force was significantly decreased at all time-points compared to control (Figure 1C, 1D). Passive joint mechanics were also significantly altered (Table 1). Internal range of motion was significantly greater in the SD group compared to control at all post-surgical time-points. No other differences were observed, except for an increase in toe region stiffness in external rotation in the SD group compared to control at 4 weeks post-surgery.

In the presence of scapular dyskinesis, viscoelastic parameters were significantly altered (Figure 2). Tendon percent relaxation was significantly greater in the SD group compared to control at 8 weeks, for both the biceps and supraspinatus tendons, indicative of inferior tissue properties (Figure 2A). No differences were observed in any tendon for cross-sectional area (data not shown) or insertion elastic modulus (Figure 2B). However, tendon mid-substance elastic parameters were significantly altered. Tendon mid-substance elastic modulus was significantly decreased in the SD group compared to control, at both 4 and 8 weeks for the supraspinatus and at 8 weeks for the biceps, also indicative of inferior tissue properties (Figure 2C).

Discussion

While the prevalence of shoulder impingement and its association with scapulothoracic kinematic abnormalities is well-documented,[3] the cause and effect relationships behind them are not well-established, making optimal clinical management difficult. In this animal model, we were able to prescribe scapular dyskinesis and rigorously evaluate the effect in a controlled manner. Results of this study demonstrate that scapular dyskinesis alters joint loading and leads to compromised tendon mechanical properties. The changes observed in the presence of scapular dyskinesis may be a result of reduced subacromial space, leading to tendon mechanical abrasion and wear. Tendon changes were localized to the mid-substance region, likely due to its anatomic location underneath the acromial arch during forward flexion, resulting in tendon impingement. Additionally, the increased internal range of motion observed may be due to a loss of dynamic restraint. The unstable scapula may not allow the rotator cuff to effectively compress the humeral head into the glenoid fossa thereby requiring the joint to rely on static restraints, such as the joint capsule, for stability and placing it at increased risk for injury. This is the first study to directly identify scapular dyskinesis as a mechanical mechanism for the development of pathological changes in the rotator cuff and biceps tendon. Future studies will examine the effect of scapular dyskinesis in the presence of overuse and following supraspinatus repair in order to help define the in vivo mechanical processes

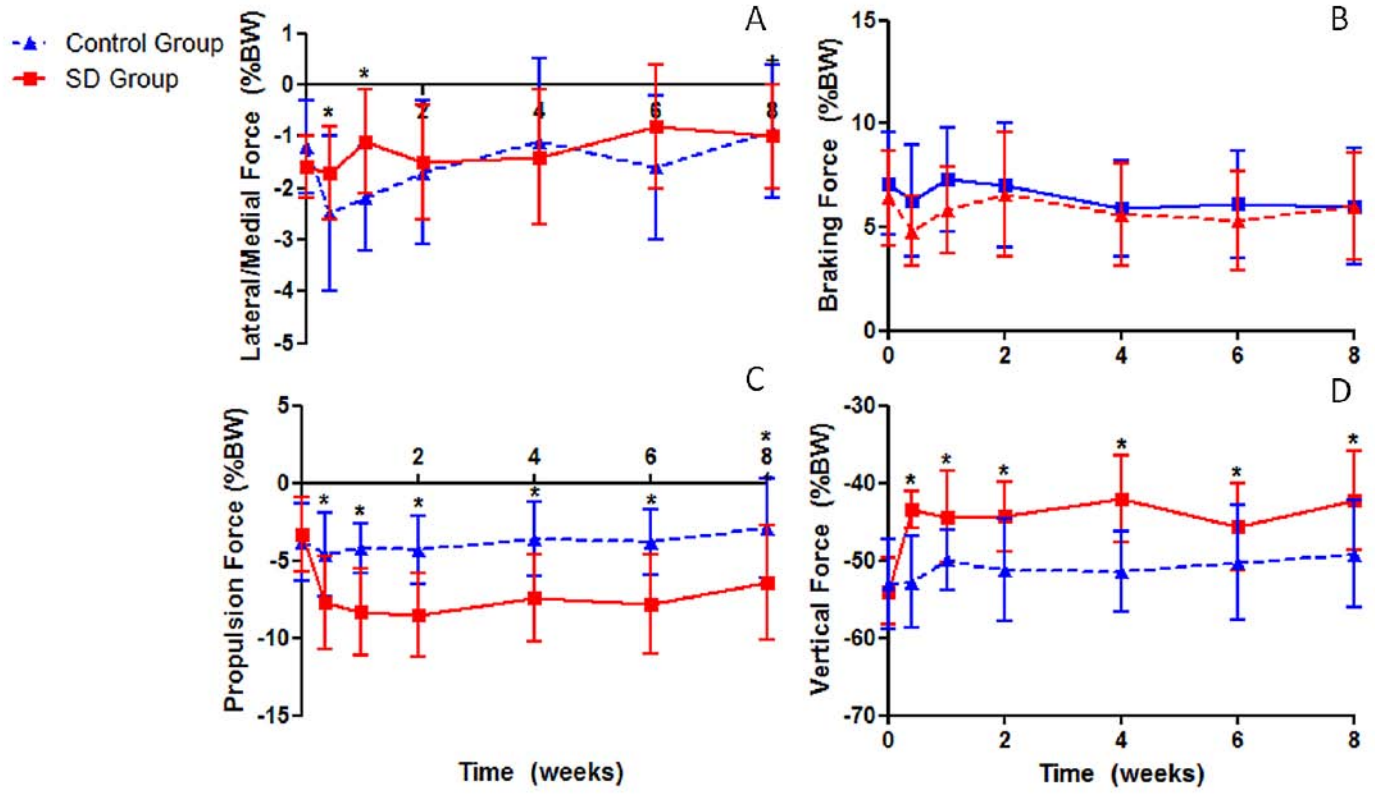

Figure 1. (A) The SD group had a significantly decreased lateral force at 5 and 7 days post-surgery compared to the control group. (B) No differences were observed in braking force between groups. (C) The SD group had a significantly increased propulsion force compared to controls at all time-points. (D) The SD group had a significantly decreased vertical force compared to control at all time-points. Data are shown as mean and standard deviation (SD) (Significance *$p<0.05$).

Table 1. Results for passive joint mechanics demonstrated increased internal range of motion (ROM) in the SD group compared to control at all time-points. Data are shown normalized by baseline values and as mean and SD (Significance *P<0.05).

Direction	Measurement	Time (wks)	Control	SD
Internal	ROM	2	0.93±0.21	1.09±0.19*
		4	0.89±0.07	1.01±0.17*
		8	0.87±0.12	1.02±0.16*
	Toe Stiffness	2	3.62±2.99	1.21±1.43
		4	3.87±3.83	1.66±1.75
		8	2.99±3.64	1.18±1.16
	Linear Stiffness	2	1.50±0.36	1.35±0.23
		4	1.47±0.31	1.30±0.28
		8	1.65±0.26	1.51±0.22
External	ROM	2	1.20±0.13	1.15±0.07
		4	1.03±0.10	0.98±0.09
		8	1.26±0.16	1.18±0.11
	Toe Stiffness	2	0.96±0.49	0.75±0.49
		4	0.82±0.29	1.50±0.86*
		8	0.87±0.42	1.03±0.58
	Linear Stiffness	2	1.10±0.28	1.10±0.32
		4	1.16±0.34	0.94±0.21
		8	1.25±0.43	1.24±0.29

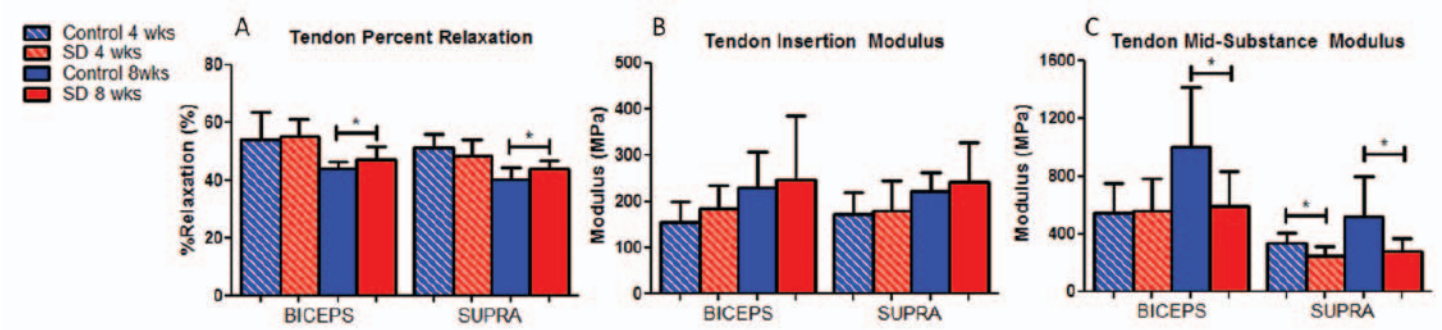

Figure 2. (A) The biceps and supraspinatus tendons demonstrated significantly increased percent relaxation at 8 weeks post-surgery in the SD group compared to control. (B) No differences were observed at the insertion site of any tendon at any time-point. (C) The biceps and supraspinatus tendons demonstrated significantly decreased tendon modulus at 8 weeks and both 4 and 8 weeks, respectively, in the SD group compared to control. Data are shown as mean and SD (Significance *p<0.05).

which lead to tendon degeneration and compromise healing potential following repair.

Significance

This study presents a new model of scapular dyskinesis and identifies scapular dyskinesis as a mechanical mechanism for shoulder tendon injury.

Acknowledgments

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The Effect of Type II Diabetes on Native Mechanical and Biologic Shoulder Joint Properties in a Rat Model

[1]Stephen J. Thomas, PhD, ATC
[1]Joseph J. Sarver, PhD
[1]Sarah Yannascoli, MD
[1]Jennica J. Tucker
[1]John D. Kelly IV, MD
[1]Rexford A. Ahima, MD, PhD
[2]Mary F. Barbe, PhD
[1]Louis J. Soslowsky, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Temple University School of Medicine, Philadelphia, PA, USA

Introduction

The incidence of type II diabetes mellitus has substantially increased over the past decade and is linked with many systemic maladies including cardiovascular disease.[1] Research has demonstrated that type II diabetes can result in increased stiffness and increased expression of inflammatory markers of the vascular walls (i.e., IL1-β).[2] Recently, type II diabetes has been linked to rotator cuff disease and adhesive capsulitis,[3] conditions with increased stiffness and inflammation as well. Unfortunately, limited research exists examining how type II diabetes affects the native shoulder (tendon and capsule) properties. A recent type I diabetic rat model study determined that the native mechanical properties of the patellar tendon were decreased after just 19 days.[4] Although this study highlighted the mechanical changes that could occur in the presence of uncontrolled type I diabetes, it was not designed to address the altered tissue properties and biologic mechanisms in the shoulder joint, following the more common type II diabetes. Therefore, the objectives of this study were to compare shoulder joint mechanics, tendon properties (mechanics and protein content), and capsule protein content of healthy control and type II diabetic rats 8 weeks following induction of hyperglycemia with a submaximal dose of streptozotocin (STZ). We hypothesized that there will be an increase in passive shoulder stiffness and a decrease in shoulder range of motion in the diabetic group. In addition, there will be an increase in tendon mechanics along with an increase in protein content (tendon and capsule) for advanced glycated end-products (AGE), IL-1β, and TNF-α

Methods

Eighteen adult male Sprague-Dawley rats were injected with STZ (30mg/kg x 3 doses) to induce diabetes or citrate buffer (control). Type II diabetes was defined as a fasting blood glucose level of ≥ 200mg/dL and was determined with a glucometer. Fasting serum insulin levels were measured by ELISA, and animals were excluded if the values were less than 70% from baseline.

Passive Joint Mechanics

Passive shoulder joint range of motion and stiffness were measured at 8 weeks following induction of diabetes using a custom instrument and methodology.[5] Briefly, under anesthesia, the forearm was placed through a fixture and secured into a rotating clamp at 90° of elbow flexion and 90° of glenohumeral forward flexion. The scapula was manually stabilized in order to isolate glenohumeral motion. The arm was then rotated through the full range of internal and external rotation three times. The range of external and internal motion was determined using data from all three cycles. A bilinear fit utilizing least-squares optimization was applied to calculate joint stiffness in the linear region for both internal and external rotation.

Tendon Mechanical Testing

After sacrifice and dissection, stain lines for local optical strain measurement were placed on the supraspinatus tendon. Cross sectional area was measured using a custom laser device. To determine biomechanical properties, tensile testing was performed as follows: preconditioning, stress relaxation, and ramp to failure.[6]

Histology

Whole shoulders were left completely intact and were processed, sectioned in the sagittal direction (7μm) and stained with hematoxylin-eosin (H&E). Cell density (cells per mm2) and cell shape (aspect ratio; 0-1 with 1 being a circle) were quantified using a bioquantification software system (Bioquant Osteo II). Immunohistochemistry was performed on the whole shoulder sections following established protocols.7 Briefly, following deparaffinization and rehydration, sections were blocked for endogenous peroxidase, washed, and then placed in a protein blocking solution. After draining, slides were incubated with the primary antibody overnight in a humidity chamber. The appropriate secondary antibody was then added followed by DAB, and rinsed. Samples were examined for IL1-β, TNF-α, and AGE. Staining was quantified using a bioquantification software system.

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sjthomasatc@gmail.com

Statistics

Joint and tendon mechanics and histology (tendon and capsule) were assessed using a one-tailed t-test. Significance was set at $p<0.05$.

Results

The diabetic group had a significantly higher fasting blood glucose level compared to controls; the fasting serum insulin levels were not significantly different, which confirms our animal model (Figure 1). Passive joint mechanics (Figure 2) demonstrated significantly less external rotation in the diabetic group compared to controls, with no other group differences. Tendon mechanics (stiffness and modulus) were not significantly different between groups at both the insertion site and mid-substance (data not shown). For histology, cell shape was not significantly different between groups at the insertion site and mid-substance of the tendon or the superior capsule. Cell density also was not significantly different between groups at the insertion site or superior capsule; however the diabetic group had a greater cell density at the mid-substance of the tendon (data not shown). Immunohistochemistry staining of the tendon and capsule

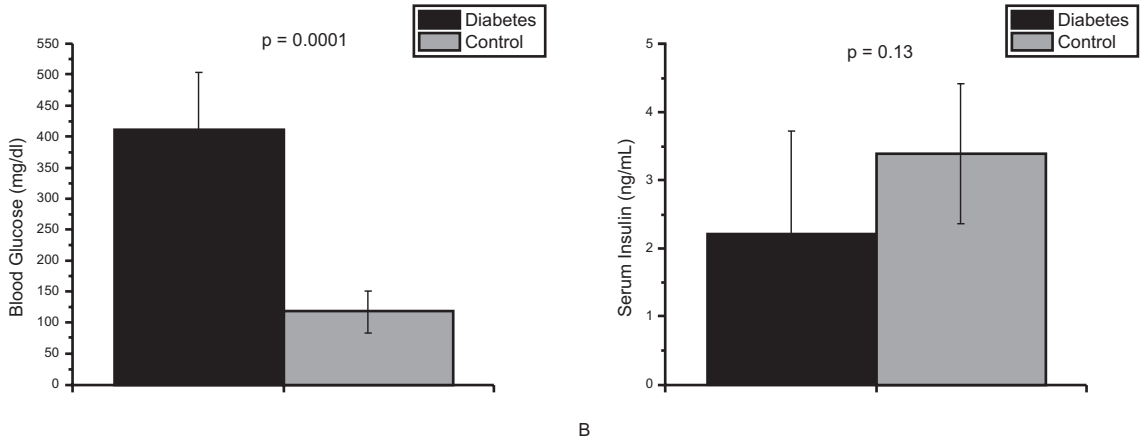

Figure 1. (A) The diabetes group had an increased fasting blood glucose level compared to the control group. (B) There was no difference in fasting serum insulin levels. Data are reported as Mean±SD.

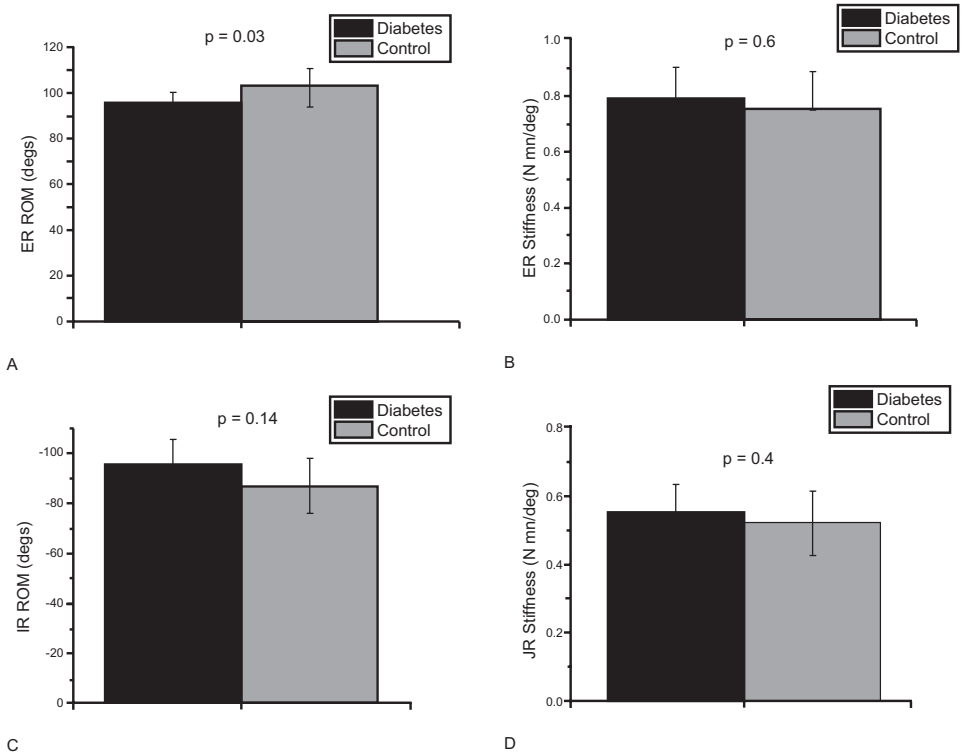

Figure 2. (A) The diabetes group had decreased external rotation (ER) range of motion (ROM) compared to control. (B) There were no differences for IR stiffness. (C) There were no group differences for internal rotation (IR) ROM. (D) There were no group differences for IR stiffness. Data are reported as Mean±SD.

Table 1. Immunohistochemistry data.

Tissue	Group	Region	IL1-β Staining Density (%)	p-value	AGE Staining Density (%)	p-value	TNF-α Staining Density (%)	p-value
Supraspinatus tendon	Diabetes	Insertion	1.78±1.29	0.03*	0.57±0.41	0.02*	2.7±1.44	0.5
	Control		0.51±0.40		0.06±0.05		2.74±1.88	
	Diabetes	Mid-substance	3.34±1.54	0.005*	2.37±0.95	0.01*	1.81±1.05	0.3
	Control		0.61± 0.34		0.62±0.51		1.31±1.1	
Superior capsule	Diabetes	Mid-substance	4.41±1.6	0.4	1.18±0.83	0.4	6.69±3.65	0.02*
	Control		4.17±1.89		1.01±0.65		2.51±1.0	

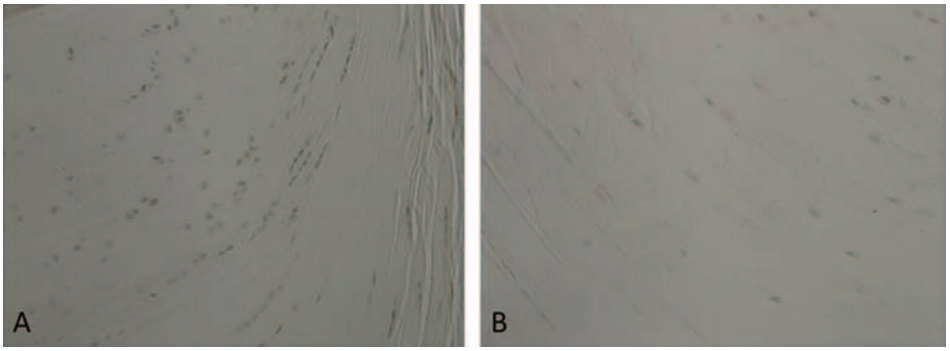

Figure 3. Representative images of the immunohistochemistry stain for IL1-β. (A) Diabetes group demonstrating increased staining at the insertion site of the supraspinatus tendon. (B) Control group demonstrating decreased staining at the insertion site of the supraspinatus tendon.

(Table 1) demonstrated significantly increased, IL1-β and AGE staining localized to the insertion and mid-substance of the tendon but not the capsule (Figure 3). In addition, TNF-α staining was significantly increased in the superior capsule but not the supraspinatus tendon.

Discussion

While the relation of type II diabetes to cardiovascular disease has been well studied, there is limited information with respect to rotator cuff disease and adhesive capsulitis. Results demonstrate that 8 weeks of type II diabetes, defined as hyperglycemia and partial insulin deficiency, leads to a decrease in external rotation range of motion but no other mechanical changes in the joint or tendon. However, there was a large biologic response with elevated levels of inflammatory markers and AGE. The decrease in external rotation and the increase in TNF-α in the superior region of the capsule are similar to the findings in patients with adhesive capsulitis[8] and should be further investigated. The lack of tendon mechanical property differences was surprising, although unlike some animal models of diabetes, this animal model had minimal reductions in insulin, which could allow maintenance of the mechanical properties. The increased biologic response (cell density and immunohistochemistry staining) agrees with findings from cardiovascular research,[3] which identify a chronic underlying inflammatory response to type II diabetes. This underlying elevation of inflammatory markers did not affect the mechanical properties of the supraspinatus tendon at 8 weeks. However, the elevated presence of inflammation in native tissue may have detrimental effects to tissue healing. Future studies will examine additional inflammatory markers and begin to investigate the effect on tendon healing.

Significance

This study demonstrates that type II diabetes does not diminish shoulder mechanical properties but does induce a chronic inflammatory response.

Acknowledgments

This study was supported by the NIH/NIAMS.

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Exercise Protocol Induces Muscle, Tendon, and Bone Adaptations in the Rat Shoulder

[1]Sarah I. Rooney, MSE
[1]Emanuele Loro, PhD
[1,2]Joseph J. Sarver, PhD
[1,3]Cathryn D. Peltz, PhD
[1]Michael W. Hast, PhD
[1]Wei-Ju Tseng, MSE
[1]X. Sherry Liu, PhD
[1]Tejvir S. Khurana, PhD
[1]Louis J. Soslowsky, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Drexel University, Philadelphia, PA, USA

[3]Henry Ford Hospital, Detroit, MI, USA.

Introduction

Rotator cuff tendinopathy, which primarily affects the supraspinatus tendon, is a common clinical condition. While late-stage tendinopathy has been fairly well characterized, earlier stages of tendon degeneration have not, partially due to the lack of an appropriate comparison model system. It is unknown how tendinopathy progresses from an early, treatable stage to a chronic, irreversible stage. A rat model of supraspinatus overuse[1] has suggested mechanisms governing tendon degeneration; however, delineating which changes are pathologic or simply physiologic adaptions to increased loading remains a question. The development of a non-injurious exercise model to which overuse can be compared is critical to the advancement of tendinopathy research; this model has not been created previously. Therefore, the objective of this study was to develop and characterize a rat exercise model that induces systemic and local shoulder adaptations. We hypothesized that a mild treadmill training protocol would produce adaptations consistent with exercise in the supraspinatus tendon and muscle and the humerus.

Methods

Adult, male Sprague-Dawley rats were divided into exercise (EX; n=8) and control cage activity (CA; n=8) groups (IACUC approved). EX rats ran on a flat treadmill at 10 m/min, 1 h/day, 5 days/wk, for 12 weeks[2] while CA rats maintained normal cage activity. Upon completion, rats were sacrificed, weighed, and stored at -20°C.

Tissue Harvest

Rats were thawed, and the right supraspinatus (supra) muscle and tendon were dissected and weighed, and muscle cross-sectional area (CSA) was measured with a custom laser device.[3] Tendon at the insertion site was isolated from the muscle for *o*-Hydroxy-proline (OHP) assay. The superficial and deep regions of the supra muscle[4] were collected separately for protein analysis. The heart and retroperitoneal and epididymal fat pads were dissected and weighed.

Tendon Mechanics

Rats were thawed, and the left supra tendon was dissected and prepared for tensile mechanical testing with preconditioning, stress-relaxation, and ramp to failure.[5]

Tendon Collagen

OHP, a measure of collagen content, was determined and normalized to tendon wet weight.[6,7]

Muscle Protein

A Western blot was performed to quantify mitochondrial proteins. Total protein from the supra muscle superficial region was probed for oxidative phosphorylation complexes I-V using Total OXPHOS antibody cocktail (MitoSciences). Bands were visualized by chemiluminescence, imaged, and analyzed with commercial software. Mitochondrial proteins were normalized to α-tubulin, and the relative quantity of target protein in the EX group compared to CA was calculated.

Bone μCT

μCT (Scanco VivaCT40) was used to determine trabecular and cortical bone structure. For trabecular bone, a 2mm region just distal to the growth plate was scanned (15μm isotropic voxels); for cortical bone, a 1.5 mm region at 60% of the humerus length was scanned (35μm isotropic voxels). Bone was segmented from marrow using a global thresholding technique and then subjected to standard microstructural analysis.

Bone 3-Point Bending

A custom fixture attached to an Instron created a 3-point bend in the humeral shaft until fracture.[8]

Statistics

Comparisons between EX and CA were made with 1-tailed t-tests for significance ($p \leq 0.05$) and trends ($p \leq 0.1$).

Results

EX rats had reduced body (−7%) and fat pad (retroperitoneal: -45%, epididymal: −39%) mass. An 8% increase in supra muscle mass was measured, and no change was detected in heart mass (Figure 1). Supra muscle CSA significantly increased 10% with exercise (Table 1).

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sarahilk@seas.upenn.edu

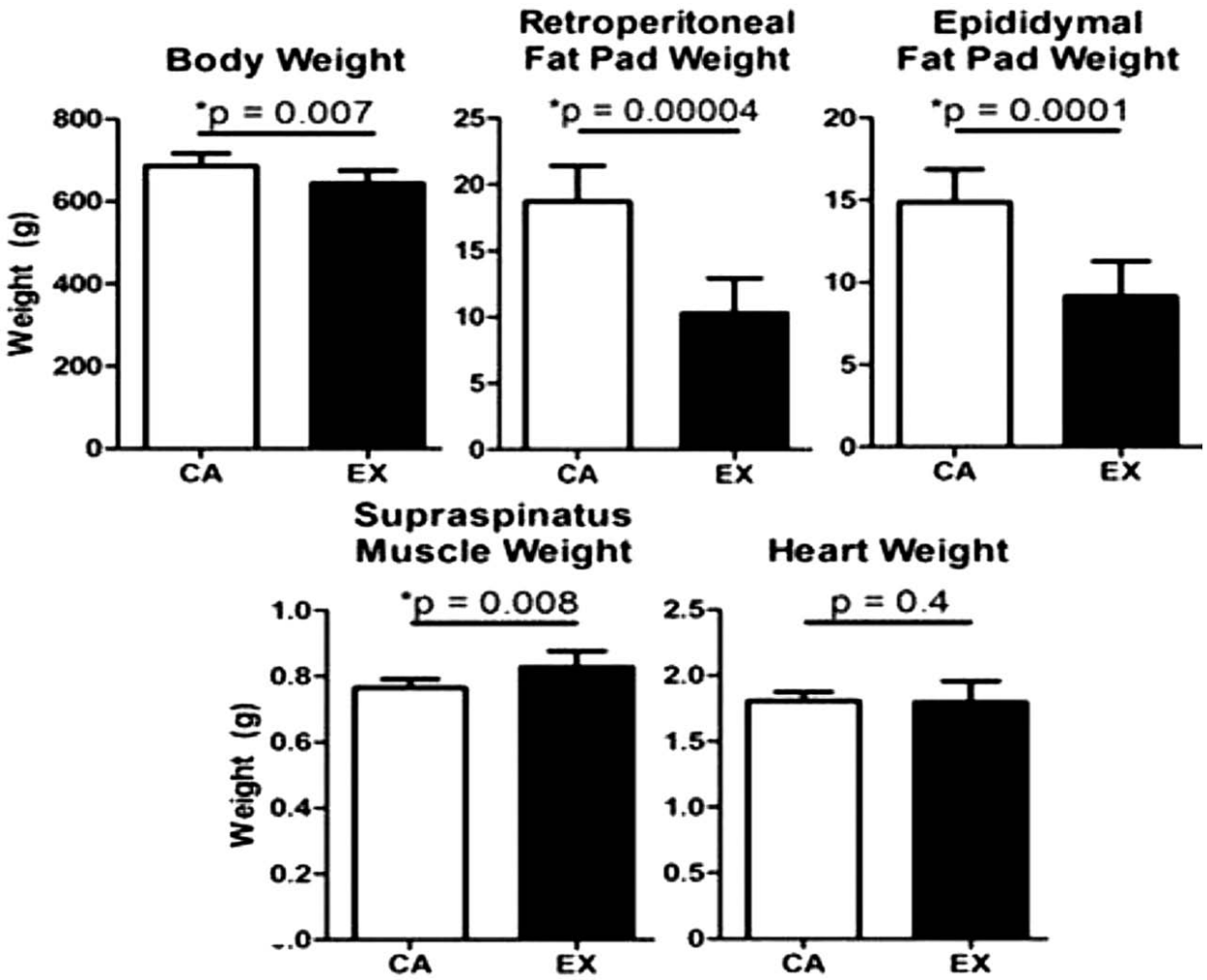

Figure 1. Consistent with adaptations to exercise, EX rats had decreased body and fat pad weight, increased supra muscle weight and no change in heart weight (Mean ± StDev).

Table 1. EX rats showed adaptations consistent with exercise in supraspinatus muscle and tendon and trabecular (Tb) and cortical (Ct) humerus bone. (mean ± StDev, * = significant, $^{+}$ = trend).

Tissue	Measurment	CA	EX	p-value
Muscle	CSA (mm^2)	34.3±3.9	37.7±2.6	*0.04
	CSA mm^2)	1.97±0.42	1.97±0.28	0.5
Tendon	Modulus (MPa)	100±42	112±38	0.3
	% Relaxation	61±9	68±5	*0.04
	Collager/Wet Weight (%)	25±5	28±1	−0.07
	Tb Conn. D ($1/mm^3$)	60±12	70±12	−0.07
	Tb N (1/mm)	3.1±0.7	3.5±0.4	−0.10
Bone	Tb Sp (mm)	0.34±0.09	0.28±0.04	−0.08
	Tb DA	1.79±0.07	1.86±0.07	*0.03
	Ct BMD ($mgHA/cm^3$)	1116±12	1126±10	*0.05
	Ct TMD ($mgHA/cm^3$)	1212±18	1227±7	*0.02

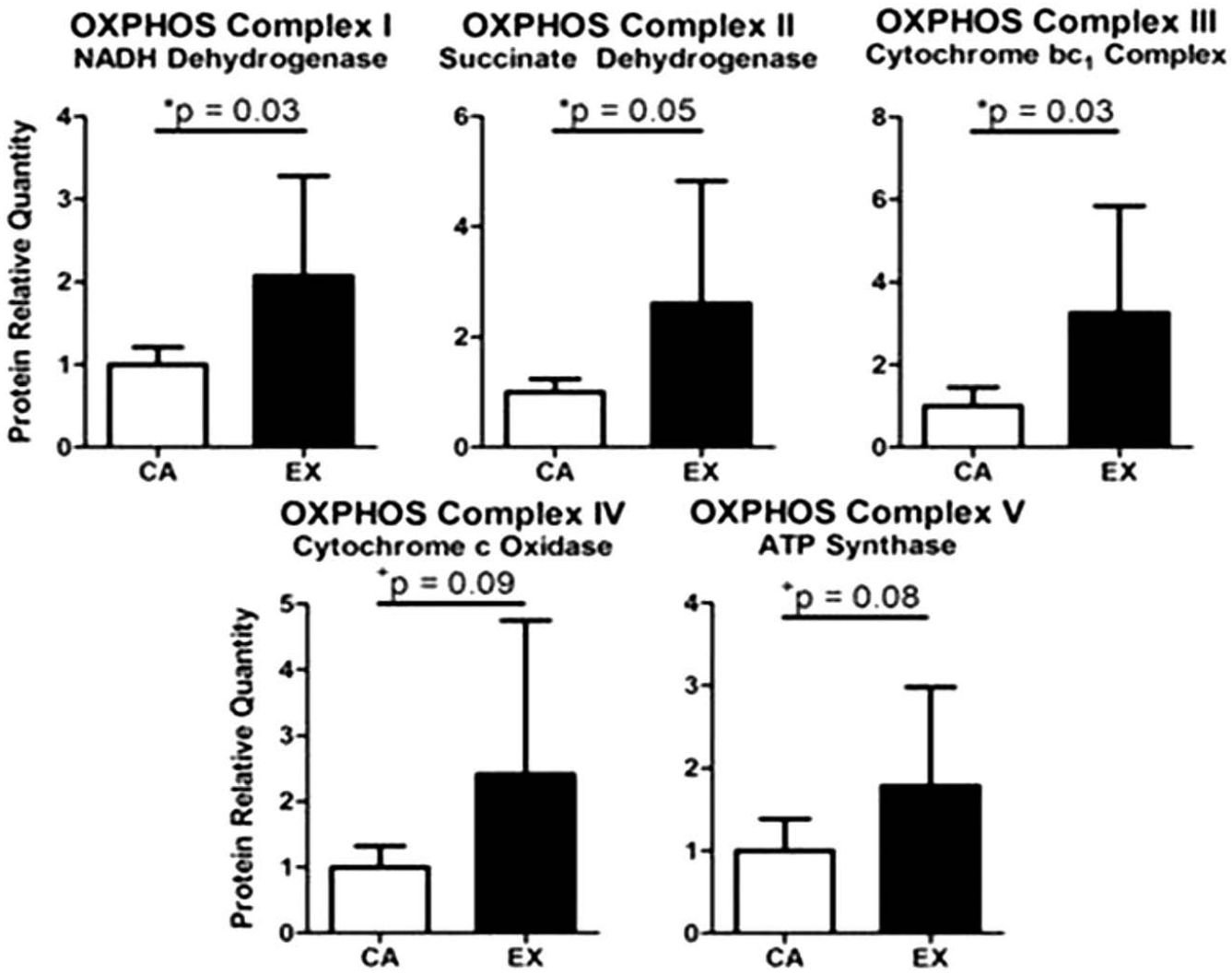

Figure 2. Consistent with adaptations to aerobic exercise, EX rats had increased expression of oxidative phosphorylation proteins. Here reported as relative quantity of expression in EX compared to CA rats after normalization with Tubulin (Mean ± StDev).

Supra tendon CSA and elastic modulus were not different between groups (Table 1). Percent relaxation significantly increased in the EX group (Table 1). Collagen content of the supra tendon normalized to wet weight trended toward an increase observed in the EX group (Table 1). Supra muscle had increased oxidative phosphorylation proteins (Figure 2).

Trabecular bone in the EX group demonstrated trends toward increased trabecular number (Tb.N) and connectivity (Conn.D) and decreased spacing (Tb.Sp) as well as significantly greater degree of anisotropy (DA, Table 1). No differences were found in trabecular bone volume, structure model index, thickness, bone mineral density (BMD), or tissue mineral density (TMD, not shown). Cortical bone in the EX group had significantly increased BMD and TMD (Table 1) with no changes in volume or cortical thickness (data not shown). No differences were found for second moment of area, max load, max displacement, modulus, flexural rigidity, or max stress (data not shown).

Discussion

After 12 weeks of treadmill training, rats showed systemic (decreased body and fat pad mass) and local shoulder (tendon, muscle, bone) changes consistent with exercise. Heart mass did not change, indicating that this protocol does not tax the cardiovascular system. No changes were seen in tendon elastic properties, but stress-relaxation significantly increased. Other studies on tendon mechanics after training show mixed results but often find no differences in modulus or CSA.[9] This study suggests that tendons may have greater viscoelastic than elastic adaptations to training, which could be due to increased fluid retention. EX tendons had decreased dry-to-wet weight ratio (not shown), consistent with increased percent relaxation. Unlike the established supra overuse model, tendons did not show decreased mechanics, indicating that this training is non-injurious to the tendon.[1] Supra muscle showed hypertrophy (increased weight and cross-sectional area), indicative of a response to loading, and increased expression of oxidative

phosphorylation proteins, indicative of endurance training. Humerus trabecular bone had increased anisotropic orientation, consistent with load-induced bone remodeling. Cortical bone showed increased bone and tissue mineral density, with no change in volume, suggesting that changes in bone mass are due to increased tissue mineralization. Other studies have also shown no changes in humerus mechanics following moderate treadmill training.[10] Although the adaptations to exercise found in this study are mild, they are consistent and present across multiple tissues using multiple assays. This study is limited by the quality of tissue available, sample size, and single time point investigated. In conclusion, this is the first non-injurious rat shoulder exercise model, which can be compared to the previously established overuse model[1] to differentiate between beneficial adaptation and maladaptation in response to loading.

Significance

This study establishes the first rat exercise protocol that induces adaptations in the shoulder, and future research can use this as a comparison model to study how the supraspinatus tendon adapts to loading and undergoes degeneration with overuse.

Acknowledgments

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Intra-Articular Tibiofemoral Injection of a Nonsteroidal Anti-Inflammatory Drug has no Detrimental Effects on Joint Mechanics in a Rat Model

Corinne N. Riggin
Jennica J. Tucker
Louis J. Soslowsky, PhD
Andrew F. Kuntz, MD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for musculoskeletal injuries due to their analgesic and anti-inflammatory properties. Recent studies have demonstrated the efficacy of injectable NSAIDs in the treatment of intra-articular pathology and postoperative analgesia.[1,2,3] However, little data exist regarding the safety of intra-articular injection on the joint, despite the recent increase in its application.[4] Therefore, the objective of this study is to investigate the effects of intra-articular NSAID injection on articular cartilage, the anterior cruciate ligament, and joint function in the rat knee. We hypothesize that intra-articular ketorolac injection will result in no damage to the articular cartilage and anterior cruciate ligament (ACL), and will not permanently alter joint mechanics.

Methods

Study Design and Animal Use

A total of 64 Sprague-Dawley rats were used to investigate the effects of an intra-articular injection of NSAID. Following anesthetization, injections of saline (0.1 mL) or ketorolac tromethamine (Toradol, Bedford Laboratories, 3 mg/0.1 mL), a commonly used NSAID, were performed bilaterally in the knee (tibiofemoral) joint with both knees receiving the same injection. All rats were returned to cage activity for the remainder of the study. Sixteen rats (8 ketorolac, 8 saline) were sacrificed at each of four time points (2, 7, 28, and 84 days). Following sacrifice, the left tibia was dissected and frozen (−20°C) for cartilage indentation testing. The right hindlimb was frozen (−20°C) for ACL mechanical testing. The 84 day group also underwent knee kinematic evaluation 1 day prior to injection and at 2, 7, 28, and 84 days post-injection prior to sacrifice.

Knee Kinematics

Knee kinematics were quantified by measuring ground reaction forces and paw positioning using a novel ambulation method.[5] All data were collected using LABVIEW and parameters of knee function were determined using a custom MATLAB program.

ACL Mechanical Testing

To assess the mechanical properties of the ACL, the right hindlimb was dissected by removing all surrounding tissue from the tibia and femur except the ACL. Three Verhoeff stain lines were placed on the ACL (Figure 1A) for optical strain tracking. Cross sectional area was determined by taking coronal and sagittal images of the ACL, defining the thickness using Mipav software, and calculating assuming an ellipse. Both the tibia and femur were embedded

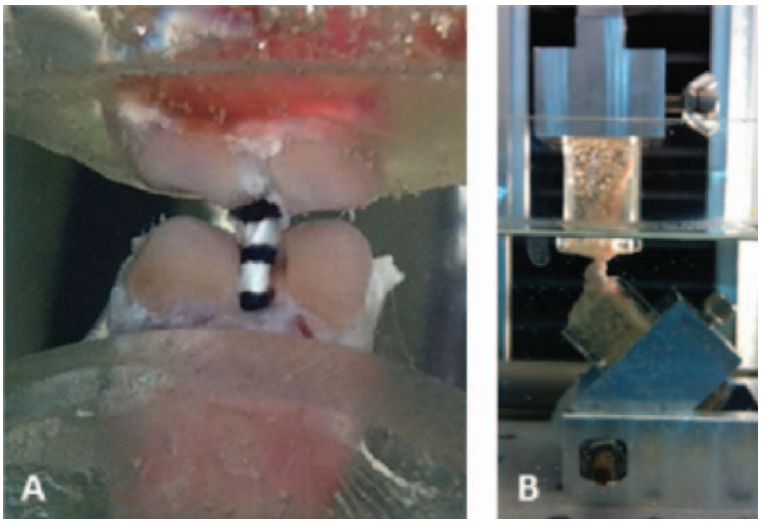

Figure 1. ACL mechanical testing setup. (A) ACL isolated between the tibia (top) and femure (bottom) embedded in PMMA in the holding fixture. Three stain lines mark the two insertions and the center of the ligament for optical tracking. (B) Sagittal view of ACL mechanical testing set-up with custom testing fixtures to hold at 45 knee flexion.

Poster No: 1689
2014 Annual Meeting
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cnriggin@gmail.com

in holding fixtures using polymethylmethacrylate (PMMA) and inserted into a custom fixture with the joint at 45° flexion (Figure 1B). The specimen was immersed in 37°C PBS bath, preloaded to 0.1N, preconditioned for 10 cycles from 0.1N to 0.5N at 1% /sec and held for 300s. Stress relaxation was performed (ramp to 5% strain at 5%/sec, then held for 600s) followed by a return to initial displacement for 60s, and a ramp to failure at 0.3%/sec. Images were taken during the ramp to failure and 2D Lagrangian strain was calculated by mapping the stain line displacements in MATLAB.

Cartilage Thickness Measurement and Mechanical Testing

Indentation testing of the center region of the medial tibial plateau articular cartilage was performed. The tibia was dissected to remove surrounding tissue and embedded in PMMA. The cartilage surface was scanned in 0.25 mm increments using a 55 MHz ultrasound probe (VisualSonics, Inc) in coronal and sagittal planes. B-Mode images of each scan were segmented and the 3D positions of the cartilage and bony surfaces were reconstructed (Figure 2A).[6] Average thickness was computed in a 0.5 mm diameter region at the center of the thickness map (Figure 2B) and cartilage indentation was performed using a 0.5 mm diameter, non-porous spherical indenter tip in the same region. A stress-relaxation test was performed, with a preload of 0.005N followed by a ramp to 20% strain at −0.05 mm/sec and a 300 second hold. Equilibrium elastic modulus was calculated[7] assuming Poisson's ratio (v=0.3).

Statistics

Significance (set at $p<0.05$) was assessed using 2-way ANOVAs to evaluate the effect of NSAID injection and time post injection.

Results

There were no differences between the ketorolac (NSAID) and saline (SAL) injection groups in any measured parameter at any time point. Specifically, for knee kinematics evaluation, we measured forces (propulsion and vertical ground reaction (Figure 3A-B), medial and lateral, braking, and moment), paw placement (stride width (Figure 3C) and length), and timing (speed (Figure 3D), rate of loading, and stance time) of ambulation over the study time course for both NSAID and SAL groups. There were no differences due to the NSAID compared to the SAL group in any of these parameters. Although not different between treatment groups, walking speed did change over time.

For ACL mechanical evaluation, we measured maximum load, stiffness, percent relaxation, modulus (Figure 4A-D), maximum stress, and cross-sectional area. There were no changes between treatment groups, but changes were observed over time in maximum load, percent relaxation, maximum stress, and cross-sectional area.

Our measurements for cartilage thickness and equilibrium elastic modulus showed no changes between treatment groups with respect to either parameter (Figure 5A, B), but both changed over time.

Discussion

Results indicate that the intra-articular administration of ketorolac in the tibiofemoral joint does not cause detrimental effects to the articular cartilage and the ACL, or cause any detrimental ambulatory changes compared to saline injection. These results support previous findings evaluating the safety of intra-articular injection of NSAIDs.[4] A pre-study power analysis determined that eight animals in each group were sufficient to achieve a power of 80% with p set at 0.05, so we are confident in our findings of "no difference" between treatment groups. Additionally, our delivered dosage of ketorolac was ~30x a normal therapeutic dose in humans. This dose was selected based on the maximum volume allowable in the rat knee without capsule damage using a standard ketorolac concentration. Given the consistent results, it is unlikely that a lower ketorolac dose would cause

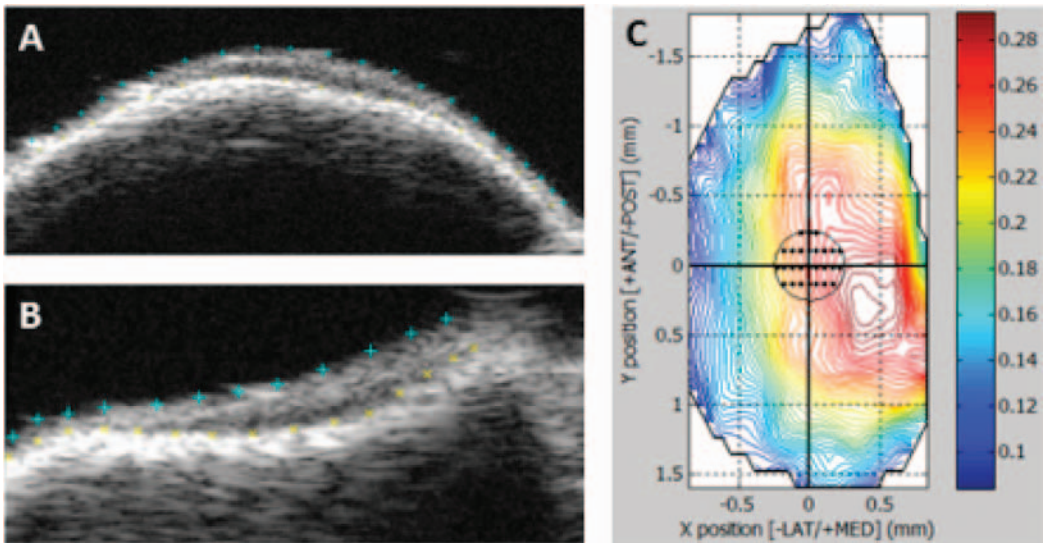

Figure 2. Medial tibial plateau articular cartilage segmentation to determine cartilage thickness. (A) Sagittal and (B) Coronal ultrasound images with markers defining the cartilage with center region of interest defined to average the segmentation points.

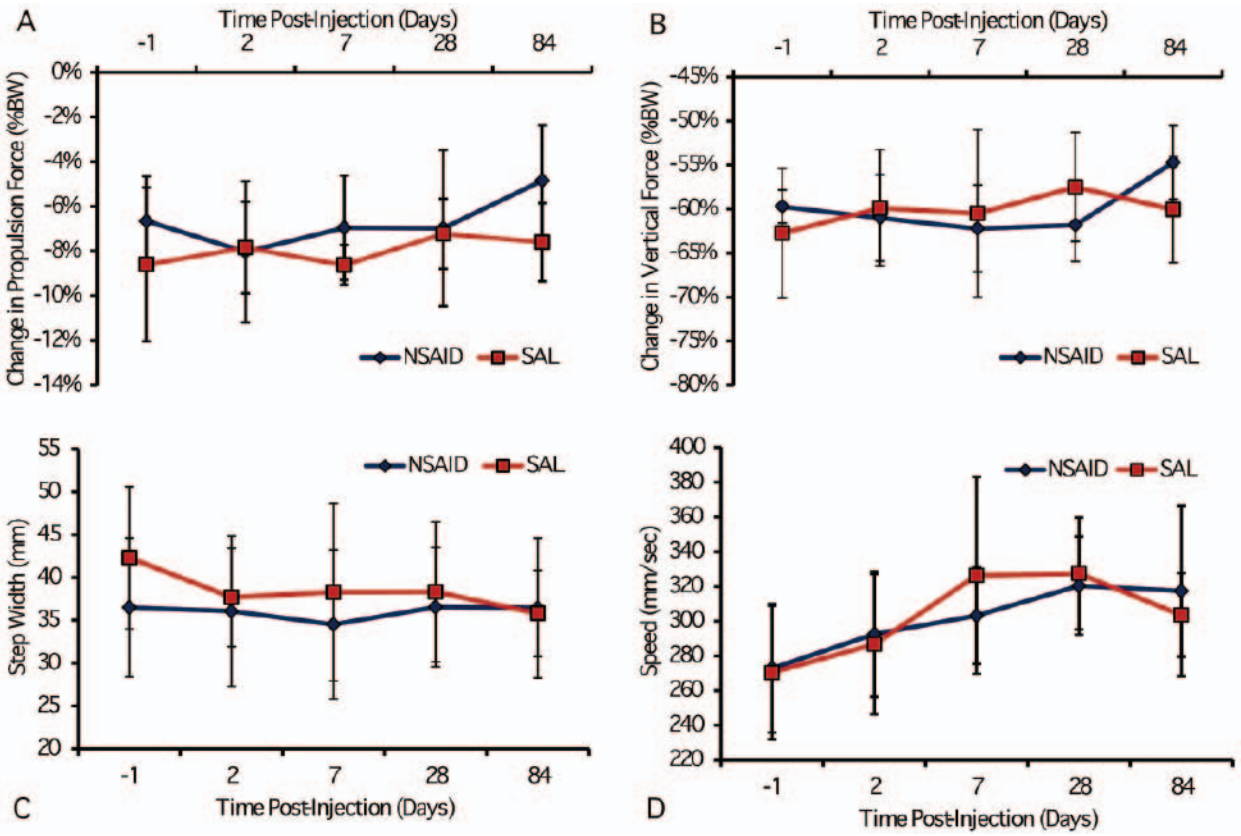

Figure 3. Rat ambulation measures, where "NSAID" is the ketorolac injection group and "SAL" is the saline injection control. (A) Propulsion force and (B) vertical force, normalized by weight and obtained from six-degree of freedom force plates. No differences were found between NSAID and SAL groups in any of these measures at any time point. Note: breaking force, medial/lateral force, momentum, stride length, rate of loading and stance time also showed no differences (data not shown).

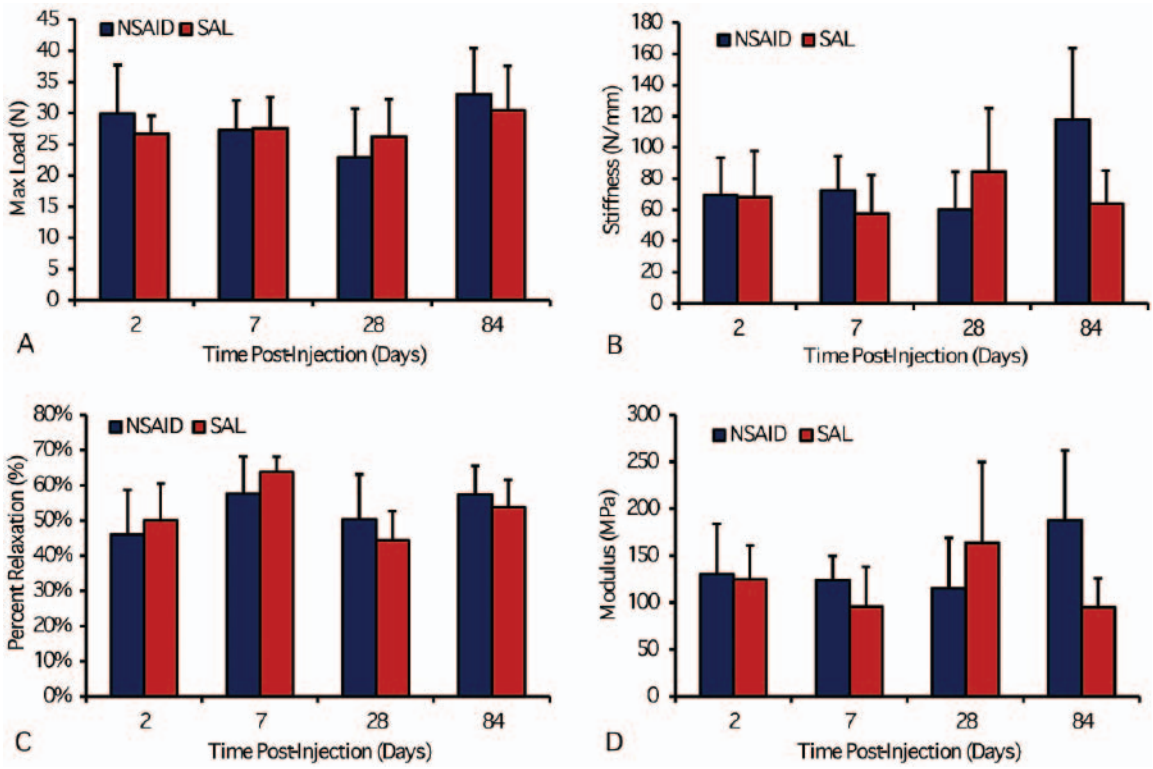

Figure 4. Representative plot of ACL mechanical properties: (A) max load and (B) stiffness determined from the load-displacement curve. (C) Percent relaxation determined from a stress relaxation test, and (D) modulus determined from the stress-strain curve. No differences were found between the NSAID and SAL group in any of these measures at any time point. Note: ACL cross sectional area and max stress also showed no difference (Data not shown).

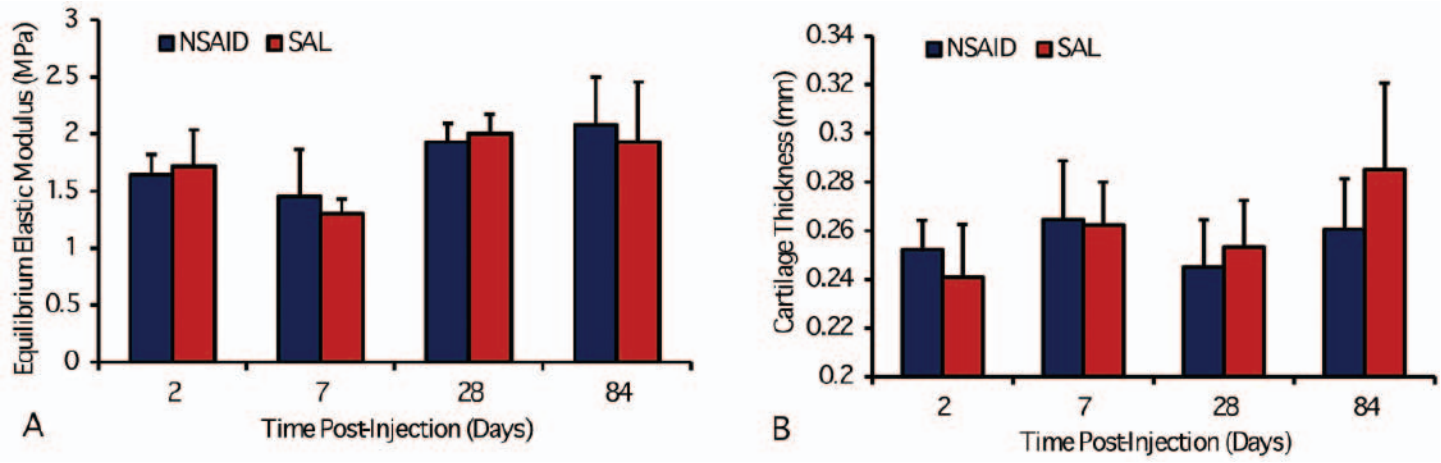

Figure 5. Medial tibial plateau articular cartilage properties: (A) Cartilage equilibrium elastic modulus from a stress-relaxation indentation test, and (B) cartilage thickness of the center region in the medial tibial plateau determined by ultrasound imaging.

tissue damage since this high dose did not. While changes were observed over time in some parameters, these changes were the same in both treatment groups, and therefore most likely due to changes in animal age and/or weight over time as is expected in this type of longitudinal study. In conclusion, since we consistently found no changes in a comprehensive set of structural, mechanical, and ambulatory parameters, we are confident that there are no effects of intra-articular injection of ketorolac. Therefore, it may be safe to use intra-articular ketorolac injection in clinical practice.

Significance

This study supports that no detrimental effects are observed in the articular cartilage, ligaments, and kinematic function of the native knee following intra-articular ketorolac injection in a rat model, demonstrating the safety of this pain management strategy. These findings serve as preliminary data to support future studies examining the therapeutic effects of injectable NSAIDs on intra-articular pathologies.

Acknowledgments

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Alterations in the Mechanical Properties of Patellar Tendons in Bone Sialoprotein-Null Mice

[1]Andrey Zuskov
[1]Andrew A. Dunkman
[2]Yohannes Soenjaya
[1]Benjamin R. Freedman
[1]Louis J. Soslowsky, PhD
[2]Harvey A. Goldberg

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]University of Western Ontario, London, ON, Canada

Introduction

Bone sialoprotein (BSP) is a highly conserved multifunctional glycoprotein of the SIBLING family with a flexible structure and a variety of known roles, from cancer biology to tissue mineralization.[1,2,3,4,5] BSP is present in a variety of mineralized tissues such as bone, dentin, and hypertrophic cartilage and is highly expressed in sites of active bone formation, during both development and fracture healing.[2,3,4,5,6,7] BSP-null mice have been shown to exhibit a phenotype of lower body mass, shorter body length and shorter long bones.[4] Although BSP is known to be expressed in some non-mineralized tissues, its effects on tendon are unknown. Therefore, the objective of this study was to use the BSP-null mouse model to assess the role of BSP on the biomechanical properties of the patellar tendon. We hypothesized that the absence of BSP would result in smaller and biomechanically inferior tendons, particularly in locations where tendon inserts into bone.

Methods

Sample Preparation

Wild-type (n=15) and BSP-null (n=15) male mice at 15 weeks of age were used with IACUC approval. Following sacrifice, patella-patellar tendon-tibia complexes were carefully dissected and cross-sectional areas of each tendon were measured using a custom laser-based device. The anterior surface of each tendon was then speckle coated with Verhoeff's stain for local optical strain measurement. Specimens were then potted in custom fixtures using PMMA.

Mechanical Testing

Specimens were tested with the following protocol: 1) preload, 2) preconditioning, 3) stress-relaxation to 5% of gauge-length, 4) return to gauge length, 5) ramp to failure (0.1%/s).

Data Analysis

Linear region modulus was calculated using optical tracking software for each tendon in three tendon regions; at the patellar origin (patella-1mm distal to the patella), tendon mid-substance and tibial insertion (1mm proximal to tibial insertion).

Statistics

Comparisons between the two genotypes were made using Student's t-tests (significance at $p<0.05$).

Results

BSP-null tendons showed a larger cross-sectional area as well as a lower failure stress compared to the wild-type tendons (Figure 1A-B). The moduli showed no statistically significant difference between the BSP-null group and the wild-type. (Figure 2A-C). Failure load, stiffness as well as percent relaxation showed no statistically significant difference between the two genotypes (Figure 2D-F). Tendon failure modality was also analyzed with no significant difference between the two genotypes in location of tendon failure, although the number of tendons in each group was small when stratified in this manner (data not shown).

Discussion

Although the skeletal phenotype of the BSP-null mice is well defined, its role in tendon biology remains largely unknown. We have shown that despite the hypotrophic skeletal phenotype exhibited by BSP-null mice, their patellar tendons are significantly larger in cross-sectional area than wild-type. Given their larger size, one might expect these tendons to exhibit superior mechanical properties, yet they exhibited a failure stress significantly lower than wild-type tendons. Taken together, this set of data describes larger, yet mechanically inferior tendons. However, our data also show no significant effect of BSP knockout on tendon tissue moduli, as well as other parameters, suggesting a limited role for BSP in adult mouse tendon biology. BSP is known to possess a strong binding affinity for fibrillar type I and monomeric collagen in mineralizing tissues[2] and although it is not known to be expressed in tendons, it is possible that BSP also interacts with non-mineralizing type I collagen in tendons as they develop. Thus, knocking out BSP function may lead to mechanically inferior collagen formation or maturation during in-utero or post-natal tendon development, forcing compensatory mechanisms to grow larger tendons during this

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ap4ap05@gmail.com

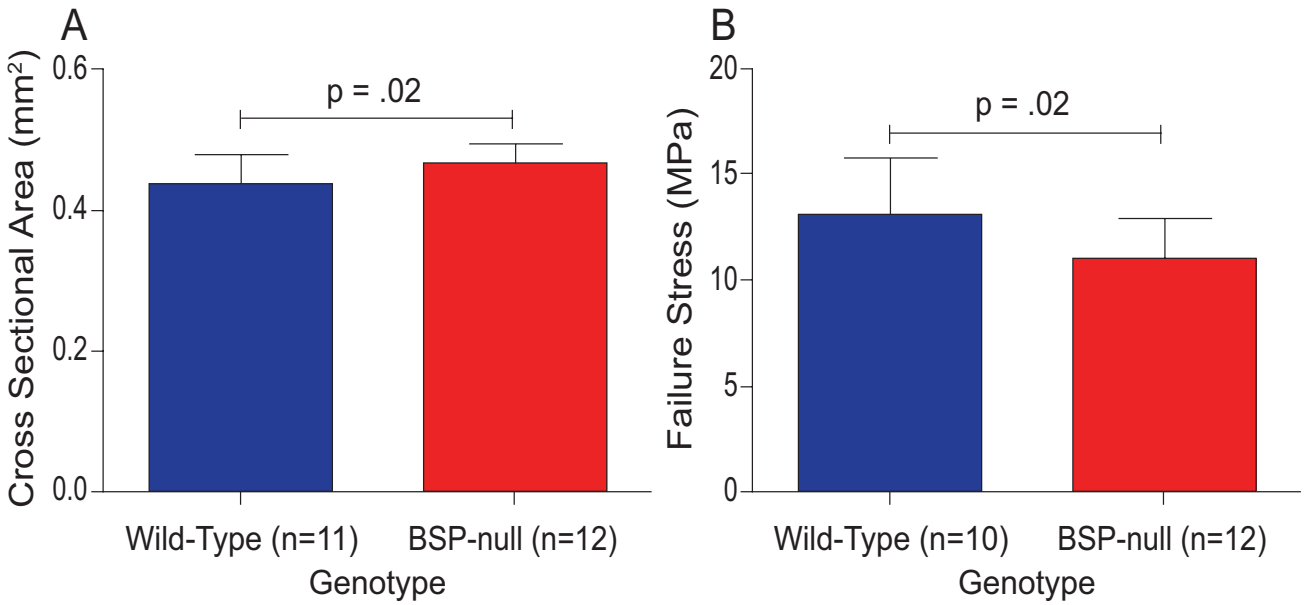

Figure 1. (A) Cross-sectional area was significantly increased in the BSP-null compared to wild-type mice. (B) Failure stress was significantly decreased in the BSP-null compared to wild-type mice. Results are presented as mean +− standard deviation with significance set at $p<0.05$.

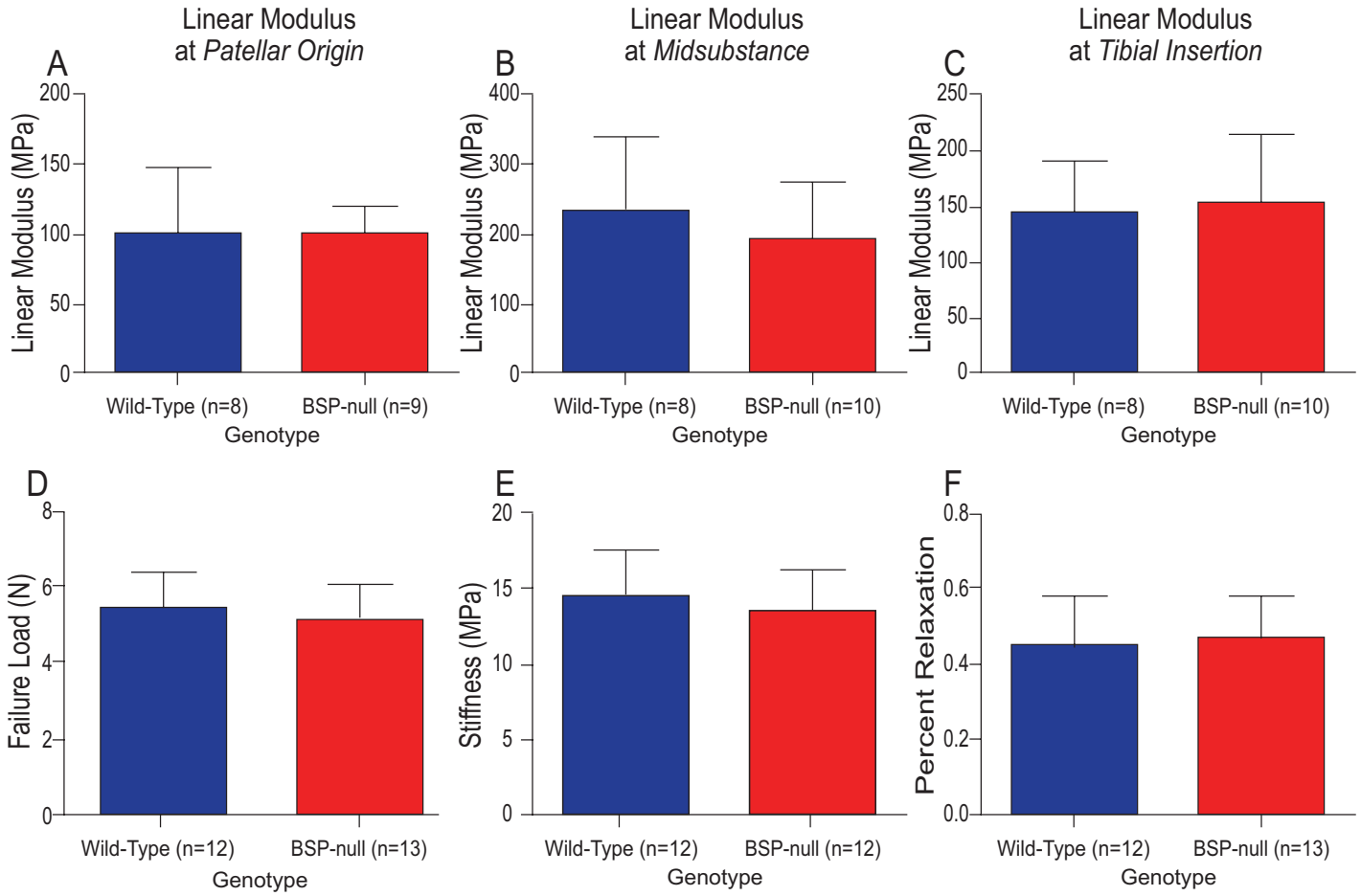

Figure 2. The linear modulus at (A) the patellar origin, (B) tendon mid-substance, and (C) tibial insertion showed no difference between BSP-null and wild-type mice. Similarly, (D) the load at failure, (E) stiffness, and (F) percent relaxation also showed no difference between BSP-null and wild type mice.

period. It is also possible that BSP plays no role or a minimal one in tendon biology and the decrease in some tendon mechanical properties can be attributable to a compensatory response to a significant skeletal phenotype. Surprisingly, there was no greater propensity for knockout tendons to fail at their entheses, given that BSP-null mice are known to have thinner cortices and a lower bone mineral density.[4] This likely indicates that, unlike its better-studied relative, osteopontin, BSP not only displays a more selective phenotype, but one that operates in a milieu with greater redundancy. Further study is necessary to characterize the contribution BSP makes during tendon development to the adult phenotype. In addition, an investigation of the histological properties of BSP-null tendons would shed light on the effect BSP may have on tendon cellularity, fibril morphology and enthesis histomorphology.

Significance

This study demonstrates that BSP likely plays a role in the structure and function of tendon. The multifunctional nature of BSP is highlighted by its continued study as, among others, a possible cancer marker as well as an osteoinductive agent for bone repair and osseous integration of implants[6,7,8]. This study illustrates a putative role for BSP in tendon biology as well as the importance of further study.

Acknowledgments

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U·P·O·J

Trajectory-Based Tissue Engineering for Cartilage Repair: Impact of Maturation State and Rate on Integration Potential

[1,2]Matthew B. Fisher, PhD
[1]Nicole Soegaard
[1,2]Elizabeth A. Henning, BS
[1,2]George R. Dodge, PhD
[1,2]David R. Steinberg, MD
[1,2,3]Robert L. Mauck, PhD

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

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

[3]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA

Introduction

Given the limitations of current surgical approaches to treat articular cartilage injuries, tissue engineering (TE) approaches have been aggressively pursued over the past two decades. Critical biochemical and biomechanical properties on the order of native tissue have been achieved in a variety of TE contexts.[1-5] However, several in-vitro and in-vivo studies indicate that increased tissue maturity may limit the ability of engineered constructs to remodel and integrate with surrounding cartilage, although results from individual studies are highly variable.[1,6-8] We recently introduced the concept of "trajectory-based" tissue engineering (TB-TE), which is based on the general hypothesis that time-dependent increases in construct maturation in-vitro prior to implantation (i.e. positive rates) may provide a better predictor of in-vivo success rather than "static" measures of construct maturation state.[9] As a first step toward evaluating this concept, we hypothesized that time-dependent increases in the biochemical and biomechanical properties of TE constructs (a metric of growth) would correlate with their ability to integrate to cartilage. To test this hypothesis, the current objective was to determine and model the time course of maturation of TE constructs during in-vitro culture and to assess their ability to integrate to cartilage at various points during maturation.

Methods

Bovine mesenchymal stem cells (MSCs) were isolated and cultured, as previously described.[1] Cells were encapsulated within methacrylated hyaluronic acid (HA) (1% w/v) at a seeding density of 60 million cells/mL. Cylindrical constructs (4 mm diameter) were formed via UV polymerization and cultured in chemically-defined media containing TGF-β3 for up to 17 weeks. Stress relaxation testing (10% compressive strain, 1000s hold) and cyclic testing (1% amplitude, 1 Hz) were performed at weekly intervals (n=4-5/timepoint) to determine equilibrium and dynamic modulus, respectively.[1,2] Collagen and glycosaminoglycan (GAG) content were quantified via the ortho-hydroxyproline and 1,9-dimethylmethylene blue assays.[1,2] Biochemical and biomechanical data were plotted versus time and fit individually with a sigmoidal curve (y=C1*e^(C2*e^(C3*x))). Using the determined parameters (C1, C2, and C3), the 1st derivative of the function was calculated. To determine integration capacity, juvenile bovine cartilage explants (8 mm diameter) were obtained, trimmed, and cored (4 mm diameter) as previously described.[1] TE constructs at 1, 2, 3, 4, 5, 6, 8, and 11 weeks of culture were press-fit into the cartilage rings and cultured in chemically-defined media containing TGF-β3 for 6 weeks. Cartilage cores were also placed back into the cartilage rings as a control. At 3 and 6 weeks, integration testing was performed (n=6) as previously described[1,6,7] using a materials testing machine and indenting with a cylindrical flat ended indenter (4 mm diameter) until failure. The peak force was divided by the area of integration to determine the integration strength, which was then normalized with respect to the cartilage control. Histological (n=2) assessments were performed to visualize GAG at the interface (Alcian Blue stain). Statistical Analysis: Pearson correlation coefficients were calculated between the biochemical and biomechanical data or their 1st derivatives and integration strength, with statistical significance set at $p<0.05$.

Results

The equilibrium modulus of the MSC-seeded HA constructs followed a sigmoidal growth trajectory over time, with an initial lag phase for the first 3 weeks, followed by a linear region with increased slope, before slowing down by 7 weeks (Figure 1A). The 1st derivative of the modulus was parabolic over time, peaking at ~5 weeks (Figure 1B). Similar findings were obtained for the dynamic modulus as well as the GAG and collagen content (data not shown). In terms of integration, TE constructs implanted after 4-6 weeks of pre-culture reached the highest values for integration strength at both 3 and 6 weeks. No significant correlation was found between equilibrium modulus or dynamic modulus of the constructs at implantation and the resulting integration strength at 3 weeks (R^2=0.01 and 0.01, respectively, $p>0.05$) (Figure 1C, Table 1).

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fishmatthew@gmail.com

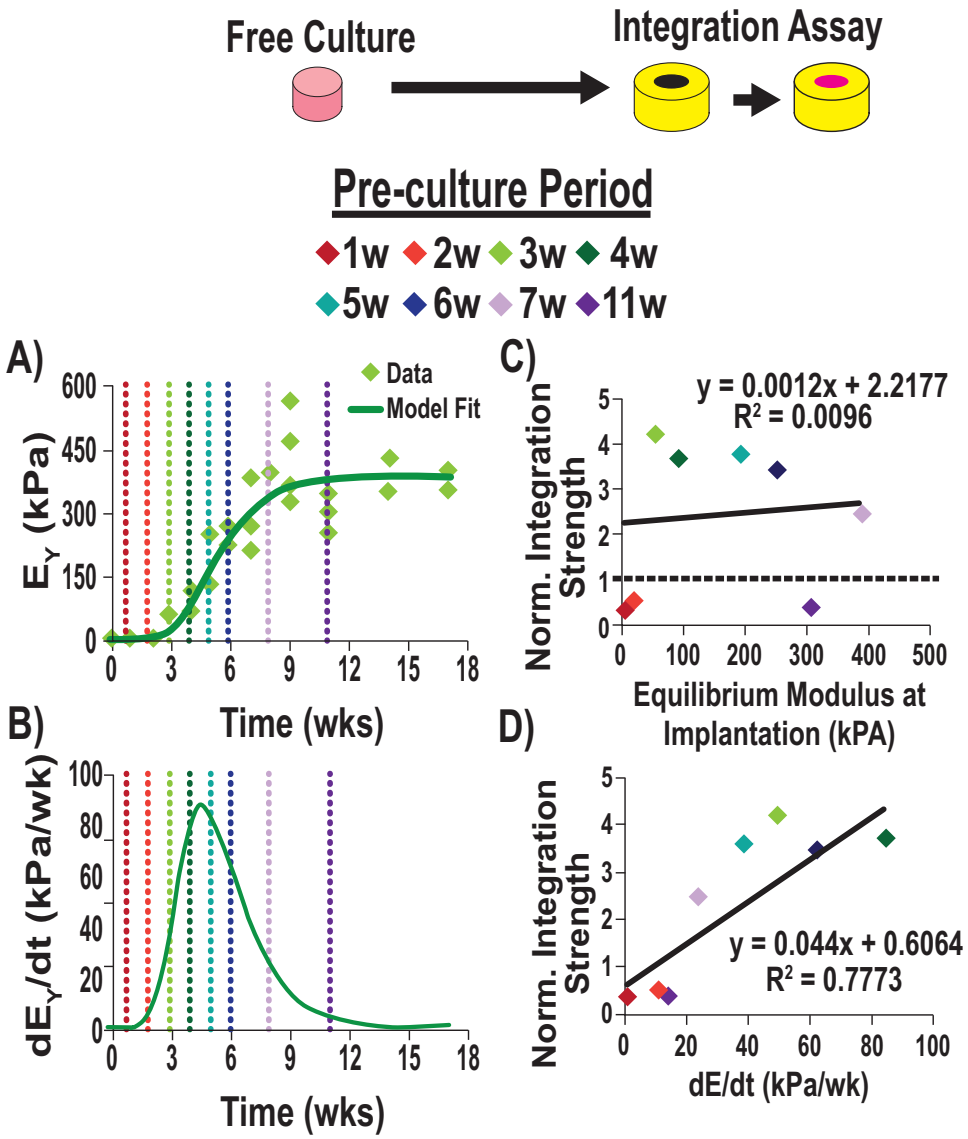

Figure 1. Correlation of maturation with integration capacity. Equilibrium modulus (A) and its first derivative (B). Dashed lines represent duration of pre-culture before initiating integration assay. Correlations between integration strength and equilibrium modulus (C) and its first derivative (D) of constructs at time of implantation.

Table 1. Correlations between integration strength and biochemical and biomechanical properties of constructs at the time of implantation and their first derivatives (*p<0.05).

	Normalized Integration Strength			
	3w		6w	
Values	**p-value**	**R^2**	**p-value**	**R^2**
Equilibrium Modulas	0.817	0.01	0.432	0.11
Dynamic Modulas	0.861	0.01	0.406	0.12
GAG Content	0.837	0.01	0.457	0.10
Collagen Content	0.794	0.01	0.186	0.27
1st Derivative				
Equilibrium Modulas	0.004*	0.78	0.013*	0.67
Dynamic Modulas	0.002*	0.82	0.004*	0.78
GAG Content	0.010*	0.70	0.002*	0.73
Collagen Content	0.027*	0.59	0.222	0.24

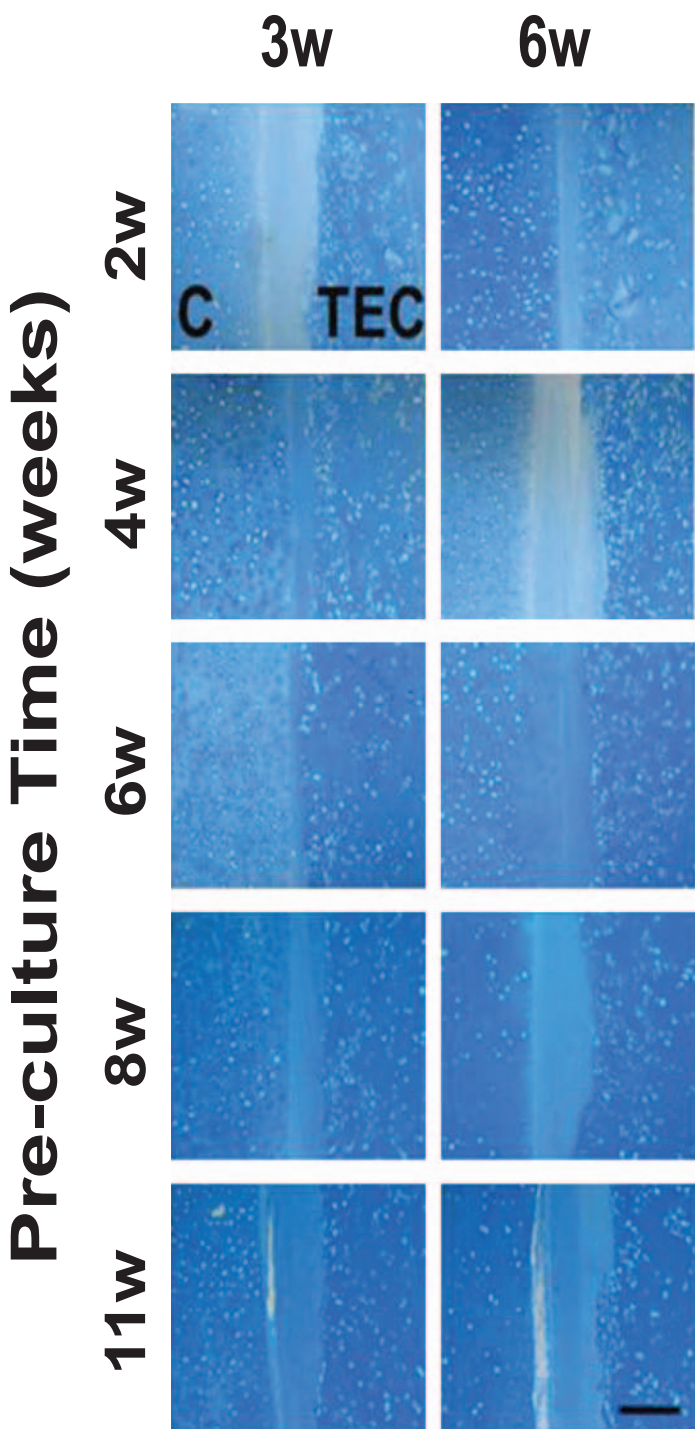

Figure 2. Histological staining for proteoglycans after integration for 3and 6 weeks (C-TEC= cartilage-tissue engineered construct). TECs were cultured for varying durations of pre-culture prior to implantation (scale bar = 200μm).

Similar findings were obtained for the GAG and collagen content (R^2=0.01 and 0.01, respectively, p>0.05, Table 1). However, a clear correlation was achieved between the first derivative of all biochemical and biomechanical measures and integration strength (R^2=0.59-0.86, p<0.05) and R^2 values ranging from 0.67 to 0.83 for their 1st derivatives (p<0.05, Table 1). These data were confirmed via histological assessment (Figure 2). The greatest integration occurred with constructs that had been pre-cultured for 4-6 weeks, with dark and homogenous staining across the interface, while earlier or later pre-culture periods showed incomplete integration with diffuse staining.

Discussion

In this study, we modeled the maturation of MSC-laden HA hydrogels during in-vitro culture and examined the importance of time-dependent parameters on the ability of these constructs to integrate to cartilage. In support of our hypothesis, the integration strength of constructs to cartilage was linearly correlated to the change in biochemical and biomechanical properties as a function of time (its rate), but not the static levels of these properties. Previous studies have attempted to correlate construct maturation to its ability to integrate to cartilage both in-vitro and in-vivo, with conflicting results.[1,6-8] The current data suggest that a TB-TE approach may be able to resolve these differences by highlighting the importance of time-dependent maturation rates, rather than static measures of maturation, allowing determination of an optimal period for in-vivo implantation. Ongoing and future work will extend these findings to the investigate maturation states and rates at the time of implantation to in-vivo outcomes using a large animal model of cartilage repair.

Significance

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

Acknowledgments

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Enhanced Nutrient Transport Improves Depth-Dependent Properties of a Tri-layered HA Construct With Zonal Co-culture of Chondrocytes and MSCs

Minwook Kim
Jason A. Burdick, PhD
Robert L. Mauck, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Biomimetic design in cartilage tissue engineering is a challenge given the complexity of the native tissue. Further, while chondrocytes (CHs) are one source for tissue engineering, they are limited in number and so mesenchymal stem cells (MSCs) are considered a promising alternative, especially when co-cultured with CH. In this context, CHs can enhance the initial efficiency of MSC chondrogenesis, as well as limit hypertrophic changes in some instances.[1,2] Moreover, a number of studies have shown that zonal CHs seeded in layered hydrogels can produce depth-dependent inhomogeneity, suggesting that these zonal CHs maintain their identity in 3D culture.[3] Recently, we showed that the zonal CH populations retained their native production levels and influenced MSC fate decisions in hyaluronic acid (HA) hydrogel co-cultures,[4,5] and created a tri-layered HA construct with mixed zonal CHs and MSC subpopulations to mimic the depth-dependent properties of cartilage.[6] One limitation of that study was that matrix deposition in the core region of the construct was limited, due to poor nutrient transport. To improve nutrient supply, recent studies have used dynamic loading, media perfusion, microbubbles and macro-channels.[7] Here, we used a porous hollow fiber (combined with cotton thread) as a transport pathway, and investigated the effects of this modification on the maturation of the tri-layered construct and on its zonal integration when used to fill a cartilage defect.

Methods

(Study 1) MSCs (P3) and zonal articular CHs were isolated from juvenile bovine knees. Full-thickness cartilage was excised from the femoral condyle and divided into three layers to obtain CHs from the superficial (SCH; top 100 μm), middle (MCH; top half of remaining cartilage), and deep (DCH) zone (bottom half of remaining cartilage). CHs were isolated by collagenase digestion and expanded through passage 4. MSC-only or mixed cell populations (MSC:CH ratio = 4:1) were encapsulated at 60×106 cells/mL in 1% w/v HA hydrogel (Lifecore Biomedical).[8] Tri-layered constructs were created by exposing the first layer (DCH-MSC) of the cell-HA solution to UV light for 2 minutes, followed by polymerization of the second layer (MCH-MSC) for 4 minutes, and finally adding the third layer (SCH-MSC) and completing polymerization via UV for another 6 minutes (Figure 1A).To improve nutrient transport, a porous hollow fiber (HF; ID=700μm, pore size=0.1μm) (alone or with a cotton thread passed through it) was inserted through the core along the axial direction on day 3 (Figure 1B-C).[9]

(Study 2) To investigate the effects of zonal chondrocytes on integration with native cartilage, tri-layered constructs were used to fill a defect (ID: 5 mm) by polymerizing the layers in situ or by placing the construct into the defect after in vitro polymerization (Figure 1J-M), with zone-to-zone matching (Figure 1L). Constructs (Ø4.8 × 3.5 mm) were cultured in a defined medium containing 10ng/mLTGF-β3, with media changed thrice weekly, and constructs were turned regularly to improve growth through the depth. Cell viability, distribution and proliferation of mixed populations of MSCs (blue), superficial (red), middle (purple), and deep (green) zone chondrocytes were followed using CellTracker (Molecular Probes). Bulk properties were assessed via unconfined compression, and local properties[10] were determined using a custom microscope compression device and texture correlation.[11] Glycosaminoglycan (GAG) and hydroxyproline contents were determined. Paraffin or cryo-sections (8μm) were stained with Alcian Blue for proteoglycans (PG). Significance was determined by two-way ANOVA with Tukey's post hoc tests ($p<0.05$).

Results

MSC and CH were viable over the 16 week culture period, with each cell population well mixed within its appropriate layer (Figure 1D-F). Constructs with HF and HF/thread maintained initial construct dimensions without swelling, and cells in the core were more viable (data not shown). Bulk properties and GAG content in all groups increased with time, reaching ~600 kPa and 4%WW at 16 weeks (Figure 1G-H), levels comparable to native cartilage (dashed line). Cells in the core region without HF enlarged (became

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kimminw@mail.med.upenn.edu

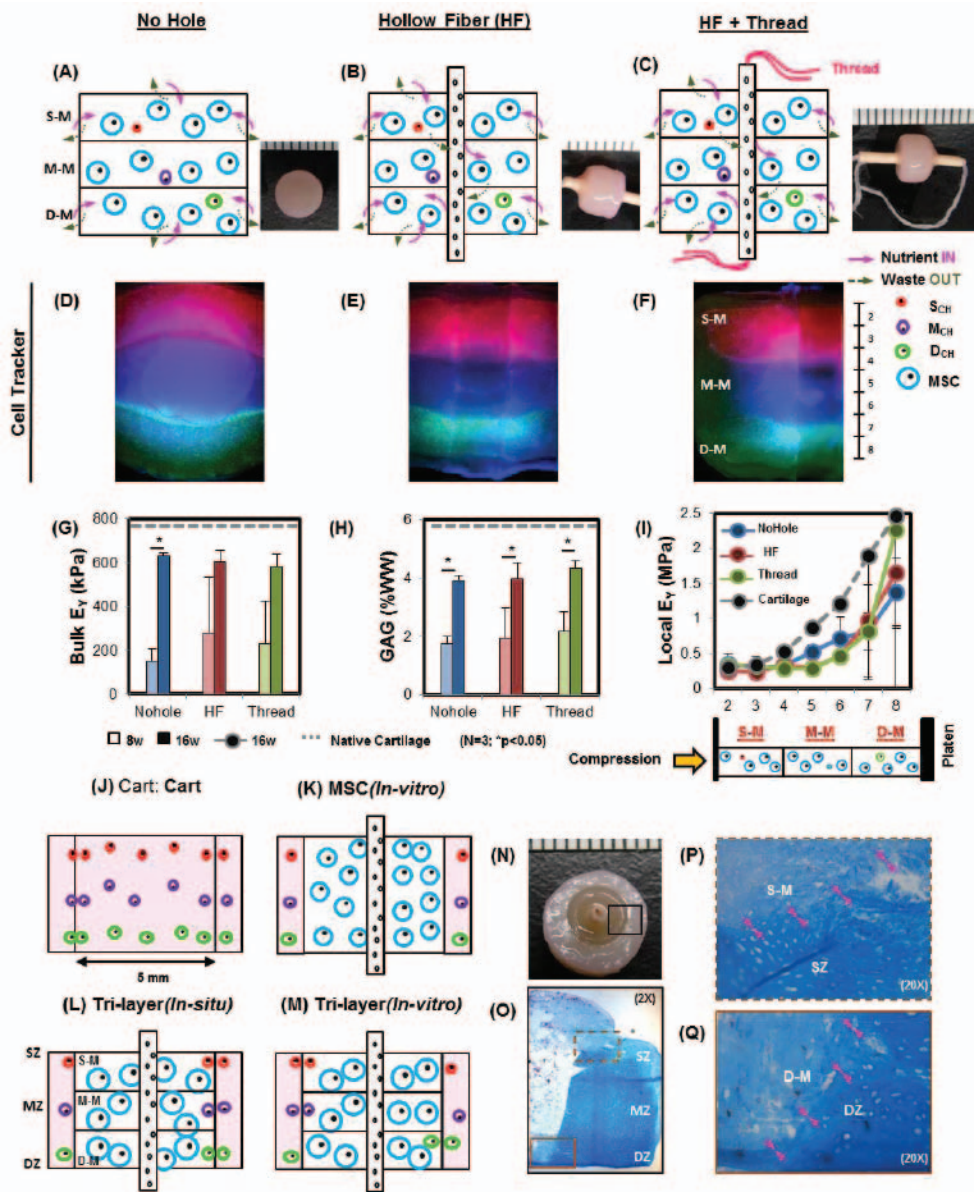

Figure 1. [Study 1] Schematics and macroscopic images (at 16 weeks) or tri-layered construct (A) No hole, (B) Hollow fiber (HF), (C) HF with thread (HF + thread). (D-F) Visualization of superficial zone CHs (red), MSCs (blue), deep zone CHs (green) at 16 weeks (cell mixture, CH:MSC = 1:4). (G) Bulk modulus (kPa), where lighter bars indicate 8 weeks and darker bars indicate 16 weeks. (H) GAG (%WW) content. (I) Local modulus (MPa) in Nohole (blue), HF (red), HF + thread(green), and native cartilage (gray), where region 8 is the deep zone (n=3 *p<0.05). [Study 2] Zone-to-zone cartilage integration schematics: (J) Cartilage/cartilage (control), (K) cartilage/MSC (in vitro), (L) cartilage:Tri-layer (in situ), (M) cartilage:Tri-layer (in vitro). (N) Macroscopic image of cartilage:Tri-layer group (in vitro), (O-Q) Alcian blue staining (pint arrows indicate interface between repair tissue and host cartilage).

hypertrophic), while those with a HF maintained a normal cell morphology (data not shown). The local modulus of the tri-layered constructs showed depth-dependent properties (~0.3MPa in the 'surface' region and ~1.4-2.3 MPa in the deep region, Figure 1I). The local modulus of the construct with HF/thread (green) in the deep region (DCH-MSC) nearly matched native levels. While the overall depth dependence mirrored native tissue, properties in the central regions were still lower than that of the native tissue. When these constructs were used to fill a cartilage defect, zonally-matched integration began from the outer surfaces (Figure 1N-Q).

Discussion

In this study, we fabricated a tri-layered HA construct with zonal co-culture of CH and MSCs in each layer to mimic the depth-dependent properties of articular cartilage. Given the thickness of the scaffold, we included a porous HF (coupled with thread) to improve nutrient transport into the core of the construct. Although the cells in the core region of the construct with HF showed robust PG production, there was neither a positive nor adverse effect on bulk properties, which are mainly governed by peripheral matrix properties. However, the HF did ensure that the tri-layered construct retained a

distinct cellular organization (without swelling) and produced constructs with near-native depth-dependent properties. The ratio of local modulus of the D-M:S-M layer in the tri-layered construct with HF/thread, HF, and control constructs was 6.8, 6.5 and 4, respectively (whereas the ratio for native cartilage was 8.1; DZ:SZ). With the tri-layered construct, we further investigated the effect of zone-to-zone cartilage integration, where zonal chondrocytes in each layer of the construct were matched to the host tissue. Filling cartilage defects in a zonally consistent manner might allow for better interaction between engineered construct and host tissue, though longer term studies are required to validate this finding. Taken together, our results demonstrate that a layer-by-layer fabrication scheme, including co-culture of zone-specific articular CHs and MSCs, can reproduce the depth dependent characteristics and mechanical properties of native cartilage. Such a tri-layered construct may provide critical advantages for focal cartilage repair. Ongoing studies will determine how individual cells within each layer communicate with one another and with adjacent layers, and scale this technology to produce constructs of anatomic relevance for cartilage repair applications.

Significance

Biomimetic design in cartilage tissue engineering is challenging. A tri-layered construct comprised of zonal CHs co-cultured with MSCs generated depth-dependent properties that mirrored native tissue by 16 weeks, particularly when the central nutrient supply was increased via a porous HF (w/ thread). This tri-layered engineered cartilage with zonal CHs/MSCs co-culture holds promise for the repair of focal defects.

Acknowledgments

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A Radiopaque Electrospun Scaffold for Engineering Fibrous Tissues: Characterization and In Vivo Application

[1,2]John T. Martin, MS
[1,2]Andrew H. Milby, MD
[1]Subash Poudel
[1,2,3]Christian G. Pfeifer, MD
[1,2]Harvey E. Smith, MD
[4]Dawn M. Elliott, PhD
[1,2]Robert L. Mauck, PhD

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

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

[3]University Clinic Regensburg, Regensburg, Germany

[4]Department of Biomedical Engineering, University of Delaware, Newark, DE, USA.

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johnma@mail.med.upenn.edu

Introduction

The healing capacity of the intervertebral disc, meniscus, tendons and ligaments is limited, and injuries to these tissues compromise function for millions.[1] Tissue engineering strategies for treating fibrous tissues have transitioned over the past ~15 years from in vitro to in vivo evaluation, using a variety of animal models. Once implanted, most engineered materials cannot be followed radiographically, however, and often are difficult to find at the time of sacrifice. Implant position is monitored in standard clinical practice; for example, radiopaque bone cements made of poly(methyl methacrylate) and a heavy metal salt (barium sulfate) are used in the fixation of prostheses. Enabling similar visualization of engineered soft tissues would be particularly useful for repairing tissues that are subject to physiological loads and resultant changes in position.[2,3] Thus, we developed a radiopaque nanofibrous scaffold by electrospinning a polymer/heavy metal salt solution, and used this material as a diagnostic tool for model development. In this study, we characterized the radiopacity, structure and mechanical behavior of the scaffold, and showed its utility in an in vivo model of intervertebral disc replacement.

Methods

Fabrication

Radiopaque scaffolds were generated from a 14.3% w/v slurry of poly(ε-caprolactone) (PCL) mixed with zirconium(IV) oxide (zirconia), a radiodense powder with a characteristic dimension <100 nm. Slurries were electrospun while continuously mixing, and collected onto a rotating mandrel to create an aligned nanofibrous sheet (th.=200μm). Four scaffold-types with varying radiodensity were fabricated: 100% PCL, 90% PCL/10% zirconia, 75% PCL/25% zirconia, 50% PCL/50% zirconia.

In Vitro Analysis

Each scaffold was assayed for structural continuity, radiodensity and mechanical strength. To assess nanostructure, samples were imaged by SEM (n=1/group). To measure radiodensity, 8 mm diameter samples were punched from each scaffold and scanned by μCT (vivaCT 75, SCANCO) at 20 μm resolution (n=5/group). The linear attenuation coefficient of each sample was calculated from volumetric reconstructions. Scaffold strips (5mm x 40mm) were tested in uniaxial tension in the fiber direction (n=5/group). The mechanical testing protocol consisted of a 0.05 N preload, followed by extension to failure at a rate of 0.1% strain/s. Tensile modulus was calculated as described previously.[4]

In Vivo Analysis

Disc-like angle ply structures[5] fabricated from radiopaque scaffold (rDAPS) were implanted into the rat caudal spine.[2] Strips were cut from aligned radiopaque scaffold 30° to the fiber direction and two strips with alternating ±30° alignment were wrapped concentrically to form the annulus fibrosus region of the rDAPS. To implant rDAPS, surgical wires were passed laterally through the mid-height of vertebrae adjacent to the C8/C9 disc, and an external fixator was applied (Figure 1). A dorsal incision was made, the native disc was removed and rDAPS were inserted into the disc space. Rats were returned to cage activity and euthanized at 28 days. Two implant types were used in this study: a radiodense implant, "50/50 rDAPS" with 2 layers of 50% PCL/50% zirconia (n=2); a radiolucent implant,"75/25 rDAPS" with 1 layer of 75% PCL/25% zirconia, 1 layer 100% PCL and one layer of degradable 75:25 poly(lactic-co-glycolic acid) (PLGA, to provide a route for cell migration once degraded) (n=3). To monitor changes in implant position and structure in vivo, rat tails were imaged longitudinally with a fluoroscope. Then, following euthanasia, tails were imaged via μCT to assess implant structure and histological sections were stained with picrosirius red (for collagen).

Results

SEM revealed that all formulations of radiopaque scaffold had continuous and aligned fibers (Figure 2A-D). Zirconia was embedded within fibers at lower concentrations, but at the highest concentration it was evident that zirconia aggregated into large pellets exterior

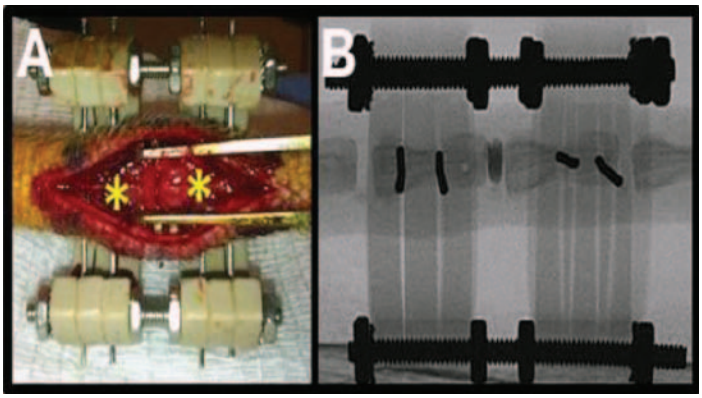

Figure 1. A) rDAPS were implanted between vertebrae (asterisk) of the rat caudal spine to demonstrate the utility of radiopaque scaffold. B) The vertebrae were stabilized with a radiolucent external fixator.

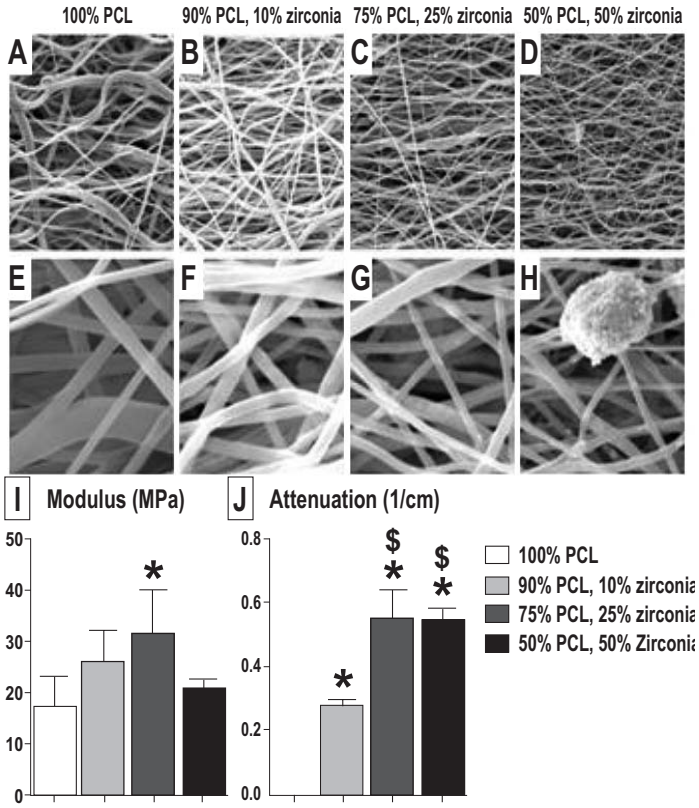

Figure 2. Characterization or radiopaque scaffold. SEM images at A-D) 2,000x magnification and E-H) 10,000x magnification, I) tensile modulus and J) linear attenuation. Statistics calculated using one way ANOVA with Bonferroni correction for post-hoc comparisons:*, $p<0.05$ vs. 100% PCL and $, $p<0.05$ from 90% PCL, 10% zirconia.

to the fibers (Figure 2E-H). In addition, as zirconia increased fiber diameter decreased. Scaffold modulus increased with zirconia content, except at the highest concentration (Figure 2I). Scaffold radiation attenuation increased with zirconia content plateauing at 25% zirconia (Figure 2J). PCL alone had no signal and thus 3D reconstruction was not possible. Both formulations of rDAPS were visualized intra- and post-operatively. 50/50 rDAPS had a distinct signal (Figure 3A), more intense than that of the native bone, while the 75/25 rDAPS cast a radiolucent shadow similar to bone (Figure 4A). rDAPS remained in the disc space over 28 days with no change in position or shape. These results were confirmed by μCT; both types of rDAPS had a signal distinguishable from bone allowing for the reconstruction of each separately. Reconstructions of 50/50 rDAPS demonstrated that the radiopaque implants occupied the disc space and did not cause an adverse reaction (Figure 3B). 3D reconstructions of 75/25 rDAPS demonstrated that lamellar structure was intact after 28 days (Figure 4B,C). Images of histological sections confirmed that new collagen was deposited between layers, though the PLGA had not completely degraded (Figure 4D).

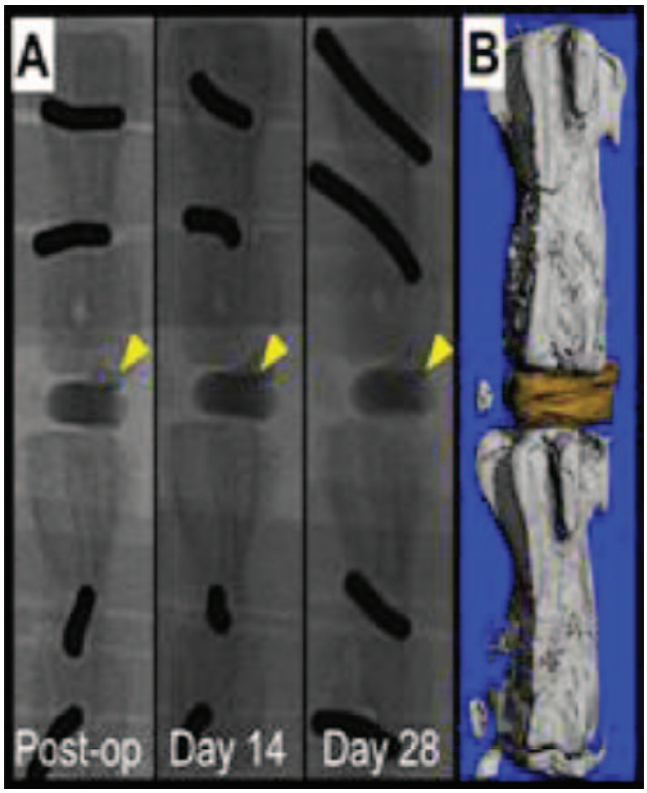

Figure 3. Implantation of high radiodensity rDAPS. A) Fluoroscopy over 28 days. B) μCT reconstruction after 28 days.

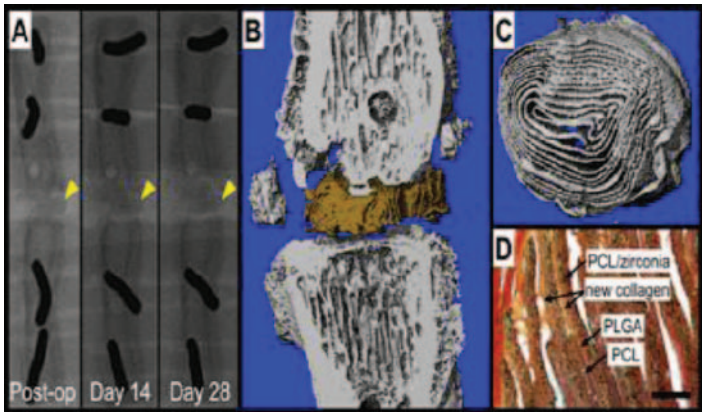

Figure 4. Implantation of low radiodensity rDAPS. A) Fluoroscopy over 28 days. B) μCT at day 28. C) μCT of rDAPS only at day 28. D) Picrosirius red-stained section at day 28. Scale = 250μm.

Discussion

We developed and characterized a radiopaque electrospun scaffold composed of PCL, a standard tissue engineering polymer, and zirconia, a heavy metal salt. We demonstrated that scaffold radiopacity and mechanics can be tuned by altering the concentration of zirconia. In addition, we fabricated radiopaque implants and validated a rat caudal spine model of disc replacement.

Scaffold mechanical properties and radiation attenuation are tunable by altering zirconia concentration. Mechanical properties increased by adding the radiopaque filler, but declined at the highest concentration. This phenomenon is also observed in electrospun scaffolds mixed with hydroxyapatite for bone tissue engineering.[6] The radiation attenuation of each scaffold increased with zirconia content and plateaued at 25% zirconia. By controlling the zirconia content, scaffold radiopacity can be tuned for a specific application. For example, in a subcutaneous model, a radiolucent scaffold may be useful, since the superficial nature of a subcutaneous model lends itself to unobstructed visualization. However, if an electrospun scaffold is used to regenerate a deeper tissue, like inside a synovial joint,[7] the abdomen,[8] or within the lumbar spine, model development may require a radiodense scaffold.

Radiopaque implants made with high and low concentrations of zirconia were visualized in the rat caudal spine. Previous work with this model demonstrated that implants were ejected from the disc space when the rat tail was not fixed.[2] Thus, this study demonstrates that fixation is necessary for rat caudal disc replacement. In addition, the radiopaque scaffold was compatible with the formation of new collagen by endogenous cells. Future work must confirm that these scaffolds do not influence cells to also produce mineralized tissue.

Significance

This study describes a radiopaque scaffold for engineering fibrous tissues and its application when fluoroscopy is useful for evaluation of the scaffold in an animal model.

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Validation and Screening in a High Throughput Mechanical Injury Model of Engineered Cartilage

[1]Bhavana Mohanraj
[1]Greg R. Meloni
[1]Rodolfo Finocchi
[1,2]Robert L. Mauck, PhD
[1,2]George R. Dodge, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Collaborative Research Partner Acute Cartilage Injury Program of AO Foundation, Davos, Switzerland.

Introduction

Joint injuries increase the likelihood of developing post-traumatic osteoarthritis (PTOA) due to the initiation of catabolic processes that lead to progressive degeneration of the joint cartilage. Several in vitro models have been developed (using chondral explants) to investigate the pathologic mechanisms of PTOA and to evaluate the efficacy of putative small molecule therapeutics to stop or reverse the degenerative process. These agents include anti-apoptotic agents that inhibit caspase activity,[1,2] free-radical scavengers,[2] and polymers that aid in the repair of cell membranes.[3,4] Unfortunately explant models are limited in their throughput and in the homogeneity of explant response to injury, making larger scale drug screening studies impractical. To address this limitation, we recently developed a high throughput mechanical testing platform capable of applying injurious compression to engineered cartilage constructs, showing increased matrix degradation and cell death comparable to that reported for cartilage injury models.[5] In the current study, we further validated this high throughput mechanical injury (HiTMI) model of PTOA by: 1) directly comparing the response of native chondral explants and engineered cartilage analogs subjected to identical injuries, and 2) using the HiTMI system to evaluate bioactive molecules previously reported to reduce cell death and proteoglycan loss post-injury.

Methods

Engineered Cartilage

Engineered cartilage tissue analogs (CTAs) were fabricated as previously described;[6] briefly, cartilage was harvested from juvenile bovine knees, minced, digested overnight in Collagenase II, washed (PBS w/ 2X PSF) and centrifuged (1750 rpm, 3X) to collect chondrocytes. Chondrocytes were seeded into polyhydroxyethylmethacrylate coated 96-well plates at $1x10^6$ cells/construct and cultured in high glucose DMEM with 10% FBS and vitamin C (50 ng/mL). CTAs were matured for ≥14 weeks and their height was measured prior to placement in 48 well plates for high throughput impact (75% strain at 50% strain/s; total impact time: 10s). CTAs were harvested 24, 48, and/or 120 hours post-injury.

Cartilage Explants

Chondral plugs were harvested from the trochlear groove of juvenile bovine knees (Ø4mm) and trimmed to similar heights, removing the subchondral bone (H: 3-4mm). Explants were injured as above, but were processed one at a time as the high peak stresses generated during injury exceeded the load threshold of the high throughput sensor.

Chemical Compounds

Immediately following injury, CTAs were treated with one of three agents: (1) N-Acetyl-Cysteine (NAC, 2mM) a nitric oxide scavenger, (2) Z-VAD-FMK (ZVF, 100μM), a pan-caspase inhibitor, or (3) Polaxamer 188 (P188, 8mg/mL), an amphiphilic polymer capable of inserting into and closing the ruptured cell membrane. All were included in culture for the initial 48 hours post-injury. As a positive control, some CTAs were treated with IL-1 (10 ng/mL) for 120 hours.

Analysis

For all time points, constructs were harvested to measure matrix content (GAG by DMMB assay and collagen by OHP assay; N=4). Medium was collected at each time point to assess release of matrix (GAG) and cell viability (LDH assay; N=2-4). Values were normalized to wet weight and to the control, un-injured group. Comparisons between treated and non-treated impacted and control groups were made using a two-way ANOVA with Bonferroni's post-hoc ($p<0.05$).

Results

Although injury of native cartilage generated peak stresses approximately 20-fold higher than engineered cartilage (~20 vs. 1 MPa; Figure 1, inset), the response to injury was similar as measured by enzyme and matrix release. Both cartilage and CTAs released similar amounts of GAG (0.18+/−0.024 vs. 0.22+/−0.003 %ww) to the medium, while LDH release was slightly higher from native tissue (650+/−123 vs. 280+/−32.9 %ww, Figure 1). Subsequent

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mbhavana@mail.med.upenn.edu

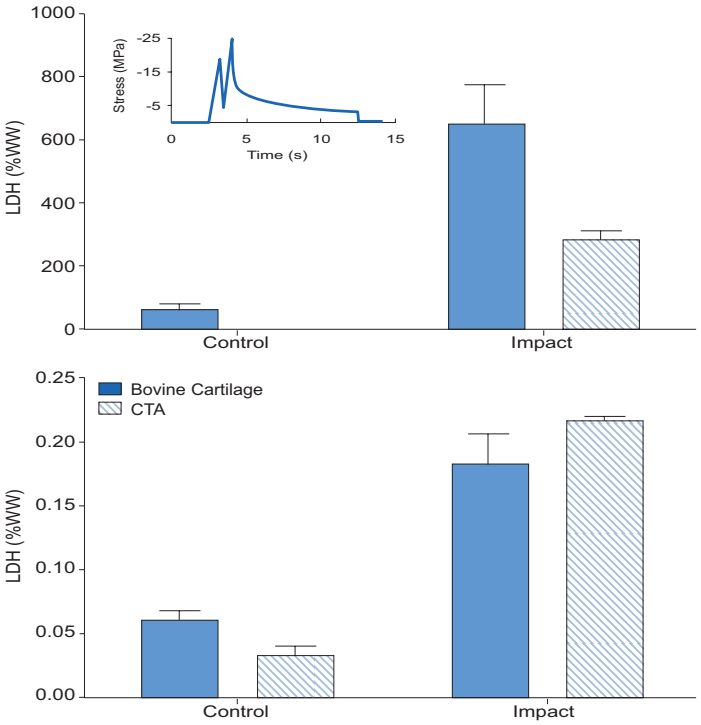

Figure 1. Comparison of cartilage and CTA response to injury shows similar trends in (A) LDH and (B) GAG release 24 hours post-injury (CTA: N=2 with two constructs/well; cartilage: N=4).

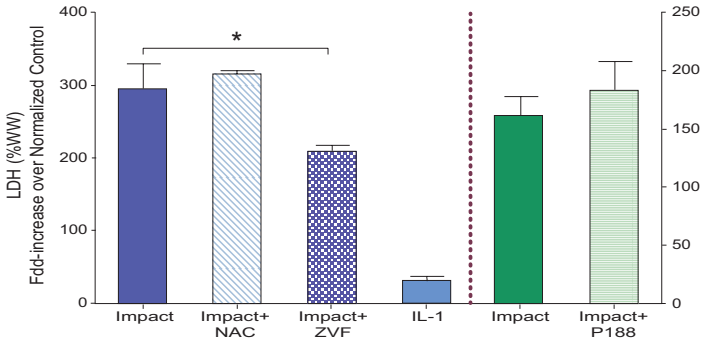

Figure 2. LDH release 24 hours post-injury. (Left) ZVF significantly reduces enzyme release by ~28%, while NAC and (Right) P188 have no effect compared to injury alone (N=2 with two constructs/well).

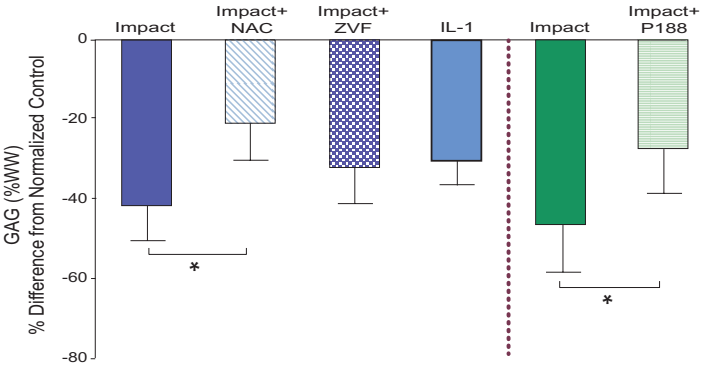

Figure 3. GAG in constructs 120 hours post-injury. While injury alone reduces GAG by ~40% compared to control, (Left) NAC and (Right) P188 treatment are able to retain ~20% more matrix as compared to injury alone.

screening of several putative PTOA therapeutics showed reduced cell death and matrix loss in the short-term following injury in this model system. In the initial 24 hours, ZVF treatment significantly reduced LDH by ~28% compared to injury alone (211+/−6 vs. 295+/−34.6; $p<0.05$), however NAC and P188 did not (Figure 2). By 120 hours post-injury, however, both NAC and P188 decreased GAG loss (by 18 and 20% respectively; $p<0.05$) compared to injury alone, although neither agent restored GAG to control levels (Figure 3). Despite increasing initial cell viability after injury, ZVF treatment did not alter GAG content in injured samples at 120 hours.

Discussion

In this study, we validated our in vitro high throughput mechanical injury (HiTMI) model by directly comparing the response of native cartilage to that of engineered cartilage under identical injurious compression conditions. Although peak stresses differed significantly with 75% strain applied at 50% strain/sec (due to differences in mechanical properties), release of GAG and LDH were comparable over the first 24 hours post-injury. Following this validation step with native tissue, we next carried out a small screen of putative PTOA therapeutics that target the first events to occur following injury. Consistent with the literature, application of these compounds to engineered cartilage injured in the HiTMI system resulted in similar protection against loss of cell viability and matrix changes. For example, ZVF is reported to increase cell viability by 15-20% with 48 hours of treatment of explants compressed to 30% strain in 500ms[1] or impacted at 7J/cm^2;[2] in this study, ZVF similarly decreased LDH release from CTAs post impact. NAC has likewise been reported to increase viability by ~30% following injury.[2] Here we found that NAC had no effect on reducing membrane damage. However, our results with NAC do match those reporting a reduction of GAG loss from cartilage by ~20% in chondral explants post-impact at 7J/cm^2.[2] Findings for P188 have been more variable, with some reports noting a ~20% increase in cell viability[3] with smaller changes in GAG loss;[4] our findings support the notion that GAG retention is improved with P188 treatment. Together, these results suggest that CTAs (and engineered cartilage in general) may serve as an appropriate surrogate for studying the mechanisms underlying the progression of PTOA. We additionally demonstrated the feasibility of using the CTA to screen even larger small molecule libraries for PTOA therapeutics using this novel HiTMI system.

Significance

We established that engineered cartilage can serve as a surrogate for the study of PTOA. Given the ability to form many such analogs in a micro-scale format, this finding sets the stage for the high throughput screening of large chemical libraries to identify novel compounds that may attenuate PTOA pathology and offset progressive degenerative joint changes.

Acknowledgments

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Material-Mediated Degradation of the Meniscus Wound Interface Enhances Integration

[1,2]Feini Qu, BS
[1,2]Michael P. Pintauro
[1,2]Elizabeth A. Henning, BS
[1,2]John L. Esterhai, MD
[1,2]Matthew B. Fisher, PhD
[1,2]Robert L. Mauck, PhD

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

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

Introduction

Meniscus tears are one of the most common indications for arthroscopic surgery, but the limited healing of adult meniscus directs clinical practice towards resection (partial meniscectomy) rather than repair, increasing the risk for early-onset osteoarthritis.[1] As such, methods to augment endogenous repair could promote long-term joint health after injury. Previously, we showed that the meniscus extracellular matrix (ECM) increases in density with age, and hypothesized that this constitutes a physical barrier to repair.[2] To test this hypothesis, we treated the adult bovine meniscus wound edge with a matrix-degrading enzyme (collagenase) and showed improved cellularity and tissue integration *in vitro*.[3] To localize enzymatic treatment, we developed a material-mediated delivery system in which bioactive collagenase was released from polymer nanofibers. In this study, we tested the hypothesis that these novel scaffolds would enhance cellularity and matrix formation in bovine meniscus 'repair' constructs *in vivo* (placed subcutaneously in athymic rats).

Methods

Scaffold Fabrication

Nanofibrous composites were formed via electrospinning using a custom tri-jet device[4] to contain a poly(ε-caprolactone) (PCL) structural fiber fraction along with two water-soluble poly(ethylene oxide) (PEO) fiber fractions (~50-60% PEO by mass). PEO fibers contained either no collagenase (PCL/PEO) or 15.6% type IV collagenase by mass (PCL/PEO-C).[3] Scaffolds were cut to 5x5 mm with a 2 mm diameter fenestration to permit tissue-to-tissue contact inside the construct.

Repair Construct Preparation

Cylindrical adult bovine meniscal explants (8 mm diameter) were harvested, trimmed to a height of 4 mm, and incised to create a horizontal defect. Four treatment groups were prepared: empty defect incubated in basal media (control, BM), empty defect incubated for 6 hours in BM with 0.4 mg/mL collagenase (C), defect with a control scaffold (PCL/PEO), and defect with a collagenase-releasing scaffold (PCL/PEO-C).

Implantation Surgery

All procedures were approved by the Institutional Animal Care and Use Committee of the Philadelphia VA Medical Center. Four dorsal pockets were prepared in each of five male athymic nude rats (Crl:NIH-*Foxn1*^{rnu}, 300-350 g, Charles River). One repair construct per group was placed in each pocket. At 1 week (n=1) and 4 weeks (n=4) rats were euthanized by CO_2 asphyxiation, and samples were harvested for analysis.

Sample Processing and Analysis

Samples were fixed with paraformaldehyde, paraffin embedded, sectioned, and stained with picrosirius red (PSR) for collagen or 4', 6-diamidino-2-phenylindole (DAPI) for cell nuclei. Immunohistochemistry for the cell surface marker CD45 was performed to identify cells of hematopoietic origin. Percent integration of the interface was calculated by dividing the cumulative length of cohesive tissue-tissue and tissue-scaffold segments by the defect length in PSR sections (n=3-4/group at 4 weeks). Cell signal intensity at the interface (n=4/group at 4 weeks) was determined by converting the cell nuclei stained with DAPI to white (intensity=255) and the background to black (intensity=0) using ImageJ (NIH). The pixel intensity along the defect was averaged starting from the interface up to 700 μm perpendicular to the interface and binned into intervals of 100 μm. Significance was assessed by one- and two-way ANOVA with Tukey's HSD post hoc tests to compare integration and signal intensity between groups, respectively ($p \leq 0.05$).

Results

After 1 week *in vivo*, untreated controls (BM) and samples containing control scaffolds (PCL/PEO) had a dense collagenous ECM and lacked matrix deposition at the center of the defect. In contrast, samples treated with aqueous collagenase (C) and collagenase-releasing scaffolds (PCL/PEO-C) showed a qualitative decrease in matrix staining and increased

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feini@seas.upenn.edu

cellularity at the interface, with defect closure across the construct. After 4 weeks, staining for collagen showed improved defect fill for all groups compared to 1 week. Tissue-tissue and tissue-scaffold integration was most abundant for PCL/PEO-C samples, with regions of the scaffold staining positive for collagen (Figure 1A). There was a trend towards improved integration for PCL/PEO-C samples (87 ± 9%) compared to BM controls (59 ± 16%) (Figure 1B, $p=0.07$). Staining of nuclei showed a significant increase in cell signal intensity at the interface for PCL/PEO-C samples vs. all other groups (Figure 2B, $p \leq 0.05$). This increase in cell number was significant for a distance of 300 μm from the interface compared to collagenase alone, and 400 μm compared to BM and PCL/PEO groups. Immunohistochemistry revealed CD45+ cells at the constructs' periphery, with some penetrating the interior (Figure 2C).

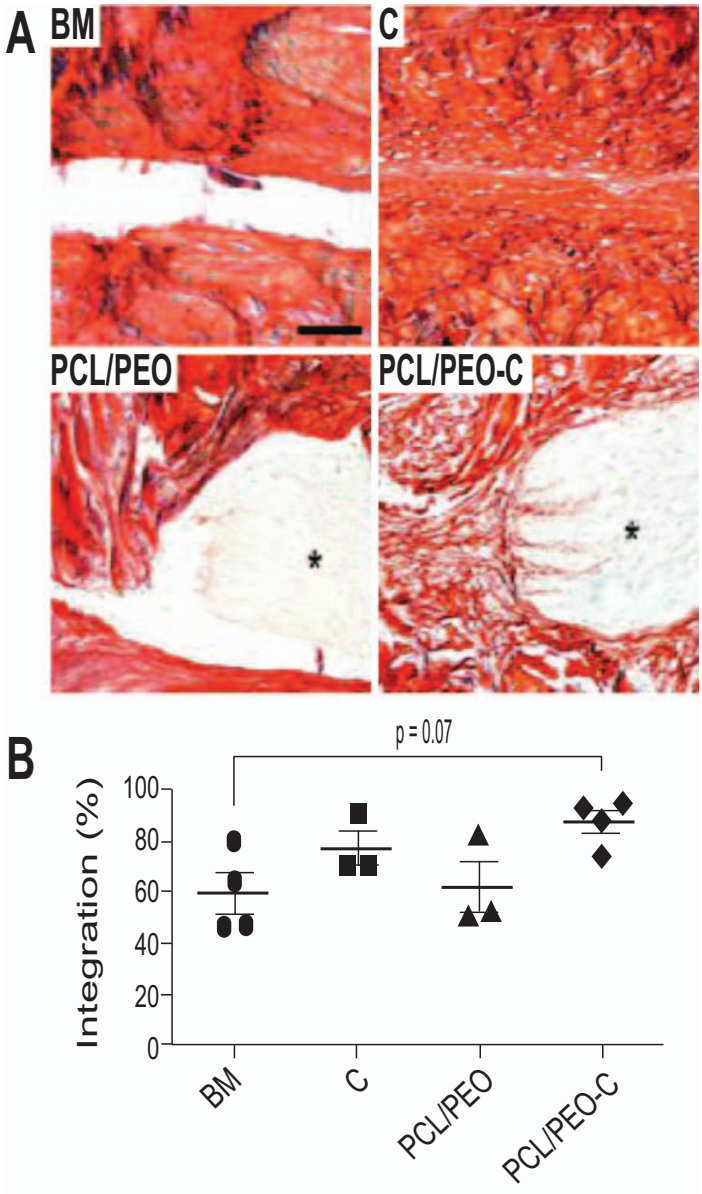

Figure 1. Improved integration of meniscus repair constructs with collagenase treatment (C and PCL/PEO-C) compared to controls (BM and PCL/PEO) at 4 weeks. (A) PSR staining of collagen at the defect. Asterisk indicates scaffold. Scale = 100 μm. (B) Integration normalized to defect length (n=3-4/group).

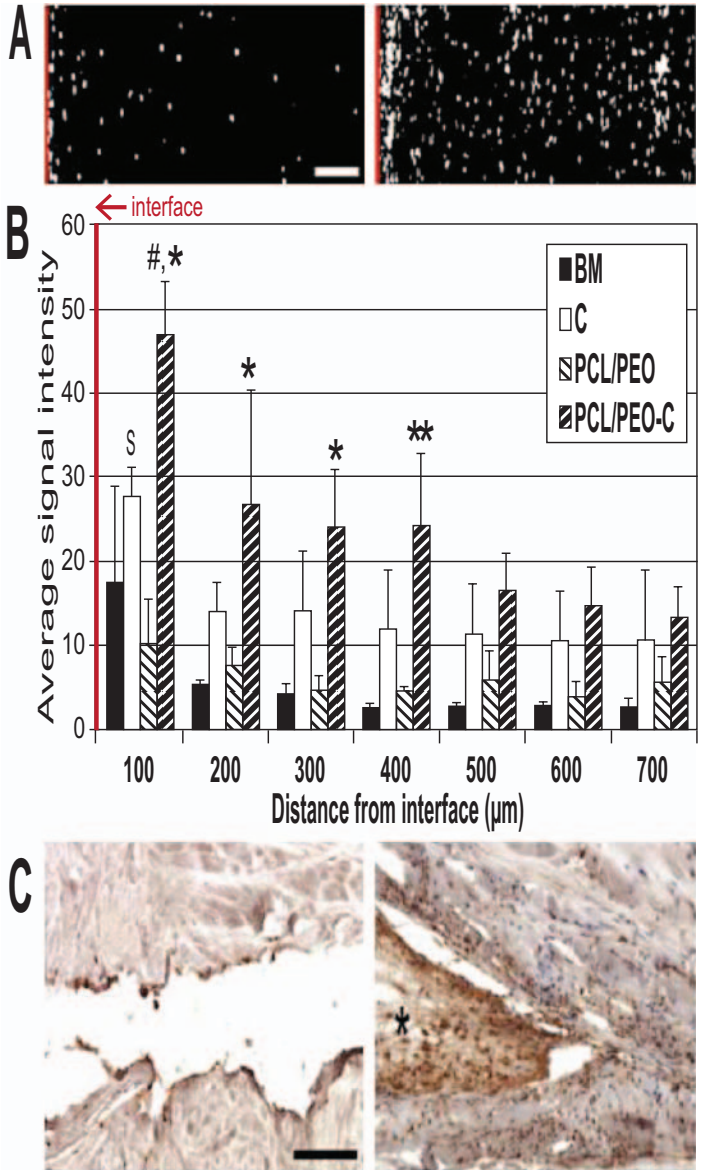

Figure 2. Collagenase treatment increased cellularity at the wound interface. (A) DAPI staining of cell nuclei for BM (left) and PCL/PEO-C (right) at 4 weeks. Interface is to the left (red line). Scale = 100 μm. (B) Average cell signal intensity vs. distance from the interface. $=p≤0.05 vs. C distances ≥400 μm, #=p≤0.05 vs. all other PCL/PEO-C distances, *=p≤0.05 vs. all groups, **=p≤0.05 vs. BM and PCL/PEO. (C) CD45 staining with hematoxylin counterstain for BM (left) and PCL/PEO-C (right) at 4 weeks, with more CD45+ cells (dark brown) evident in enzyme-treated samples. Asterisk indicates scaffold. Scale = 100 μm.

Discussion

Our *in vivo* results suggest that material-mediated and localized delivery of a matrix-degrading enzyme to the meniscus wound interface enhances cellular infiltration and tissue integration. Without matrix digestion, few cells populated

the wound site or the PCL/PEO scaffold alone, leading to little or no integration at the defect center. However, collagenase-treated groups showed significant increases in cellularity and deposition of new matrix across the length of the defect, including within the PCL/PEO-C scaffold. The fenestration in the scaffold promoted integration, as cells colonized the empty space and synthesized collagen that bridged the wound gap. While some CD45+ cells, possibly macrophages, entered the repair, the majority of reparative cells did not stain positive and are likely meniscal cells or host-derived fibroblasts. Scaffolds may be modified to deliver anti-inflammatories[5] and growth factors[6] to limit inflammation and further promote matrix synthesis. Future studies will evaluate the efficacy of these scaffolds to enhance meniscus repair in an orthotopic large animal model. By combining multiple bioactive components that promote cellularity, colonization, and matrix deposition at the wound interface, these novel scaffolds offer a promising approach towards improving meniscus repair.

Significance

Meniscus integration was enhanced by localized degradation of the extracellular matrix via collagenase-releasing scaffolds in a rat subcutaneous implantation model. This technology may be combined with meniscus repair to expedite healing, thus avoiding the need for partial meniscus removal.

Acknowledgments

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Maturation and Material Dependent Response of AF and NP Cells to Mechanical Perturbation

[1]Dong Hwa Kim, PhD
[1,2,3]Lachlan J. Smith, PhD
[4]Dawn M. Elliott, PhD
[1]Robert L. Mauck, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

[3]Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA, USA

[4]University of Delaware, Newark, DE, USA

Introduction

The mechanical environment of the intervertebral disc (IVD) plays an important role in regulation of extracellular matrix (ECM) biosynthesis and maintenance of the unique disc cell phenotypes. The adult IVD comprises cell populations of two distinct lineages (nucleus pulposus cells (NPCs) and annulus fibrosus cells (AFCs)) that are segregated into different functional compartments in the disc, and exposed to different loading environments.[1] NPCs, which reside in a proteoglycan-rich hydrated NP extracellular matrix, are exposed to compressive and hydrostatic pressure. AFCs, which reside within a dense organized fibrous AF network, experience tensile deformation.[2,3] Because cells can rapidly lose their phenotypic characteristics when isolated from tissue, in vitro culture in an appropriate 3D physical environment is crucial. For instance, encapsulating NPCs in hydrogels and culturing AFCs on aligned nanofibrous scaffolds provides a 3D physical environment that is consistent with the native tissue architecture, while also promoting retention of phenotype and organized matrix formation with in vitro culture.[4] The objective of the current study was to investigate the response of NPCs and AFCs subjected to short term physiologically-relevant mechanical stimulation in 3D culture systems appropriate to the cell phenotype (i.e., compressive loading in hydrogel culture for NPCs and cyclic tensile strain in nanofibrous scaffolds for AFCs), and to determine whether the response to mechanical loading would change as a function of culture duration.

Methods

NPCs and AFCs were isolated from adult bovine caudal discs.[5,6] NPCs (passage 2) were encapsulated in 1% methacrylated hyaluronic acid (HA) at 60×10^6 cells/ml and photopolymerized into cylindrical constructs (diameter and thickness, 4 mm and 2.25 mm, respectively).[7] AFCs (passage 2) were seeded onto aligned poly(ε-caprolactone) nanofibrous scaffolds at 2×10^6 cells/scaffold.[8] Constructs of both types were cultured in a chemically defined medium [CM(−)] for two days, after which they were subjected to mechanical loading. Another set of constructs was cultured in chemically defined media supplemented with TGF-β3 [CM(+)] for 42 days, followed by transfer to CM(−) for 5 days, before being subjected to the same loading protocol. At both time points, NPC-seeded constructs were loaded in dynamic compression (2% pre-strain, 10% strain, 1 Hz),[9] while AFC-seeded constructs were subjected to cyclic tensile strain (6%, 1Hz) for 4 hours.[9] Construct mechanical properties for each condition were determined via unconfined compressive stress relaxation and tensile testing of NP and AF constructs, respectively, as previously described.[8,9] The equilibrium modulus of NP constructs was determined from the equilibrium stress and strain values normalized to construct dimensions. The tensile modulus of AF constructs was determined from the linear region of the stress-strain curve (1%/sec extension), based on the sample geometry and gauge length. Cell viability was assessed via Live/Dead staining (Molecular Probes) and routine histological staining of matrix (collagen and proteoglycan) was performed. Real time RT-PCR was used to analyze expression of matrix proteins [aggrecan (ACAN), collagen type I (COL1A1), collagen type II (COL2A1)], SOX9, and TGF-β normalized to GAPDH. Statistical differences were established by t-tests or ANOVA with Fisher's LSD post-hoc.

Results

Both NPC-seeded and AFC-seeded constructs increased in mechanical properties with time in culture. By day 42, the equilibrium modulus of NPC-seeded HA constructs was 4-fold greater than at day 2 (Figure 1A, $p<0.05$). Similarly, the tensile modulus of AFC-seeded nanofibrous scaffolds was 1.8-fold greater for day 42 constructs compared to day 2 constructs (Figure 1B). Cell viability in both NPC-seeded and AFC-seeded constructs was high at both time points (not shown), and abundant extracellular matrix was present by day 42 (not shown). NPCs were generally rounded/stellate in HA gels, while AFCs were highly aligned with the nanofiber direction. When NPC-seeded constructs were subjected to mechanical perturbation, ACAN

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kimd1@mail.med.upenn.edu

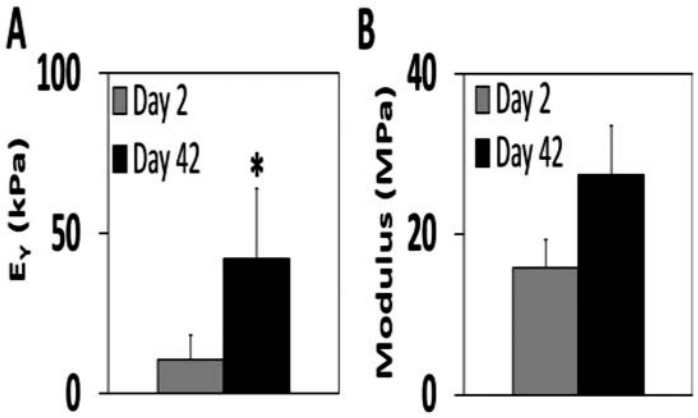

Figure 1. (A) Equilibrium compressive modulus of NPC-seeded HA constructs and (B) tensile modulus of AFC-seeded nanofibrous scaffolds over 42 days of in vitro culture (*: $p < 0.05$ vs. Day 2, n=4~5/group/time point).

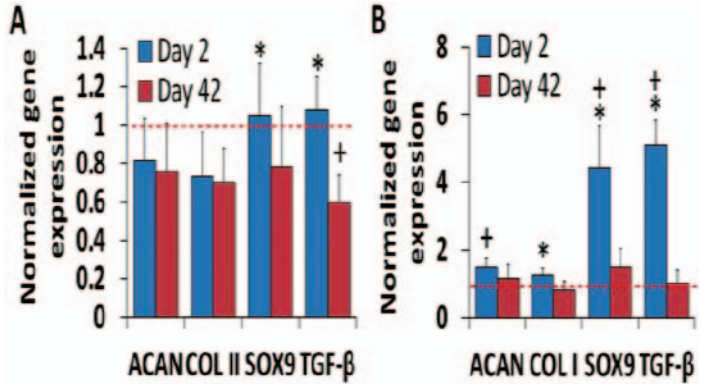

Figure 2. (A) Gene expression in NP constructs with compressive loading (dashed line: free swelling condition, n=4~5, *: $p<0.05$ vs. Day 42, +: $p<0.05$ vs. free swelling). (B) Gene expression in AF constructs with tensile loading (dashed line: free swelling condition, *: $p<0.05$ vs. Day 42, +: $p<0.05$ vs. free swelling).

and COL2A1 expression decreased at early time points, while SOX9 and TGF-β expression did not change (Figure 2A). At later time points, compressive stimulation resulted in a decrease in expression levels of all genes assayed, with SOX9 and TGF-β expression levels at this later time point were significantly lower than at the early time point (Figure 2A). In AFC-seeded constructs, dynamic tensile loading at the early time point significantly increased ACAN, SOX9 and TGF-β gene expression. Conversely, after these constructs had matured through day 42, dynamic stretch did not alter expression of any gene assayed (Figure 2B).

Discussion

In this study, we investigated the effect of physiologic mechanical loading on AF and NP cells cultured 3D physical environments that promote their respective phenotypes, at both early and late time points. Gene expression of ECM and signaling molecules differed based on material context and duration of culture before mechanical perturbation. In NPC-seeded constructs, compressive loading generally inhibited gene expression, particularly after constructs had been matured for longer durations. Conversely, dynamic tensile loading of AFC constructs markedly increased expression of select genes early in culture, but had a lesser effect at later time points. These data suggest that as matrix is deposited, the manner in which cells within these materials interpret physical signals changes, most likely due to cell-mediated matrix deposition. Future studies will explore how these responses are modulated by culture duration and ECM deposition, and how these cell types signal to one another with physiologically relevant mechanical perturbation.

Significance

The mechanical environment of the IVD is complex, with different regions of this composite tissue exposed to different loading configurations. In this study, we investigated the effect of physiologically relevant mechanical stimulation of NPC and AFC seeded in 3D culture systems that promote their phenotypic stability. Findings show that duration of maturation alters the response of these cells to physical signals.

Acknowledgments

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Enhanced Integration with Treatment of Sprifermin (rhFGF18) in a Cartilage Injury-Repair Model

[1]Alexandra JE Farran
[1]Ryan A. Cocca
[1]Gregory Meloni
[1]Bhavana Mohanraj
[2]Anne Gigout
[1]Robert L. Mauck
[1]George R. Dodge

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Merck KGaA, Darmstadt, Germany

Introduction

Osteochondral autograft transplantation (OAT) is a common procedure for the treatment of focal articular defects. Multiple factors likely influence the effectiveness of this procedure, including the source of donor cartilage, health of cartilage surrounding the defect site, and ultimately the degree to which integration occurs at the interface with native tissue. In animal models and in vitro experiments it has been shown that sprifermin (recombinant human FGF18, rhFGF18) promotes chondrocyte proliferation and extra-cellular matrix (ECM) biosynthesis,[1] and stimulates cartilage repair.[2] Since in many instances OAT procedures result in poor integration (due to low cellularity and fibrous tissue formation at the interface), we tested the hypothesis that addition of Sprifermin would increase cartilage-to-cartilage integration by increasing cell proliferation and ECM accumulation at the interface. We tested this hypothesis in an in vitro cartilage explant injury model and evaluated outcomes using mechanical, histological, and micro-computed tomography (μCT) assays of the interface.

Methods

Fresh hyaline cartilage was harvested from the trochlear groove of juvenile bovine knees (3-6 months old). Cylindrical explants (8mm, Figure 1A) were removed with a biopsy punch and cultured overnight in complete medium (DMEM 4.5g/L D-Glucose and L-Glutamine, 10% FBS, 1% PSF, 1% Fungizone, 1% MEM Vitamins, 25mM HEPES and 50μg/ml Vitamin C). Samples were trimmed of bone and defects (4mm diameter) were created to form a core and annulus repair construct (Figure 1B). Both the inner core and outer annulus were cultured separately for 24 hours before the defect was filled with the original core. Samples were then cultured in complete medium, or treated with Sprifermin (rhFGF18, 100 ng/ml). Treatments consisted of one dose of rhFGF18 for 24 hours, applied once a week (and repeated weekly) (1+6) or one 24 hour treatment followed by 1 month of culture in complete medium (1+30 days). Samples were harvested after 4 weeks of culture. Push-out mechanical testing (n=4-6) was performed (Instron 5848, Instron, Norwood, MA) using a custom testing rig (Figure 2E[3]). Integration strength was calculated by dividing the peak force by the integration area. For 3D visualization, samples (n=6 were soaked in a modified Lugol's solution (2.5% I2 and 5% KI in dH2O) for 24 hours[4] and scanned by μCT at an energy level of 55kV and intensity of 145μA with a voxel size of 6μm and 10.5μm (μCT 35 and vivaCT 40, SCANCO Medical, Wayne, PA). Scans were analyzed and reconstructed using the manufacturers software, and cross sections were used to evaluate defect integration. Additional samples (n=3) were fixed overnight in 4% PFA and analyzed histologically for cell and matrix deposition at the interface.

Results

The integration strength (Figure 2D) of control samples was the lowest (2.5±1.4 kPa), with progressively increasing properties with the 1+30 (5.0±2.4 kPa) and 1+6 (10.2±3.7 kPa) treatments. While the results are striking when comparing controls and treated groups, with the replicate numbers possible in this study, statistical significance was not achieved. μCT analysis of control constructs (Figure 3, top left) showed a distinct dark circle, indicating separation between the outer annulus and inner

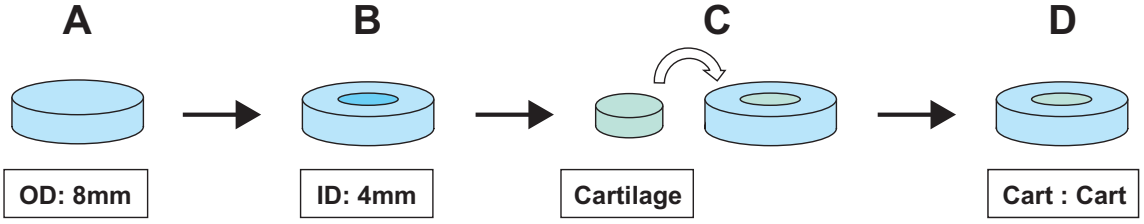

Figure 1. Preparation of cartilage defect-repair model: (A) 8mm cartilage plug, (B) central 4mm defect creation, (C) insertion of cartilage into defect, and (D) long-term culture of repair construct.

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farranalexandra@gmail.com

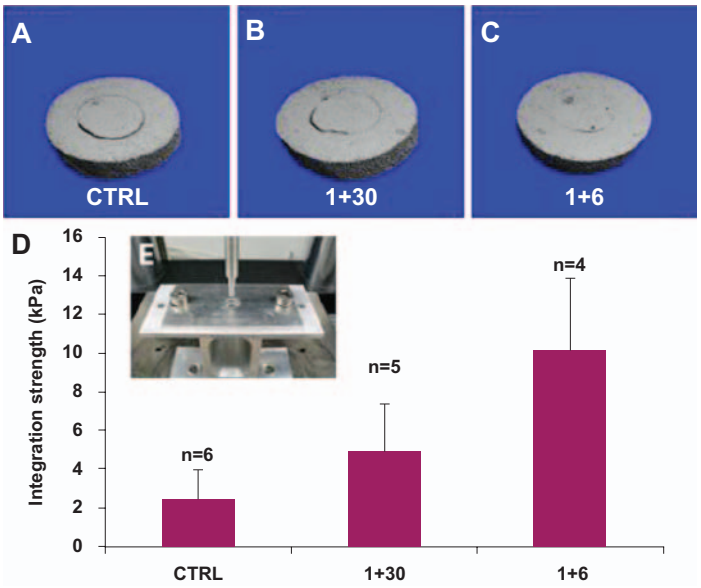

Figure 2. (A-C) Transverse cross sections of 3D μCT reconstruction with different treatments. (D) Integration strength of the repaired defect showing increasing strength from the control to the 1+30 treatment to the 1+6 treatment. (E) Experimental setup of the push-out testing rig. Error bars are SEM.

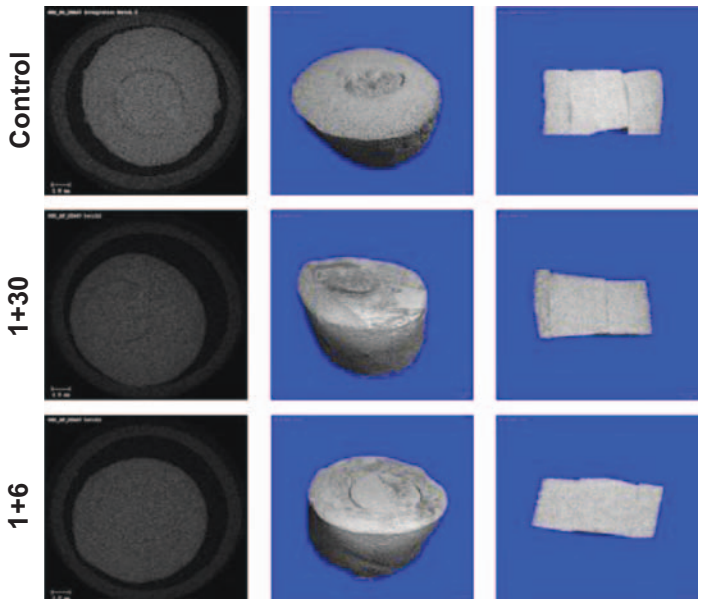

Figure 3. μCT scans of cartilage-to-cartilage repair constructs. Left: single μCT scan slice representative of the sample. Center: 3D reconstruction. Right: cross-section of the reconstruction. The μCT scans demonstrate increasing integration from control to 1+30 to 1+6 treatments.

core, and thus poor integration. The 1+30 treatment (Figure 3, middle left) showed a less distinct circle, suggesting a smaller gap and greater integration, and the 1+6 treatment (Figure 3, bottom left) showed very homogenous μCT signal across the interface, indicative of the greatest degree of integration. Evidence of this increased integration was apparent on both vertical and transverse cross sections throughout the samples.

Discussion

A successful cartilage repair requires that the repair material (engineered or native) be well-integrated into the surrounding cartilage to ensure continuous load transfer (and lack of stress concentrations) across the interface. In this study we investigated the potential of Sprifermin to enhance integration of cartilage in a well-defined ex vivo (explant) cartilage repair model. Sprifermin has an established pro-proliferative effect on chondrocytes,[1] where transient (24 hour) exposure to this biologic agent elicits the most striking response. Using this dosing regimen, our findings clearly demonstrate that Sprifermin improves integration strength and matrix deposition at the interface (as evidenced by contrast-enhanced μCT showing a more uniform attenuation by increase in GAG-containing proteoglycans). In this study, one 24 hour administration weekly for 4 weeks leads to an overall better outcome than one 24 hour treatment over one month. This study represents for the first time a biologic (and in particular an FGF) has improved the integration of cartilage surfaces in a clinically relevant repair model.

Significance

This study demonstrates that the biologic Sprifermin improved the integration of cartilage surfaces in a model of cartilage repair. The findings implicates its potential usefulness in surgical procedures such as OATS and in tissue engineering approaches where cartilage like biomaterials will be required to successfully integrate with native cartilage in order to achieve clinical success.

Acknowledgments

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Perlecan Expression is Strongly Reduced in Aging Cartilage but Increased by Physiological Loading

[1]Ryan A. Cocca
[2]Arjan van Caam
[1]Alexandra Farran
[1]Bhavana Mohanraj
[1]Gregory Meloni
[1]Robert L. Mauck
[2]Peter M. van der Kraan
[1]George R. Dodge

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands

Introduction

Perlecan is a large multi-domain heparan sulfate proteoglycan (HSPG) with a core protein of ~460kDa widely distributed throughout the body in basement membranes. Perlecan is involved in development of the musculoskeletal system and is found in articular cartilage. Perlecan has a multi-faceted molecular composition and, through its multiple domains, can exert a number of biological functions, including cell adhesion, growth factor delivery and sequestration. This latter function is one of the mechanisms by which perlecan influences the pericellular microenvironment. In addition, HS bearing perlecan domain I binds several growth factors important in cartilage growth, including BMP-2; therefore, it can serve as an effective growth factor delivery system for chondrogenic cells.[1] It is not known what changes occur for perlecan expression in aging cartilage, and our hypothesis is that if reduced, loss of perlecan would substantially impact the biosynthetic activity of aging chondrocytes to maintain proper cellular function. In this study we explored the changes of perlecan expression in a large number of bovine cartilages at various ages and tested methods to increase perlecan expression via hydrostatic loading, a component of the physiological loading environment.

Methods

For the study of perlecan expression as a function of donor age, full thickness cartilage explants were harvested (<3 hours post mortem) from bovine metacarpophalangeal joints. Macroscopically, all animals were negative for any indications of osteoarthritis. mRNA was subsequently isolated using TRIzol (Life Technologies) and extracted via the RNeasy mini kit (Qiagen). cDNA was prepared and gene expression measured by SYBR-green qPCR using perlecan domain I specific primers 5'-GTGACCCATGGGCTGAGGGCATA-3' and 5'-GGGCACTGTGCCCAGGCGT-3'. Using the ΔCT method, the expression of perlecan was compared to the average of four housekeeping genes; GAPDH, RPS14, RPL22 and Gusb. For loading studies, fresh hyaline cartilage was harvested from the condyles and the trochlear groove of juvenile bovine knees (3-6 months old). The cartilage was washed in 2X PSF PBS for 30 minutes, minced and digested overnight in DMEM with 10% FBS, 1X PSF and 1mg/ml collagenase type II (Worthington). The suspension was filtered through a 70μm mesh filter and chondrocytes were isolated by centrifugation. The isolated chondrocytes were then aggregated in poly 2-hydroxyethyl methacrylate 96-well plates (Corning) creating cartilage tissue analogs (CTA) at 1 x 10^6 cells/CTA. CTAs for 1 and 2 loading sessions were matured for 5.5 weeks and CTAs for 3 loading sessions were matured for 10 days prior to loading.[2,3] A custom bioreactor was utilized to apply dynamic loading (750 psi, 0.1 Hz, 3 hours) to the CTAs. Loading was applied 1, 2 and 3 times a week for 1 week (n=3). CTAs were harvested 72 hours after the final loading session. Harvested CTAs were crushed in liquid nitrogen and isolated as above. cDNA was synthesized with iScript and qPCR performed using iTaq (Bio-Rad) on a StepOnePlus Real-Time PCR System (Life Technologies) with bovine specific GAPDH primers. Results were analyzed using the $2^{-\Delta Ct}$ method for relative gene expression to GAPDH.

Results

Perlecan expression in cartilage was determined in 41 bovine donors from 0-12 years of age. An inverse correlation exists between donor age and perlecan expression, as the amount of perlecan mRNA decreases with donor age (Figure 1, 2). This is more evident when the donors are grouped in 2 year age brackets (Figure 2). We see the most substantial downregulation of perlecan after 2, 4 and 10 years (40.98%, 56.39% and 67.25%, respectively) when compared to the previous age group. By 10-12 years of age, a drastic >90% downregulation of perlecan expression was observed compared to the 0-2 year age group. Applying a physiologic, cyclic hydrostatic pressure load using a custom designed real-time bioreactor, perlecan expression was quantified under multiple dynamic loading regimens using our CTA model.[2,3] Perlecan expression was not altered by 1 loading session over 1 week (5.9%). However, specific loading regimens of 2

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cocca@mail.med.upenn.edu

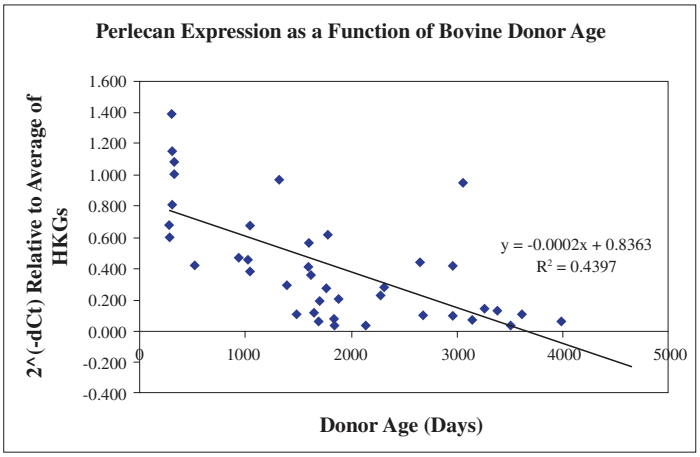

Figure 1. Perlecan expression as a function of bovine donor age.

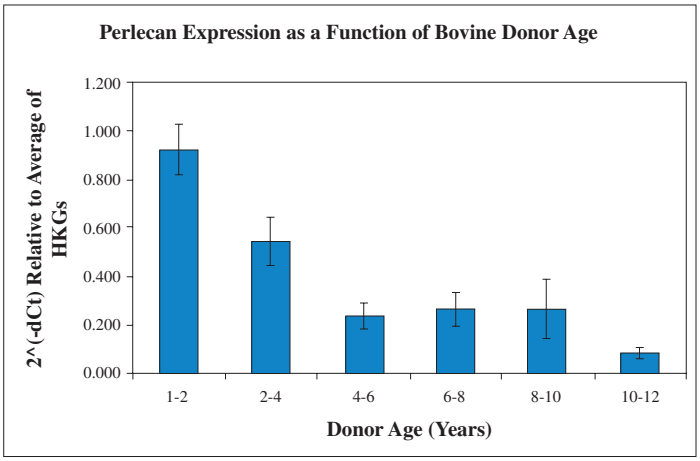

Figure 2. Perlecan expression as a function of bovine donor age in 2-year age groups.

and 3 loading cycles increased perlecan expression in CTA compared to their unloaded counterparts (198.8% and 77.3%, respectively, Figure 3). While result values are sticking and consistent through multiple experiments, they only approach statistical significance.

Discussion

In this study, we identified a significant negative association between age and perlecan mRNA expression via analysis of a large cohort of fresh cartilage specimens (that were not subjected to culture conditions or removal from native tissue that would alter expression levels). Given the increased predilection for developing osteoarthritis with aging, this reduction in perlecan expression as a function of age suggests that perlecan might play a critical role in protecting against the degradation of cartilage and in maintaining proper

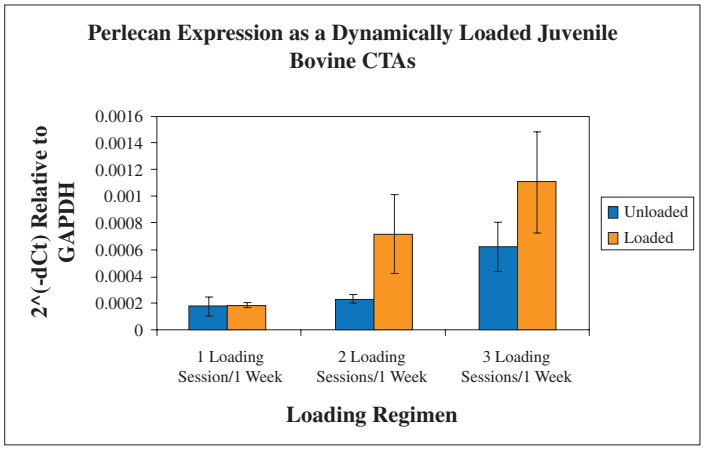

Figure 3. Perlecan expression in dynamically loaded juvenile bovine CTAs.

chondrocyte function. Interestingly, increased perlecan expression was observed when engineered CTAs were exposed to physiologically relevant dynamic hydrostatic loading. It is known that dynamic loading both improves cartilage homeostasis and maintains the chondrogenic phenotype in cartilage. Therefore, it can be suggested that perlecan expression in loaded CTAs is a parallel to normal joint function and in vivo pressure.

Significance

Aging is the main risk factor for OA. We show that perlecan expression is strongly reduced by aging. In contrast, physiological loading increases perlecan expression. Our data suggest that physiological loading might play a role in maintenance of perlecan expression in adult cartilage and in this way contributes to cartilage homeostasis.

Acknowledgments

This work was in part supported by the Netherlands Organisation for Scientific Research (NWO), National Science Foundation (USA) and the AO Foundation.

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Rapid and Sustained Changes in Nuclear Architecture and Mechanics in Mesenchymal Stem Cells in Response to Dynamic Stretch

[1]Su-Jin Heo, MS
[2]Stephen Thorpe, PhD
[1]Tristan P. Driscoll, BS
[1]Sohaib K. Hashmi, BS
[2]David A. Lee, PhD
[1]Robert L. Mauck, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Queen Mary, University of London, London, United Kingdom

Introduction

Mechanical cues direct lineage-specification of mesenchymal stem cells (MSCs)[1,2] and regulate gene expression and cell function via histone modification.[3] Chromatin condensation, often mediated by histone methylation, leads to an overall silencing of transcription, while preserving the activity of lineage-specific genes in less condensed (euchromatic) regions.[4] In previous work, we showed that dynamic loading (DL) could evoke remodeling of the nucleus, involving Lamin A/C reorganization and changes in heterochromatin, more rapidly than addition of soluble differentiation factors.[5] However, the mechanisms by which physical cues are translated to MSC lineage commitment remains unclear. In the current study, we interrogated the time scales over which DL regulates chromatin condensation, determined whether such changes in chromatin condensation altered nuclear mechanics, and the duration over which these changes were "imprinted" on the nucleus to establish a mechanical "memory." Further, we identified ATP as a key signaling molecule, and several mechanically regulated genes that may be responsible for stabilizing nuclei in the condensed state with mechanical perturbation.

Methods

Aligned poly(ε-caprolactone) nanofibrous scaffolds were fabricated via electrospinning.[2] Bovine bone marrow derived MSCs (2×10^5 cells) were seeded onto scaffolds (5×60 mm^2) and samples were dynamically stretched (3%, 1Hz)[2] for 4 different durations (short term: 150 or 600s sec, long term: 1 or 3 hour) in a chemically defined media (CM). Another set of constructs was pretreated with 10μM of the Rho kinase inhibitor, Y27632 for 1 hour (Y27) to block acto-myosin contractility. A chromatin condensation parameter (CCP) describing internal nuclear structure was calculated for individual nuclei stained with DAPI using a gradient-based Sobel edge detection algorithm.[6] To measure the permanency in nuclear condensation, samples were cultured for up to 18 hours after loading. At set time points, the degree of nuclear deformation (defined by change in nuclear aspect ratio (NAR)) was determined for statically stretched samples.[7] To investigate ATP as a potential mediator of chromatin remodeling, 5 UN of Apyrase (AP, Sigma, an extracellular ATP diphosphohydrolase) was added 30mins before loading. To determine the factors involved in mechanical memory, a further set of constructs was dynamically loaded for 3 hours/day, returned to free swelling culture for 48hours, and then subjected to another round of loading for 3 hours. CCP, NAR, and real time RT-PCR for expression of genes associated with chromatin remodeling (normalized to GAPDH) were assessed through 48hours after loading. Statistical analysis was performed by ANOVA with Fisher's post-hoc tests.

Results

Chromatin condensation (increased CCP) was evident in nuclei after just 600s of dynamic loading (Figure 1a,b). Blockade of contractility abrogated load induced change in CCP at early times (Figure 1a,b). Chromatin condensation persisted for durations that depended on the length of the original stimulation: after 150s or 600s of loading CCP gradually decreased to base line levels by 3 hours, while with 1 hour of loading chromatin relaxation was slower (Figure 1c). Interestingly, with 3 hours of DL, chromatin condensation did not decrease, but rather increased through an 18-hour window of observation (Figure 1c). Under these conditions, nuclei did not deform either 600s or 1 hr after cessation of loading (for 600s) compared to unloaded controls (Figure 1d). However, by 3 hours after loading, NAR once again increased with stretch, matching controls (Figure 1d). AP treatment blocked increases in CCP with 150s or 600s of loading, suggesting that ATP may mediate increases in CCP (Figure 2). Interestingly, a 2nd loading event (applied 48 hours after the first, Figure 3c) resulted in more chromatin condensation than during the 1st loading event (Figure 3a). Moreover, this condensation was sustained for a longer time period with the 2nd loading than with the 1st loading. Further, while nuclear deformation was apparent 48 hours after the first loading when cells were stretched, nuclei did not deform when static stretch was applied 48h after the 2nd loading

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heosc@mail.med.upenn.edu

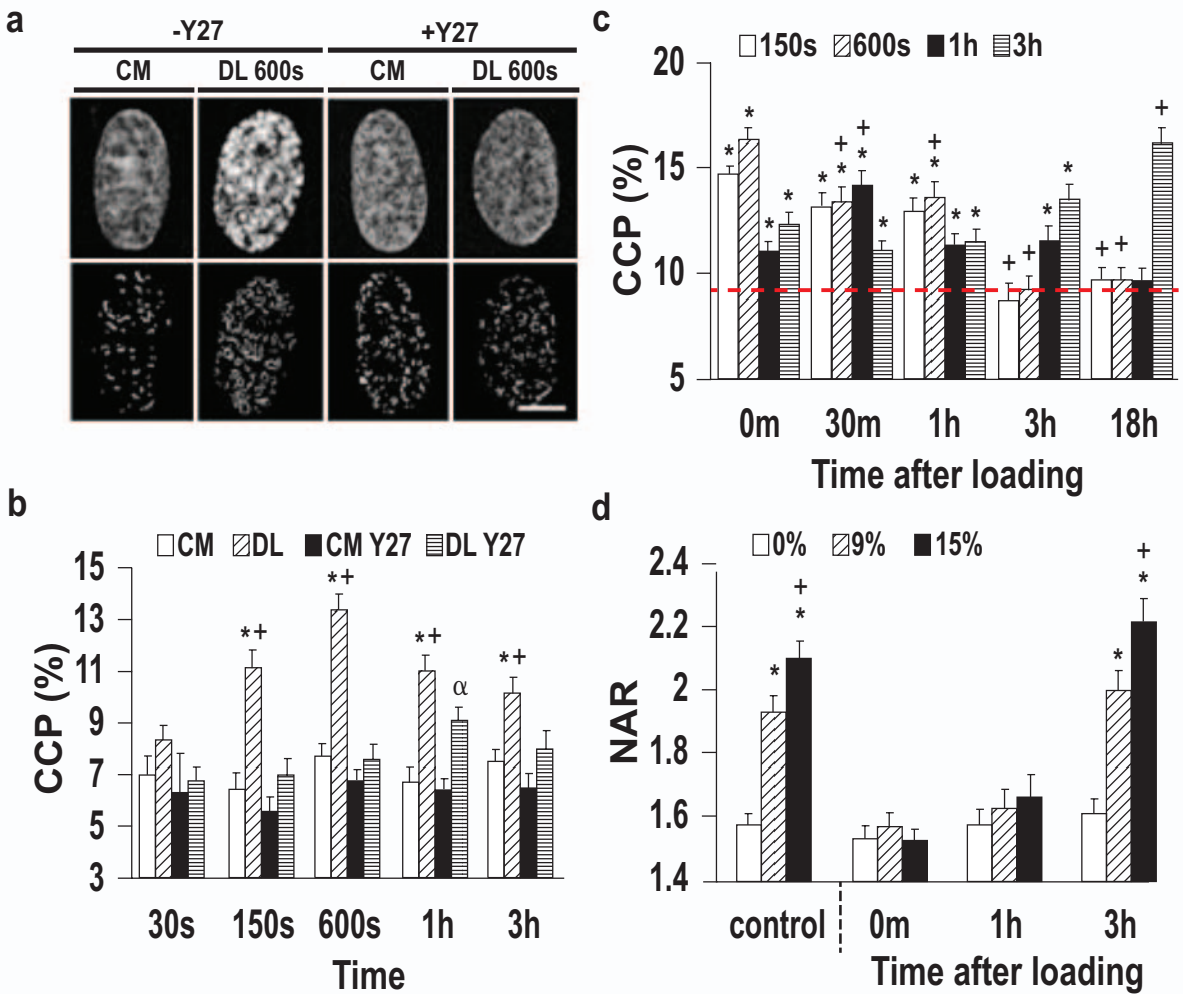

Figure 1. (a) Representative DAPI stained nuclei (top row) and corresponding edge detection (bottom row) with treatments (DL or Y27, bar = 3 μm). (b) CCP with treatments (DL or Y27, n=30, *: p<0.05 vs. CM, +: p<0.05 vs. Y27, α: p<0.05 vs. CM Y27, mean±SEM). (c) Permanency of CCP induced by DL (dashed line: CM condition, n=30, *: p<0.05 vs. CM, +: p40, *: p<0.05 vs. 0%, +: p<0.05 vs. 9%, mean±SEM).

event (not shown). Gene expression of SMC1A, a subunit of the cohesion complex that mediates chromatin condensation, was up-regulated as a consequence of both loading events, and was sustained at this higher level during rest periods between loading (Figure 3c). The 2nd loading event resulted in a greater increase in AGG gene expression than with the 1st loading event, and this level continued to increase after the 2nd loading (Figure 3d).

Discussion

In this study, we demonstrated that, in the absence of exogenous differentiation factors, short term loading of MSCs results in rapid chromatin condensation. This finding suggests that dynamic mechanical inputs can induce a rapid change in nuclear structure. The load induced condensation was abrogated with addition of a Rho kinase inhibitor, suggesting the requirement of a patent acto-myosin contractility apparatus.[8] In addition, removal of extracellular ATP blocked increases in CCP, consistent with the notion that mechanical forces can induce extracellular ATP release.[9] Interestingly, chromatin condensation persisted for durations that depended on the

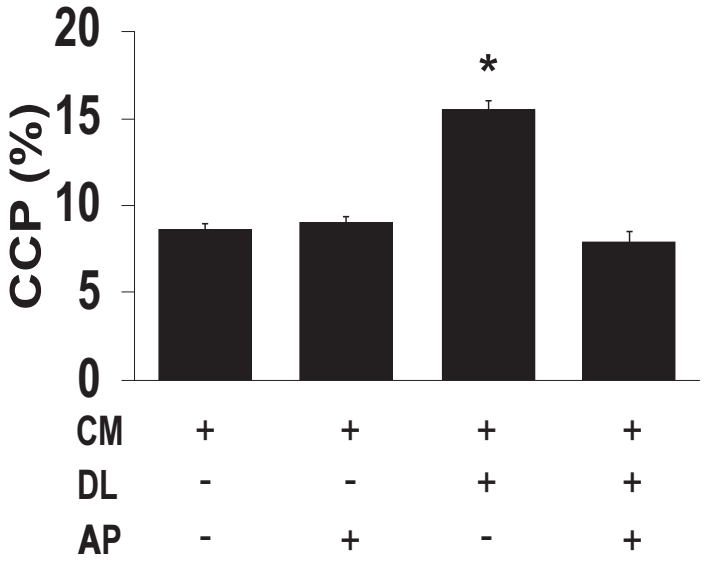

Figure 2. CCP with treatments (600s of DL or AP, n=30, *: p<0.05 vs. CM only).

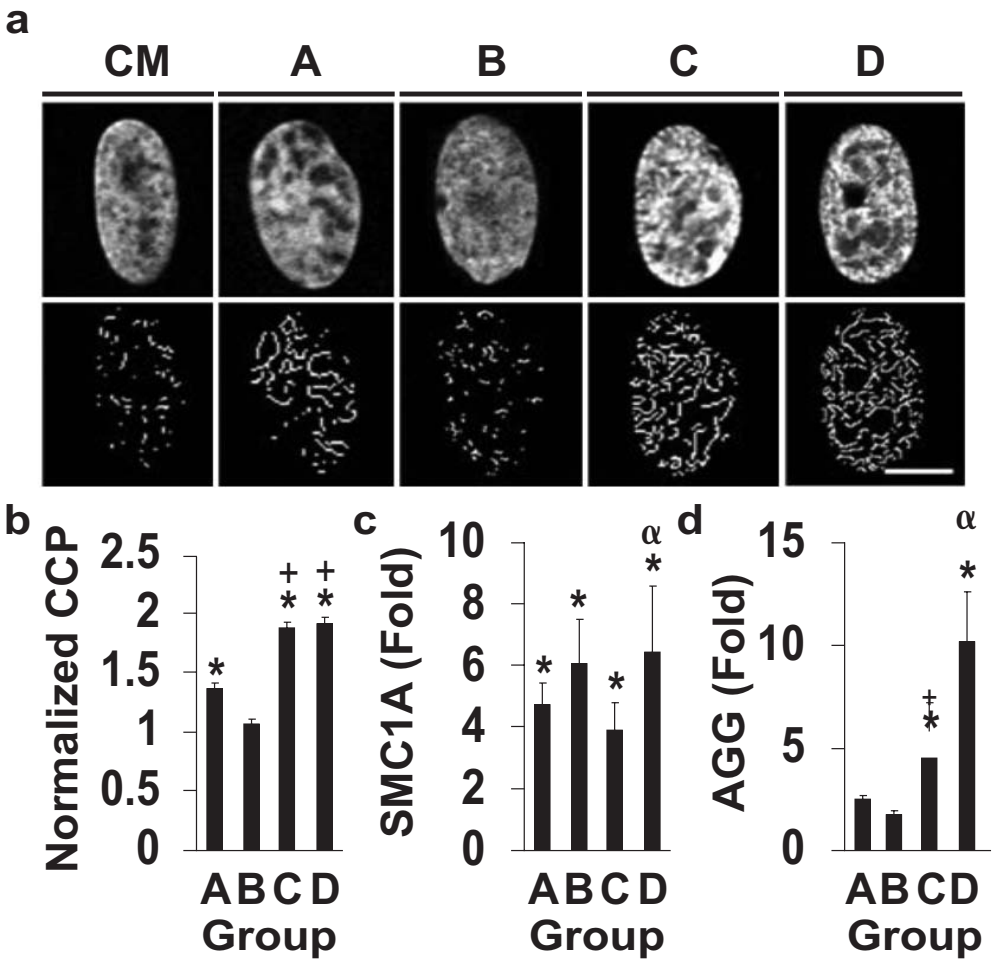

Figure 3. (a) Representative DAPI stained nuclei (top row) and corresponding edge detection (bottom row) (A: 1st loading, B: 48 hours after the 1st loading, C: 2nd loading, D: 48 hours after the 2nd loading, bar = 3 μm). (b) CCP normalized to CM condition (n=200 from 4 replicates, *: $p<0.05$ vs. CM condition , +: $p<0.05$ vs. B, mean ± SEM). (c) SMC1A and (d) AGG gene expression (n=3, *: $p<0.05$ vs. CM, +: $p<0.05$ vs. B, α: $p<0.05$ vs. C, mean±SD).

length of the original stimulation, and altered the manner in which nuclei deformed in response to static stretch. More interestingly, increasing the number of loading cycles increased the magnitude of chromatin condensation, and up-regulated expression of genes associated with chromatin movement (SMC1A) and ECM expression. This finding suggests that MSCs might establish a mechanical memory, encoded in structural changes in the nucleus that sensitizes these cells to future mechanical loading events.

Significance

Mechanical cues play an important role in directing MSC lineage specification. However, the mechanism is poorly understood, and the role of nuclear structure and mechanics has not yet been fully elucidated. Here, we show that mechanical stimulation results in a rapid remodeling of nuclear chromatin, that loading duration influences the persistence of these changes, and that loading establishes a mechanical "memory," priming cells to respond to further mechanical perturbation.

Acknowledgments

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Inherent and Emergent Heterogeneity in Clonal Stem Cell Populations

[1,2]Brian D. Cosgrove
[1,2]Megan J. Farrell
[1]Margaret Dunagin
[1,2]Claire M. McLeod
[1,3]Allison J. Cote
[1]Arjun Raj, PhD
[1,2]Robert L. Mauck, PhD

[1]University of Pennsylvania, Department of Bioengineering, Philadelphia, PA, USA

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

[3]University of Pennsylvania, Department of Cell and Molecular Biology, Philadelphia, PA, USA

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bcosg@seas.upenn.edu

Introduction

One limitation in the use of mesenchymal stem cells (MSCs) for tissue engineering is the heterogeneity inherent to these cell populations. Previous studies have characterized variability between clones with respect to differentiation potential for various lineages,[1] single cell mechanical properties,[2] and traction force generation.[3] Our previous work showed large variations between clones from the same donor (inter-clonal) and within individual clones (intra-clonal) with respect to traction force generation in clonal bMSC populations (passage 4, >28 days of culture).[4] The goal of this study was to better characterize when heterogeneity develops within primary MSC populations, using both biophysical (cell traction) and transcriptional assays (single molecule RNA FISH). By evaluating both non-selected MSC populations ("Mixed") derived from standard isolation protocols and donor-matched clonal populations in various culture conditions, we better defined the heterogeneity that is inherent to these populations. Further we showed how increased variability emerges during early clone isolation and with the addition of soluble factors.

Methods

Cell Culture and Clonal Isolation

Juvenile bovine MSCs were isolated from bone marrow as in Huang *et al*.[5] Multiple clonal populations from one donor were isolated using the trypsin spot method.[6]

Traction Force Microscopy (TFM)

5 kPa polyacrylamide hydrogels (ν=0.45) were prepared as in Aratyn-Schaus *et al*.[7] In short, 0.2μm-diameter fluorescent microspheres were mixed into PA at 1% v/v. Fibronectin (20 μg/mL) coating of gel surfaces was accomplished with 2 mg/mL sulfo-SANPAH. For early timepoint TFM studies, clones were acquired following 14d of culture in basal medium ("BM": DMEM & 10%FBS). Additional TFM studies evaluating cells cultured in chemically defined media supplemented with and without 10 ng/mL TGF-β3 ("CM− & CM+") were performed using passage 3 (p3) mixed MSC populations. TFM data analysis (PIV, FTTC, stack alignment) was performed using a freely available plugin suite for ImageJ created by Q. Tseng.[8] Cellular areas were measured in ImageJ.

Fluorescent In-Situ Hybridization (RNA FISH)

Probe hybridization was completed as detailed in Raj *et al*.[9] In short, multiple singly-labeled oligonucleotide probes (for aggrecan [AGC], GAPDH, and cartilage oligomeric matrix protein [COMP] gene sequences) were applied to fixed and permeabilized cells. Single mRNA molecules were quantified using a custom MATLAB script.[9] In these studies, p3 clonal and mixed populations were cultured in either CM− or CM+ for 7 days before FISH was performed. To query expression in fresh isolates, colonies were identified after 11 days of culture in BM. At this point, the media was changed to CM+ for four additional days before FISH analysis of these nascent colonies.

Statistics and Data Analysis

Mann-Whitney U tests adjusted for multiple comparisons were used to compare across TFM groups. Violin plots and kernel density data were generated using the ggplot2 library.

Results

Traction forces across two clones ("clone 1 & 2") and a donor matched mixed MSC population ("Mixed") were measured after 3d of culture (Figure 1). While there were no significant differences in cell area, TFM showed significant inter-clonal differences in traction stress generation, with intra-clonal standard deviations that were of similar magnitude to those within the Mixed population (c1: 50% of Mixed, c2: 115% of Mixed). Non-selected MSC populations (p3) were cultured for 16 hours with and without TGF-β3 (CM-/CM+) and then subjected to TFM. In these populations, the addition of TGF-β3 increased cellular contractility by ~2.7-fold, with the CM+ population exhibiting a much higher variability in traction stress (Figure 1C). Next, later passage (p3) mixed and clonal MSC populations were analyzed by RNA FISH. In the presence of TGF-β3, average COMP expression (across all groups) increased ~200-

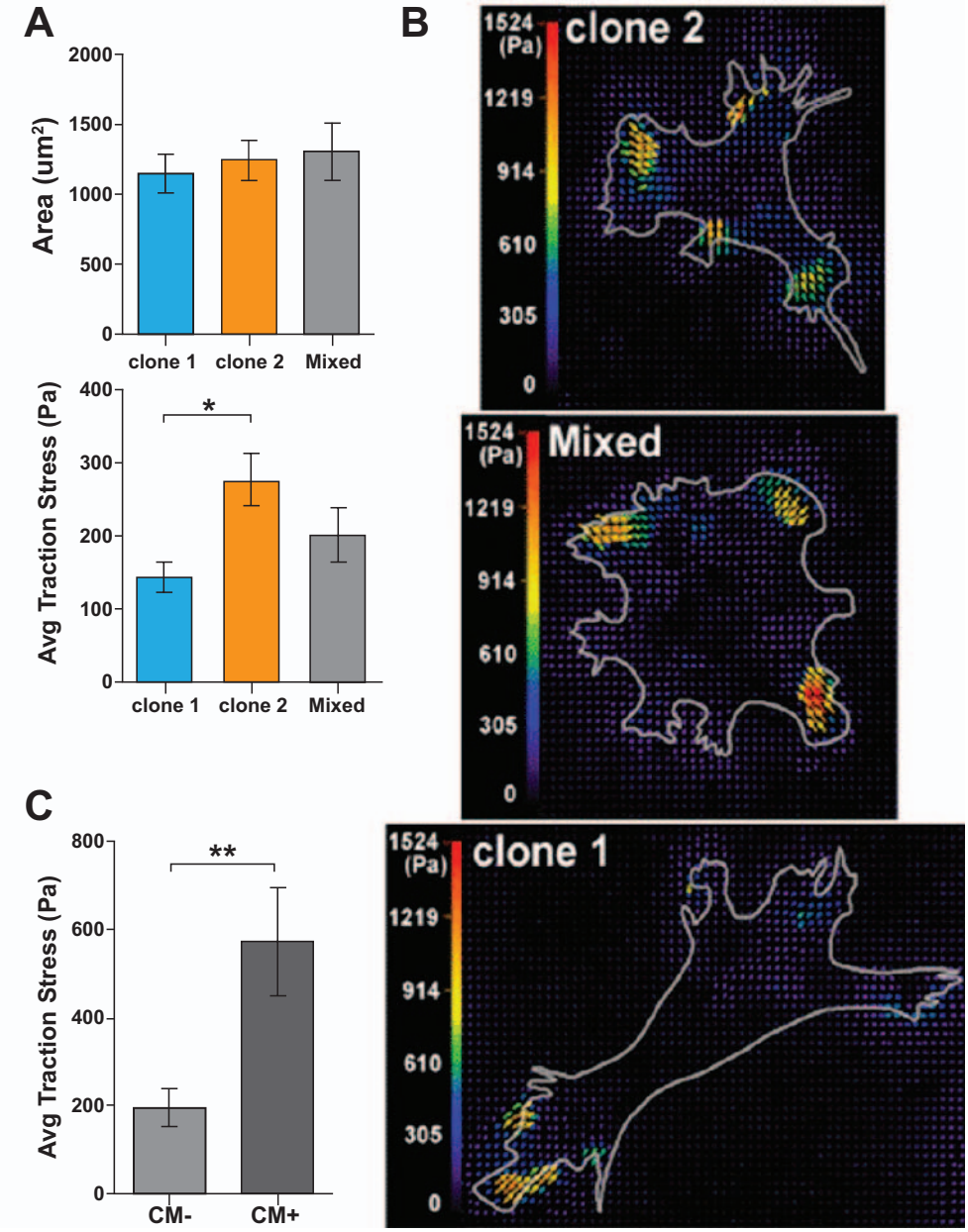

Figure 1. (A) Cellular area and average traction stress generation. n=13-19 cells per group. * denotes p<0.05. (B) Representative traction stress vector maps from Figure 1A. (C) Average traction stress generation of a late stage MSC population (p3) in CM− or CM+ n=21-23 cells per group. ** denotes p<0.01.

fold, while AGC expression increased by ~20-fold (Figure 2A/B). Interestingly, not every clone responded the same way (inter-clonal variability), and within the same clone, copy number showed a wide variability, in most cases more so than the variation seen in the mixed population. Finally, RNA FISH of very early passage colonies (i.e., those still in their initial colony) revealed that intra-clonal mRNA levels were heterogeneous with chondroinduction, before any passaging had occurred, and that this heterogeneity did not appear to depend on location within the colony (Figure 3).

Discussion

Since each MSC clone arises from the division of an initially adherent parent cell, it has been assumed that clones should represent a distinct subpopulation and be more homogeneous than non-selected MSCs acquired using traditional methods. Surprisingly, extensive biophysical heterogeneity exists both between clones and within clones. RNA FISH of initial p0 colonies revealed that this intra-clonal heterogeneity exists at very early stages of colony formation, suggesting that MSC heterogeneity emerges very early. When MSC populations were cultured for longer time periods, and induced with TGF-β3, MSC heterogeneity was further amplified. After only 16 hours of induction, MSC populations (normal and clonal) induced with TGF-β3 exhibited more variability in traction stress than those without TGF-β3 exposure. Interestingly, mRNA levels of cartilage markers (COMP/AGC) within a clone did not always correlate (clone D). Nearly every clone exhibited a much

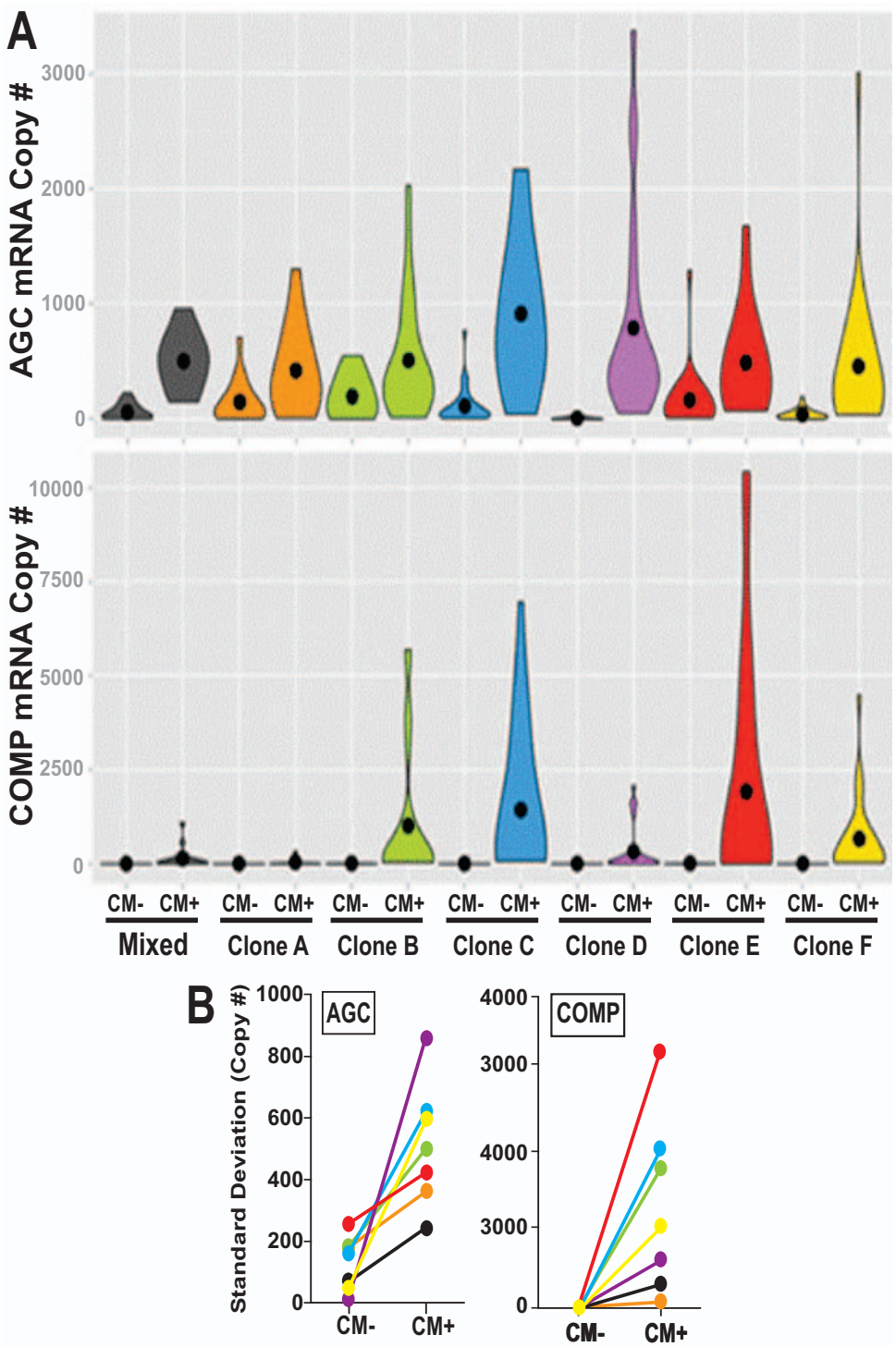

Figure 2. (A) Violin plots of mRNA copy numbers (for each group: y-axis = range of data, x-axis = normalized probability density function of data, black dot = group mean). n=16-31 cells per group. (B) Standard deviation values for each group from Figure 2A.

larger range of mRNA copy number than the donor-matched parent MSC population.This suggests that the traditional idea of the heterogeneity in a mixed MSC population being the sum of its clonal parts may not be entirely correct. Rather, our data suggests a more complicated scenario in which both emergent and inherent heterogeneity prevails in MSC populations. Further studies will examine how this variability can be reduced during the expansion process and work towards a better understanding of how such heterogeneity influences MSC differentiation.

Significance

Cartilage tissue engineering approaches have been hampered by MSC heterogeneity, but characterizations of this heterogeneity have not clearly established at what point this heterogeneity arises. Results from this study suggest

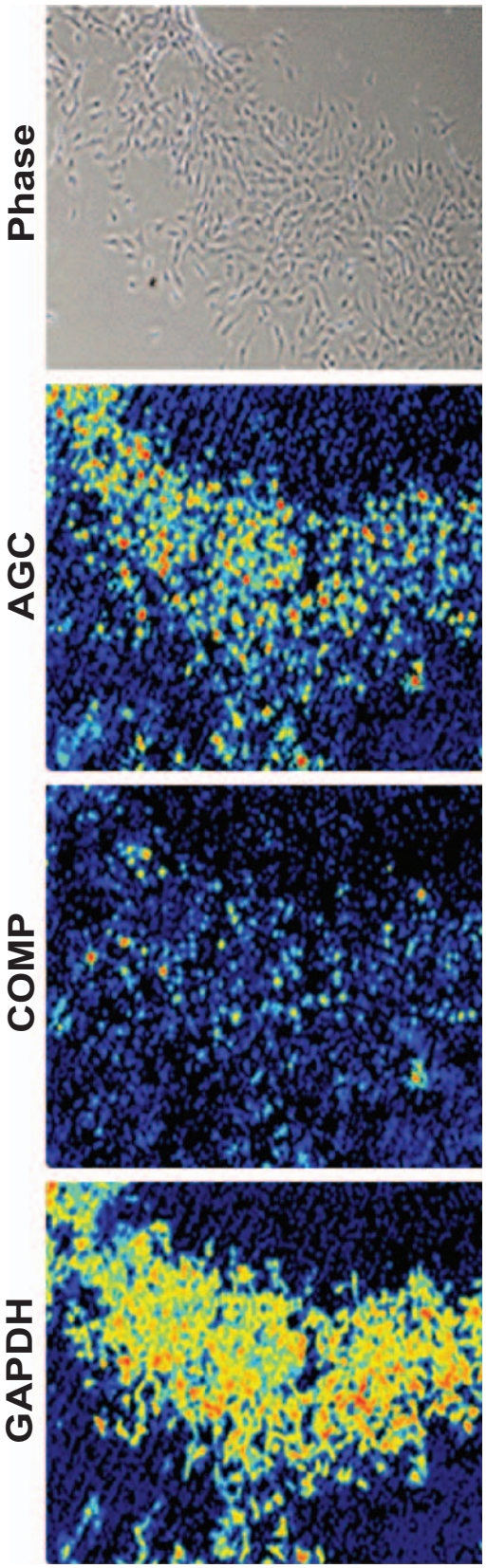

Figure 3. RNA FISH cluster scans of an initial passage (p0) MSC colony. Nucleus-centered pseudocolor dots represent the number of mRNA molecules within a single cell (relative scale is from: dark blue=no copies, to red=most copies).

that heterogeneity emerges early in the derivation of MSC clonal populations, exists both within and between clonal populations of MSCs, and persists throughout later passages.

Acknowledgments

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Engineered Fiber Crimp Alters Scaffold Mechanics, Cell Shape, and Strain Transfer to the Nucleus

[1]Tristan P. Driscoll
[2]Jefferson Chang
[3]Ty'Quish S. Keyes
[4]Michael W. Hast, PhD
[1]Su-Jin Heo
[1]Robert L. Mauck, PhD
[2]Pen-Hsiu Grace Chao, PhD

[1]University of Pennsylvania, Departments of Orthopaedic Surgery and Bioengineering, Philadelphia, PA, USA

[2]National Taiwan University, Taipei, Taiwan

[3]Morehouse College, Atlanta, GA, USA

[4]University of Pennsylvania, Department of Orthopaedic Surgery, Philadelphia, PA, USA

Introduction

Tendons and ligaments are composed of highly aligned collagen fibers that, at the micron-scale, have an intrinsically crimped micro-architecture.[1] With stretch, crimped fibers straighten, resulting in a non-linear mechanical response.[2,3] Crimp is thus a critical structural adaptation providing function under physiologic strain[4] and is lost with pathological conditions.[5] When such tissues are damaged, one treatment strategy is to engineer replacement tissues using highly aligned arrays of polymer nanofibers, created by electrospinning.[6] Recently, this technique has been further refined to generate fiber crimp by heating scaffolds to their glass-transition temperature.[7] In our previous work, accelerated cellular infiltration was achieved by increasing scaffold porosity with inclusion of a water-soluble sacrificial poly-ethylene oxide (PEO) component.[8] In this study, we increased scaffold crimp by increasing scaffold porosity prior to heating, thus providing increased space for scaffold crimp formation. We then probed the bulk scaffold mechanics and the micromechanical response of both the scaffold and attached cells, identifying differences that will likely regulate mechanotransduction in cells interacting with this material.

Methods

Aligned nanofibrous scaffolds were generated by electrospinning, onto a rotating mandrel, a 8.5% w/v solution of poly-L-lactide (PLLA) in HFP either alone or in combination with a second spinneret containing a 10% w/v solution of PEO in 90% ethanol.These two scaffold types (PLLA only or PLLA/PEO dual) were washed with decreasing concentrations of ethanol (to hydrate and/or remove PEO) or heated to 65° between two glass plates (to induce crimp). Dual scaffolds were washed (DW), heated and then washed (DHW), or washed and then heated (DWH). This last group (DWH) is expected to produce the highest degree of crimp, due to the increased porosity present during heating. Scaffolds (40x5mm^2) were measured using a laser based device (cross-section) and tested in uniaxial tension using an Instron 5848 (n=3/grp) with a custom cross-polarized light fixture to measure fiber alignment.[3] Linear modulus and transition strains were calculated using bi-linear fits (Matlab). Additional scaffolds (70x5mm^2) were coated with fibronectin (20μg/ml), seeded with p1 bovine mesenchymal stem cells (MSCs, 100k cells), and cultured for 2 days in chemically defined media. F-Actin (phalloidin) and nuclear (DAPI) staining of cell-seeded scaffolds (n=2/grp) was performed to assess cell shape and alignment; fibers were imaged from autofluorescence. Dual scaffold groups were stained with Hoechst (nuclei) in DMEM (20 min; 37°C) then stretched (n=4/grp) in 1% increments to 8% strain using a microscope-mounted tensile device. Micro-scale Lagrangian strains were calculated from nuclear triads, and a Poisson's ratio was calculated for each triad. Nuclear deformation was quantified using the ratio of nuclear principal lengths (nuclear aspect ratio, NAR) and nuclear orientation quantified as angle of the nuclear principal axis (0-90° where 90° = fiber/stretch direction). One-way ANOVA with Tukey's post hoc (mechanics) and two-way ANOVA with Bonferroni post hoc (nuclear angle and NAR) were used to determine statistical differences between groups.

Results

Mechanical testing showed that heating or inclusion of sacrificial PEO fibers resulted in a decrease in the linear modulus (Figure 1A) and an increase in the transition strain (Figure 1B,C) with the most crimped scaffold (DWH) having the highest transition strain and yield strain (not shown) and the lowest degree of alignment (as measured by cross-polarized light, not shown). Imaging of actin/DAPI stained scaffolds (Figure 1D) showed that PLLA-only scaffolds had the least crimped fibers (red) and the most elongated cells (green) and nuclei (blue), whereas the DWH scaffolds had the most crimped fibers and the least elongated cells and nuclei, with some cells following the crimp pattern. Stretch of cell seeded scaffolds showed that all scaffolds displayed similar positive Lagrangian strains in the stretch direction (E_{11}, Figure 2A) that reached close to the applied strain, but that the DWH scaffolds displayed the least lateral compression (E_{22}), resulting in significantly lower micro-scale

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TristanD@seas.upenn.edu

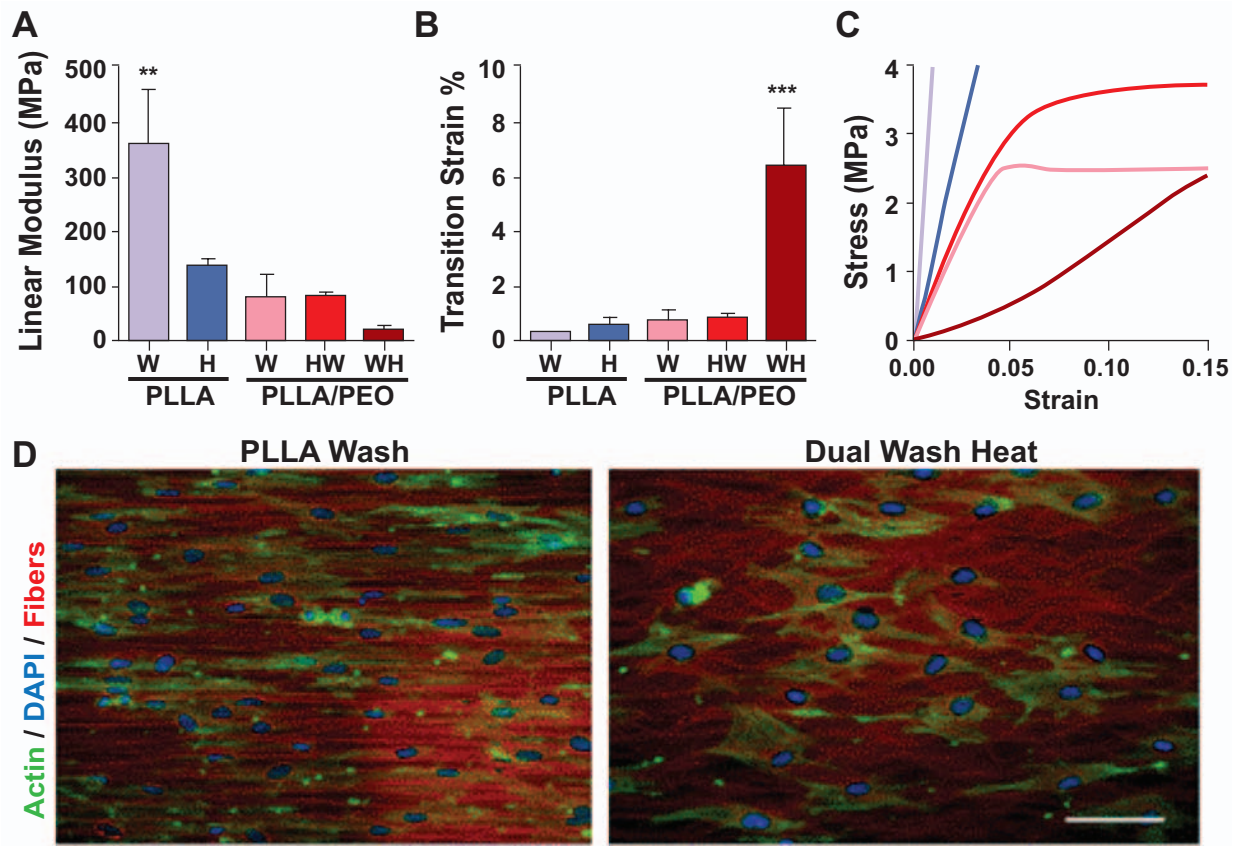

Figure 1. Tensile mechanics of PLLA and PLLA/PEO (Dual) scaffolds with various heat and wash treatments. Quantification of Linear Modulus (A) and Transition Strain (B) (mean +/−SD, **p<0.01 ***p<0.001 vs. all other groups). Average stress-strain curves (C) for each group show increased toe-region in the most crimped scaffolds (DWH). Phalloidin (green) and DAPI (blue) stained scaffolds with auto-fluorescent fibers (red) for normal PLLA scaffold and crimpy DWH scaffold (D). Scale bar = 75 μm.

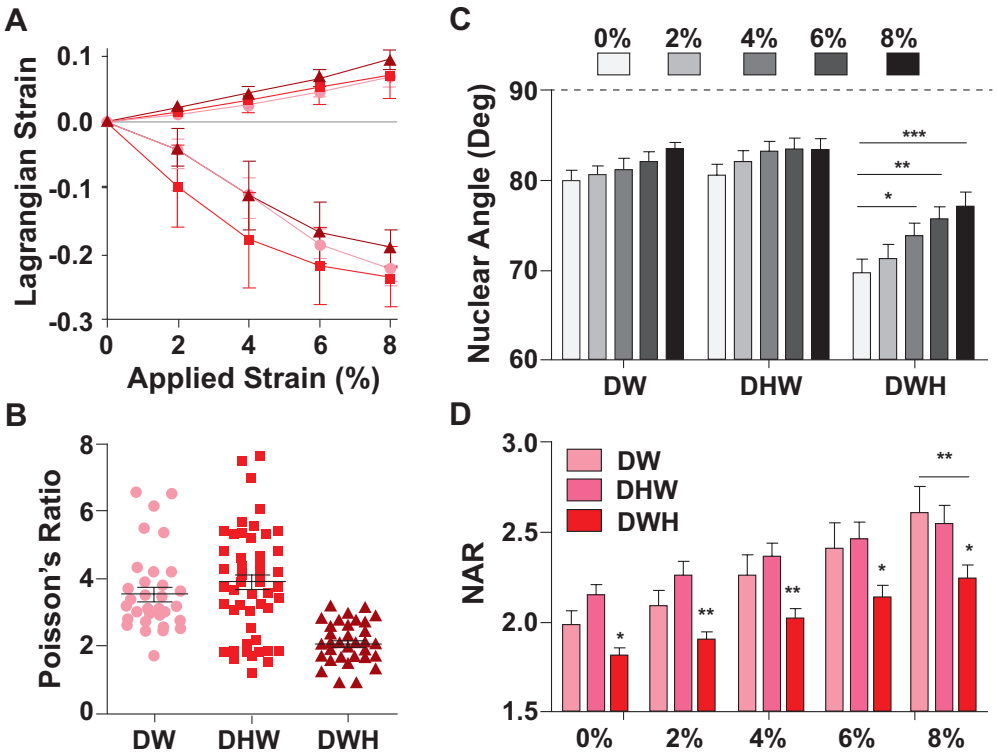

Figure 2. Lagrangian strains (mean +/− SD) in the fiber/stretch direction (A, top) and in the perpendicular direction (A, bottom) calculated from triads of MSC nuclei stained with Hoeschst and stretched on a microscope mounted device to 8% strain. Micro-scale Poisson's ratios were calculated for each triad at 8% (B). Quantification of nuclear orientation (C, where 90° = fiber/stretch direction) and nuclear aspect ratio (D, NAR) with applied strain (n>45 nuclei). Mean +/− SEM, bars indicate significance between groups, *= p<0.05, **=p<0.01, ***=p<0.001.

Poisson's ratios (Figure 2B). These scaffolds also displayed the least aligned nuclei at 0% strain and significant nuclear reorientation at 4, 6 and 8% strain (Figure 2C), whereas other scaffolds showed only slight (not significant) reorientation. Additionally, cells on DWH scaffolds had significantly lower NAR compared to DHW scaffolds at every strain level (Figure 2D).Although all groups showed significant nuclear elongation with applied stretch, this elongation was delayed on DWH scaffolds, and did not reach DW baseline levels until 4% strain.

Discussion

The crimp structure of tendons and ligaments is vitally important for their mechanical function, but is also likely important in regulating cellular mechanotransduction within these tissues. This structure may prove important for appropriate differentiation of progenitor cells used for engineering replacement tissues and may regulate the manner in which they interpret mechanical signals they receive within the dynamically loaded host environment. Here, by including a sacrificial PEO fiber population and controlling phase transitions in fibers, we generated aligned, porous, and crimped electrospun PLLA scaffolds that display much higher transition strain than heating PLLA alone. These scaffolds also alter baseline cellular and nuclear shape and response to stretch, potentially altering cellular interpretation of these mechanical signals. Future work will focus on understanding cellular deformation and biologic response in more mature/infiltrated constructs.

Significance

Fiber crimp is an important structural and mechanical characteristic of fibrous orthopaedic tissues and likely influences mechanotransduction within these tissues. Engineering replacement tissues will require both replication of this functional structure and understanding of its biologic influence on resident cells.

Acknowledgments

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Bone Morphogenetic Protein and Fractures: A Meta-Analysis

Mara L. Schenker, MD
Sarah M. Yannascoli, MD
Derek J. Donegan, MD
Keith D. Baldwin, MD, MSPT, MPH
Jaimo Ahn, MD, PhD
Samir Mehta, MD

University of Pennsylvania,
Philadelphia, PA, USA

Introduction

Bone morphogenetic protein-2 and -7 are FDA-approved for use in acute open tibia fractures and nonunions, respectively. However, off-label use of these agents is common and there continues to be much debate regarding their effectiveness. The aim of this study was to systematically review, for acute fractures and nonunions, the association between BMPs and bone healing (nonunion, healing times), the need for secondary intervention, and infections.

Methods

Computerized literature databases and manual search of bibliographies were performed. Randomized controlled trials and cohort studies (retrospective and prospective) evaluating the association between BMPs and long bone healing, need for secondary intervention, and infection were included. Descriptive and quantitative data were extracted. A meta-analysis was performed using a random effects model for union, secondary intervention, and infections in BMP and non-BMP treated groups. Time to healing was evaluated using frequency-weighted means, and group weighted standard deviations. Sensitivity analyses were performed to evaluate the effects of BMP type (BMP-2 vs. 7), control group type (autograft vs. "standard-of-care"), tibia fractures, open fractures, level of evidence, and author/funding conflict of interest. Study heterogeneity, criteria of methodological quality and publication bias-adjusted for using trim and fill analysis-were also evaluated.

Results

Initial search identified 1652 references. Of the 307 articles further inspected by abstract, 19 were included (10 RCT (1,3-7,10,12,14,17), 6 prospective cohort (2,8,9,11,13,15) and 3 retrospective cohort (16,18,19). In acute fractures alone, union rates were similar for BMP-treated and non-BMP treated groups for all acute fractures, acute fractures treated with BMP-2, and acute open fractures treated with BMP-2 ($p=0.07$). Healing times were not different between the groups for acute fractures (BMP 32.2 wks vs. non-BMP 34.0 wks, $p=0.70$). In the nonunion groups, union rates were similar for BMP-treated and non-BMP treated groups ($p=0.14$); however, for the FDA-approved indication (tibial nonunions treated with BMP-7), there was a significantly higher rate of union in the BMP-treated group (OR 2.5, CI: 1.1, 6.0, $p=0.04$). For study level of evidence, there was a trend towards significance in lower level of evidence studies ($p=0.06$), compared to level 1 studies ($p=0.21$) for bony union. In level 1 studies, union rates were comparable to autograft ($p=0.07$), and there was a significantly higher rate of union ($p=0.04$) when compared to "standard of care" protocols. No difference was found in reported union rates for studies with documented conflict of interest ($p=0.42$) compared to those reporting no conflict of interest ($p=0.07$). There was a decreased overall need for secondary intervention in the BMP-treated groups for both acute fractures and nonunions ($p=0.002$). There were similar rates of infection in the BMP and non-BMP treated groups (OR 1.0, 95% CI: 0.7, 1.4, $p=0.95$). There was publication bias noted in the infection and nonunion groups, with small studies showing a larger effect size than larger studies. Trim and fill analysis was performed which resulted in similar results to the original meta-analysis.

Discussion

BMP was not found to improve union rate or healing times in any subset analysis of acute fractures. For nonunions, BMP-7 was found to have higher union rates for the FDA-approved indication compared to controls. Due to the variation in effectiveness noted in the sensitivity analyses, we would encourage further well-designed studies to identify the precise fracture population, timing, and delivery mechanism that BMP can be used to optimize bony healing.

Significance

This study provides a comprehensive review of the effects of BMP on healing of acute fractures and nonunions. Our results suggest that outcomes are highly variable according to indication, implying that more rigorous prospective studies are needed to precisely identify the fracture population, timing, and delivery mechanism that BMP can be used to optimize bony healing.

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Mara.Schenker@uphs.upenn.edu

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Deficient Geriatric Fracture Healing is Associated with Alterations in Immune Cell Function and Cell Cycle

Luke A. Lopas, BS
Lee McDaniel, MS
Nicole S. Belkin, MD
Patricia L. Mutyaba, BS
Derek Dopkin, BA
Kurt D. Hankenson, DVM, MS, PhD
Jaimo Ahn, MD, PhD.

University of Pennsylvania,
Philadelphia, PA, USA

Introduction

Fragility fractures lead to significant patient morbidity, mortality, and cost to both the individual and society.[1,2] Geriatric patients often experience a protracted healing course and are at higher risk for poor outcomes. Discriminating underlying differences in local gene expression at the fracture site can be used to understand the mechanistic dysfunctions in geriatric healing. The objective of this study was to compare fracture healing gene expression profiles of young and geriatric mice in a traumatic long bone fracture model.

Methods

Five month-old (mo) mature but young mice and 25 mo geriatric mice underwent bilateral, closed, traumatic 3-point bend tibial diaphyseal fractures with intramedullary pin fixation. Five mo "young adult" mice and 25 mo "geriatric" mice (corresponding to human age of 70-85)[3] were obtained from the National Institute of Aging (NIA) C57BL/6 colonies in which geriatric mice have been show to have delayed and decreased fracture healing[4]. Tibae were harvested at 0, 5, 10, and 20 days post fracture (DPF). RNA was harvested from homogenized callus. Global gene analysis was performed using the Affymetrix MoGene v1 r4 array. Significance was determined by a t-test using permutation based false-discovery rate (FDR) and $p<0.05$ with MeV software. Positive genes were uploaded into DAVID bioinformatics for gene set enrichment analysis (GSEA) and uploaded to Cell Type Enrichment Analysis for Microarray Data (CTen) for determination of cell populations present throughout fracture healing.

Results

Time from fracture (DPF) was the strongest determinant of global expression profile change with age being a modifying factor. CTen analysis showed changes in gene expression profiles consistent with increases in stem cells and osteoblasts in both young and old mice between 0, 5 and 10 DPF and a reduction by 20 DPF. In contrast, a large relative decrease in macrophages was predicted in young mice from 5 to 10 DPF but not in geriatric mice.Additionally, geriatric mice exhibited an increase in CD8+ T-cell expression not seen in young mice (10-20 DPF). GSEA DAVID analysis provided ranked differences in numerous pathways (Table 1); most strikingly, pathways that are different between aged and young healing are related to the immune system and cell cycle.As an example, cell cycle related genes are highly expressed early (0, 5, and 10 DPF) in young mice but later (20 DPF) in geriatric mice (Figure 1).

Discussion

As expected, time post-fracture was more predictive of changes in gene expression than chronological age. However, differences in the timing and duration of the immune response and the regulation of the cell cycle were present. These differences may be partially responsible for the observed deficiencies in aged fracture

Table 1. DAVID gene set enrichment analysis showing the top pathways that differ between young and old mice

DPF	Pathways
0	1. Antigen processing and presentation; 2. Cell adhesion molecules (CAMs); 3. Graft-versus-host disease; 4. Allograft rejection; 5. Type 1 diabetes mellitus
5	1. Glycerolipid metabolism; 2. Cell cycle; 3. Prostate cancer; 4. Focal adhesion; 5. Biosynthesis of unsaturated fatty acid
10	1. Regulation of actin cytoskeleton; 2. Pathways in cancer; 3. ECM-receptor interaction; 4. Focal Adhesion; 5. Chronic myeloid leukemia
20	1. Leukocyte transendothelial migration; 2. Chemokine signaling pathway; 3. Focal Adhesion; 4. Natural Killer Cell Mediated cytotoxicity; 5. Fc epsilon RI signaling pathway

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Jaimo.Ahn@uphs.upenn.edu

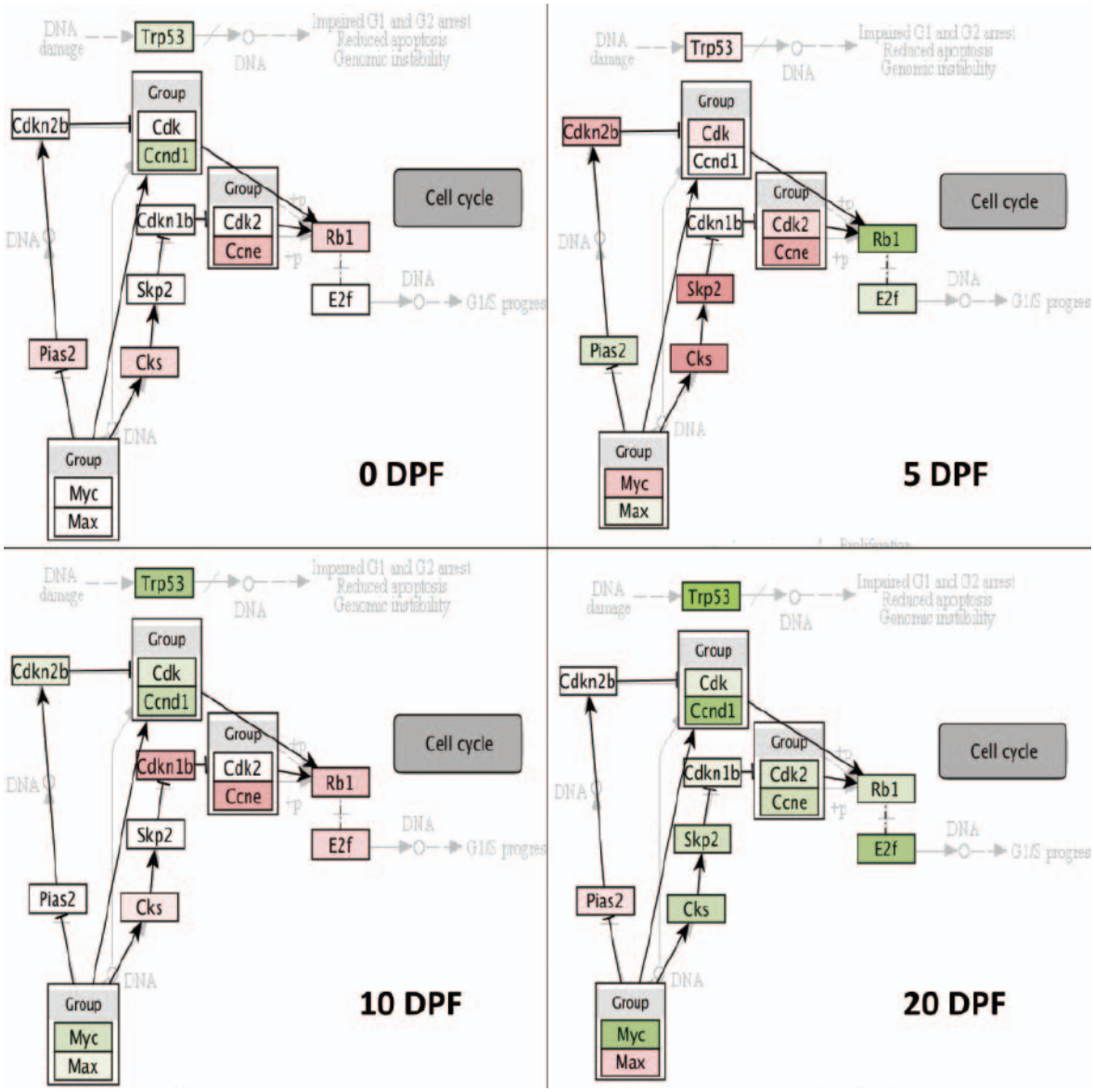

Figure 1. Expression of genes involved in the cell cycle. Diagrammatic representation of cell cycle genes that are changed in association with fracture healing of young and geriatric mice. Red coloring indicates higher expression in young mice, whereas green coloring indicates higher expression in geriatric mice. Note the generally enhancing levels of cell cycle genes at 0, 5, and 10 DPF in young mice, while at 20 DPF, geriatric mice show increases in cell cycle-associated genes relative to young mice.

healing and potentially be targets for improving fracture healing in the future.

Significance

Understanding global genomic expression and cell population patterns in murine geriatric fracture patterns can lend insight into the fundamental biology of altered fracture healing in aged animals. This knowledge can be used for further investigation and manipulation of rationally selected deficits in aged fracture healing.

Acknowledgments

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Local Activation of Notch Signaling Enhances Geriatric Bone Regeneration

[1,2]Patrick N. Domerchie
[2]Derek Dopkin, BA
[2]Kurt D. Hankenson, DVM, PhD
[2]Jaimo Ahn, MD, PhD

[1]University of Groningen, Groningen, Netherlands

[2]University of Pennsylvania, Philadelphia, PA, USA

Introduction

The elderly have an increased incidence of fragility fractures, which are prone to heal more slowly and develop into mal-unions at a higher rate. In turn, this results in high rates of morbidity. It is therefore important to develop new therapeutics to increase the robustness and speed of geriatric fracture healing. We have recently developed a model of geriatric fracture healing in very old mice. Geriatric mice with closed tibial fractures show reduced callus size and therefore a reduction in callus bone formation, compared to their younger counterparts and provide a suitable model to study mechanisms that influence geriatric fracture healing.[1] Notch signaling has been shown to enhance healing of injured skeletal muscle.[2] Our laboratory has previously shown that Notch pathway components are upregulated during fracture healing and that inhibition of canonical Notch signaling during fracture healing alters bone healing.[3] The objective of this study was to determine whether activation of Notch signaling could increase fracture healing in geriatric mice. The Notch-pathway consists of a number of cell bound ligands and receptors, such that when a ligand binds to a receptor, it triggers proteolysis of the extracellular and transmembrane part of the receptor and 'frees' the Notch Intracellular Domain (NICD), which then translocates into the cell nucleus where it triggers effector genes. We hypothesize that upregulating NICD using localized adenoviral delivery will enhance bone regeneration.

Methods

We used 21 young adult (5-month-old) and 21 very old (25-month-old) mice. We surgically inserted an intramedullary pin in both tibiae, after which we the bones were fractured using the three-point bending apparatus described in previous studies.3 Five days after surgery, mice received a 30 µl injection with an NICDeGFP adenovirus (Notch Intracellular Domain, enhanced Green Fluorescent Protein) in one leg, and a GFP adenovirus (Green Fluorescent Protein) in the other. After 10, 20 and 40 days post-fracture (DPF) we euthanized the mice and harvested the tibiae. All tibiae were scanned using a Scanco 35 MicroCT and were analyzed for bone in the callus by outlining the callus and semi-manually excluding the bone. RNA was harvested for expression analysis and microCT'ed bone was processed for histology. For statistical analysis we used an unpaired, one-sided student's T-test using Excel© and a two-way ANOVA using SPSS14©.

Results

NICD treatment significantly increases callus volume (20% increase) in both young and old 20 DPF mice relative to GFP treatment (young: $p=0.0497$, old: $p=0.028$, see Figure 1A). Furthermore, NICD results in increased bone volume fraction (BVF) (~50% increase) and trabecular thickness in old 40 DPF mice ($p=0.030$ and $p=-0.038$ respectively, see Figure 1B and 1C), and an increased tissue mineral density (10% increase) in young DPF 40 mice ($p=0.01907$, see Figure 1D).

Discussion

These results clearly show a positive effect of Notch activation on both callus size and bone formation, particularly in the geriatric mice.. Consistent with our previous results, the increase in callus size with NICD treatment is phenotypically opposite of what was seen when Notch signaling was inhibited during fracture healing using dominant negative mastermind (dnMAML) over-expressing mice.[4]

Significance

This is the first demonstration that local activation of Notch signaling positively influences bone regeneration. This research represents an important step in developing Notch activation as a therapeutic for enhancing bone regeneration.

Acknowledgments

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Jaimo.Ahn@uphs.upenn.edu

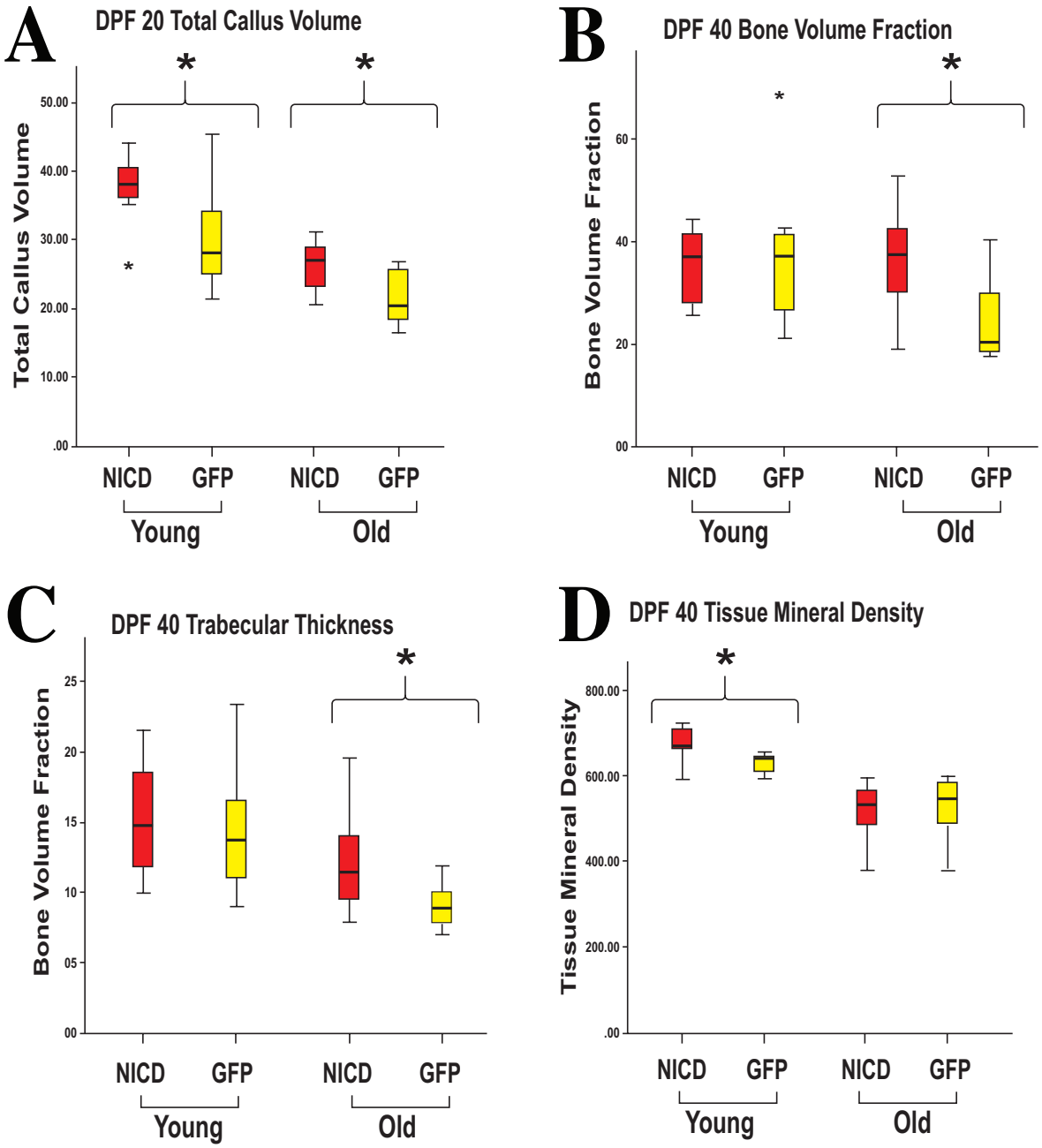

Figure 1. Micro-CT analysis of NICD treated fractures. NICD is red, GFP is yellow. * = significance between groups within brackets. A) *DPF 20 Total callus volume.* Shows significant difference in both young and old mice (p=0.0497 and p=0.028, respectively). B) *DPF 40 Bone volume fraction.* Shows significant difference in old mice (p=0.030). C) *DPF 40 Trabecular thickness.* Shows significant difference in old mice (p=0.038). D) *DPF 40 Tissue mineral density.* Shows significant difference in young mice (p=0.01907).

would also like to acknowledge Lorraine Mutyaba, Luke Lopas, and Drs. Feng Zhu and Michael Dishowitz for their scientific and technical support.

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Enhanced Individual Trabecular Repair and its Mechanical Implications in PTH and Alendronate Treated Rat Tibial Bone

Allison R. Altman, PhD
Chantal M. de Bakker
Abhishek Chandra, PhD
Beom Kang Huh
Ling Qin, PhD
X. Sherry Liu, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Aging shifts bone remodeling toward a negative balance between bone formation and resorption, causing bone loss and increased fracture risk. Anti-resorptive agents are commonly used to inhibit bone resorption and stabilize bone mass. While they are effective to prevent further bone loss, there is also a great need for anabolic agents which can reverse bone deterioration and regain lost skeletal integrity. PTH is the only FDA-approved anabolic treatment for osteoporosis, which greatly stimulates bone formation. Combined therapy of anti-resorptive treatments, such as alendronate (ALN), and PTH have been proposed and are expected to further increase bone mass. Despite conflicting results in the literature,[1,2,3] previous work in our lab has shown that combined PTH and ALN therapy results in an additive effect, with enhanced bone volume fraction beyond that of PTH or ALN monotherapy.[4] This additive effect was driven by preferential plate thickening, resulting in an increase in the relative number of plate- versus rod-like structures.[4] The current study was aimed at identifying the mechanism through which plate-structure was enhanced, and the resulting implications on the mechanical behavior of the trabecular bone. A novel *in vivo* imaging technique allowed the precise alignment of subsequent scans in such a way that changes in each individual trabecula can be explored. By viewing the individual trabecular dynamics (ITD), we may gain insight into the mechanisms of combined PTH and ALN therapy. In addition, using computational modeling, this study aimed to determine the mechanical implications of combined therapy when compared to monotherapy. We hypothesized that combined treatment would result in enhanced structural repair and strength than PTH or ALN monotherapy. Furthermore, we expected that a small percent increase in bone volume by structural fortification would result in a significant strength enhancement.

Methods

24 3-mo-old SD rats were assigned to vehicle (Veh) (n=5), PTH (daily 60 μg/kg s.c. injections, n=6), ALN (50 μg/kg s.c. injections every 3 days, n=6), and PTH+ALN (both PTH and ALN treatments, n=7) treatment groups. *In vivo* μCT scans (VivaCT 40, Scanco Medical, 10.5 μm/voxel) were performed at baseline and after 12 days of treatment. A 1.575x1.575x1.05 mm^3 cube of trabecular bone was precisely registered between time points using several iterations of 3D image registration.

Individual Trabecular Dynamics (ITD) Analysis

Each registered and thresholded pair of baseline and follow-up images of trabecular bone was subjected to ITD analysis. Sites of structural deterioration (rod disconnection or plate perforation) and structural repair (rod connection or plate perforation filling) were identified and the percent occurrence was calculated as the number of occurrences of the above structural changes normalized by the total number of trabeculae analyzed (468 trabeculae/sample on average).

Finite Element Analysis (FEA)

Registered baseline and follow-up scans were converted to voxel FE models and subjected to axial compression tests using a customized software. An additional model was generated based on the baseline image and ITD analysis where only enhancements due to thickening were present, rather than structural repair identified by ITD. Stiffness was calculated for the baseline models, the models with enhancement due to thickening, and the models with both thickening and structural repair.

Statistical Analysis

All ITD and FEA measurements were compared using a one-way ANOVA between treatment groups. The relative increases in bone volume (BV) and stiffness due to structural repair or thickening were compared using a one-way ANOVA between groups.

Results

ITD

The tracking of individual trabecular structures' connectivity over the course of

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alaltman@mail.med.upenn.edu

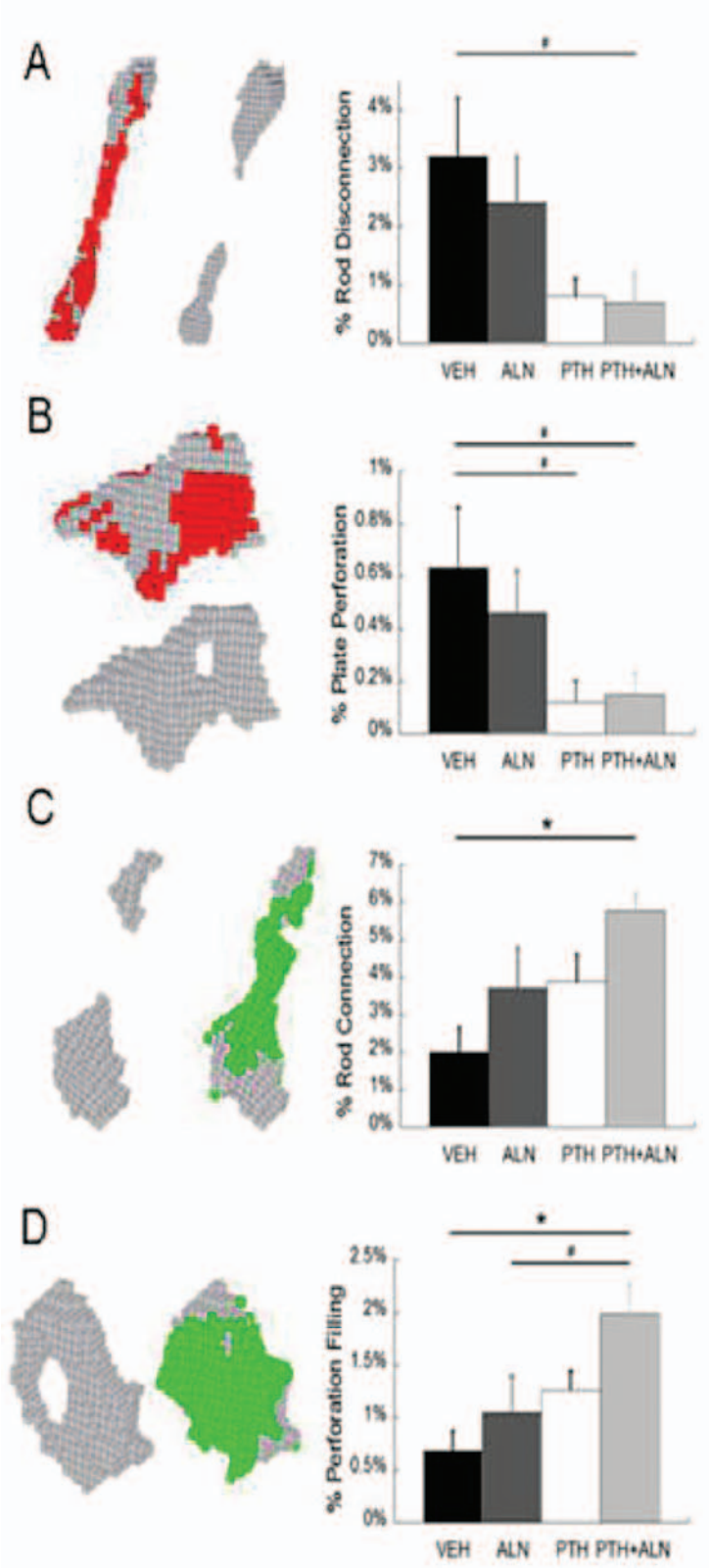

Figure 1. Comparison of percent occurrences of (A) rod disconnection, (B) plate perforation, (C) rod connection and (D) perforation filling. Red = Bone loss, and Green = new bone. *Significant differences ($p<0.05$) # trend differences ($p<0.1$).

treatment indicated several rod disconnections and plate perforations even in the Veh-treated trabeculae (3.2% and 0.6% of the total trabeculae respectively). In contrast, this was balanced by similar structural repair with 2.0% connected rods and 0.7% filled plates. In the ALN-treated group this balance was tipped towards structural repair with 3.7% connected rods, and 1.0% filled plates. Interestingly, the PTH-treated group had a similar amount of structural repair (3.9% connected rods and 1.3% filled plates) to that of the ALN group. In addition, the PTH group tended to have a lower incidence of plate perforation (0.1%, $p<0.1$) compared to the Veh group. The combined PTH+ALN-treated group tended to have similarly reduced rod disconnection (0.7%) and plate perforation (0.1%, $p<0.1$), and displayed significant structural repair beyond that of the Veh group (5.8% connected rods, and 2.0% filled plates), resulting in the greatest net gain in connectivity by both structural fortification and increased protection against lost connectivity (Figure 1).

FEA

There were significant increases in BV over time for all treatment groups (6.6% ALN, 25.5% PTH, and 35.8% PTH+ALN), which correspond to significant increases in stiffness over baseline (14.8% ALN, 46.6% PTH, and 87.4% PTH+ALN) (Figure 2). For all treatment groups, increases in BV due to thickening were far greater than those due to structural repairs, with 5.1% vs. 1.5% in ALN group, 23.9% vs. 1.7% in the PTH group, and 33.5% vs. 2.3% in the PTH+ALN group. Trabecular thickening itself caused 10.3%, 41.0%, and 75.1% increases in stiffness in the ALN, PTH, and PTH+ALN

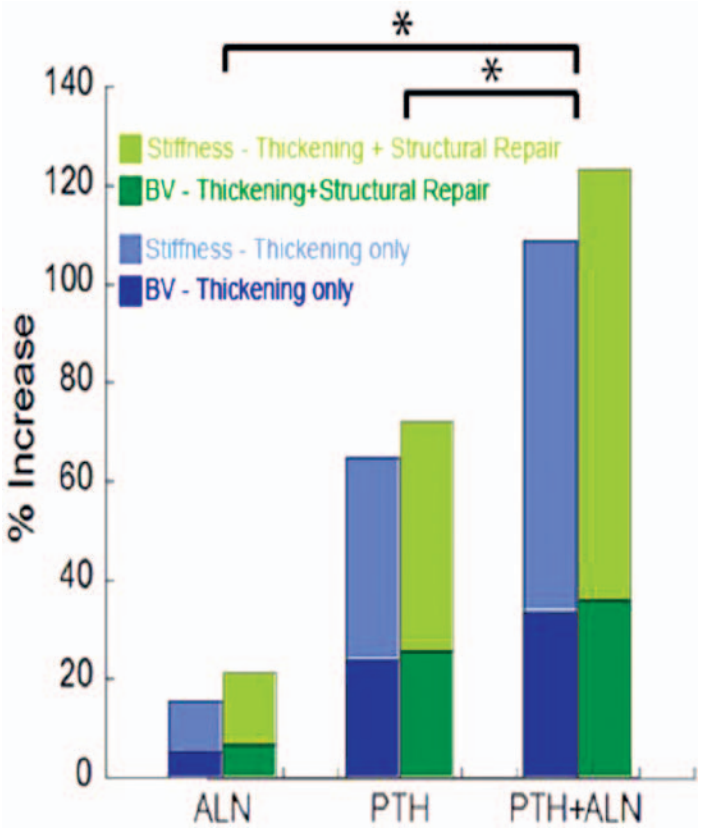

Figure 2. Comparison of relative increases in bone volume and stiffness due to thickening, and both, thickening and structural enhancements for each treatment group. Black* indicates differences in relative increases in stiffness due to structure alone between treatment groups ($p<0.05$).

groups, respectively. Moreover, the trabecular structural repair led to an additional improvement in stiffness, with the highest in PTH+ALN (by an additional 12.4%), which was significantly greater than either PTH (5.6%) or ALN (4.5%).

Discussion

Higher structural repair resulted in substantial increases in stiffness in the combined therapy group after only 12 days of treatment. The ITD results indicate similar amounts of structural repair in both monotherapies. The combined treatment group had enhanced structural repair, as well as reduced structural deterioration for both plate and rod structures, yielding the greatest net gain in trabecular integrity. In combination with our previous work, this suggests that combined therapy can more effectively repair damaged trabeculae despite a similar bone formation rate as those treated with PTH. The relative increase in bone volume due to structural repair did not differ between the treatment groups; however, the relative increase in stiffness in the combined therapy group was significantly higher than either monotherapy group, demonstrating the functional significance of structural repair. In conclusion, enhanced structural repair and reduced structural deterioration allow combined therapy to further improve the stiffness of the trabecular bone. This increased stiffness may help to enhance bone quality, and ultimately improve the bone's resistance to fractures.

Significance

Combined PTH and ALN therapy has the potential to more efficiently rescue trabecular structural deterioration and enhance structural repair over either monotherapy. Although associated with a minimal amount of new bone volume, rod connection and plate filling result in a significant increase in trabecular bone stiffness. Through such structural repair mechanisms, combination therapy showed an advantage in improving bone strength over either monotherapy.

Acknowledgments

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U·P·O·J

Delayed Chondrocyte Differentiation and Altered Indian Hedgehog Signaling Contribute to Failed Vertebral Bone Formation in Mucopolysaccharidosis VII

Chelsea M. del Alcazar, BS
Joseph A. Chiaro, BS
Eileen M. Shore, PhD
Mark E. Haskins, VMD, PhD
Lachlan J. Smith, PhD

University of Pennsylvania, Philadelphia, PA, USA.

Introduction

Mucopolysaccharidosis VII (MPS VII) is a lysosomal storage disorder characterized by deficient activity of the enzyme β-glucuronidase, resulting in accumulation of poorly-degraded chondroitin, heparan, and dermatan sulfate glycosaminoglycans (GAGs).[1,2] While MPS VII results in multi-systemic disease manifestations, skeletal abnormalities are particularly prevalent and significantly impact patient quality of life.[1,2] In the spine, manifestations include accelerated disc degeneration, and malformed and misaligned vertebral bodies, leading to kyphoscoliotic deformity and spinal cord compression. There are currently no therapies that effectively treat spine disease in MPS VII. In previous studies, we demonstrated the presence of radiolucent, cartilaginous lesions at the vertebral epiphyses, which significantly compromise the structural and mechanical integrity of the intervertebral joint.[3,4] We hypothesize that these lesions represent failed cartilage-to-bone conversion during post-natal development; the underlying pathological mechanisms responsible, however, remain unknown. During endochondral ossification, chondrocytes undergo distinct stages of differentiation, a process that is tightly regulated by a complex array of secreted growth factors.[5] One such growth factor, Indian Hedgehog (IHH), performs crucial roles to regulate chondrocyte hypertrophic differentiation.[5] The stability, distribution, and binding of IHH is regulated in part by GAGs, particularly heparan and chondroitin sulfates.[6,7] The objective of this study was to investigate the mechanisms responsible for failed cartilage-to-bone conversion in MPS VII, and specifically, to examine associations between abnormal GAG accumulation, abnormal chondrocyte differentiation, and altered IHH signaling in developing MPS VII vertebrae, using the naturally occurring canine model.

Methods

All animal studies were performed with IACUC approval. Normal and MPS VII affected dogs were euthanized at either 2 weeks of age (each n=3) or 6 weeks of age (each n=2). These ages represent developmental stages immediately before and after commencement of secondary ossification in the vertebral bodies of normal animals. MPS VII dogs were identified at birth by DNA mutation genotyping. Following euthanasia with 80mg/kg of intravenous barbiturate, thoracic and lumbar vertebral bodies were isolated. For histological analysis (both 2 and 6 week old animals), whole vertebral bodies were fixed in 4% paraformaldehyde and processed into paraffin. For analysis of GAG accumulation, sections were either stained with Alcian blue, or immunostained for chondroitin sulfate. For analysis of growth plate morphology, sections were stained with hematoxylin and eosin. The mean height of the proliferative zone and the total number of proliferating chondrocytes were calculated from a standardized 2mm-wide region in the center of the growth plate. To examine cells responding to IHH, sections were immunostained for the IHH receptor patched-1 (PTC1), which is upregulated downstream of IHH pathway activation. All slides were imaged and analyzed under bright field microscopy. For mRNA analysis (2 week old animals only), cartilage was isolated from vertebral epiphyses and RNA isolated. Expression of hypertrophy markers (COL10A1 and RUNX2) and hedgehog pathway genes (IHH and PTC1) was determined using real time RT-PCR. All target genes were normalized to β-actin, and analyzed via the comparative CT method. Differences in measured parameters between normal and MPS VII at each age were established using Student's t-tests (significance = $p<0.05$).

Results

Alcian blue and chondroitin sulfate staining demonstrated significant abnormal increased GAG accumulation in the vertebral epiphyses of MPS VII animals, even at 2 weeks of age (Figure 1). In MPS VII dogs, the height of the growth plate proliferative zone was lower for MPS VII veterbrae compared to normals (69% of normal at 2 weeks of age ($p<0.05$), and 57% of normal at 6 weeks-of-age ($p=0.07$)), as was the total number of growth plate proliferating chondrocytes (63% of normal at 2 weeks of age ($p<0.05$), and 56% of normal at 6 weeks of age ($p=0.06$)). At 6 weeks of age, decreased and aberrant PTC1 staining

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chelsd@vet.upenn.edu

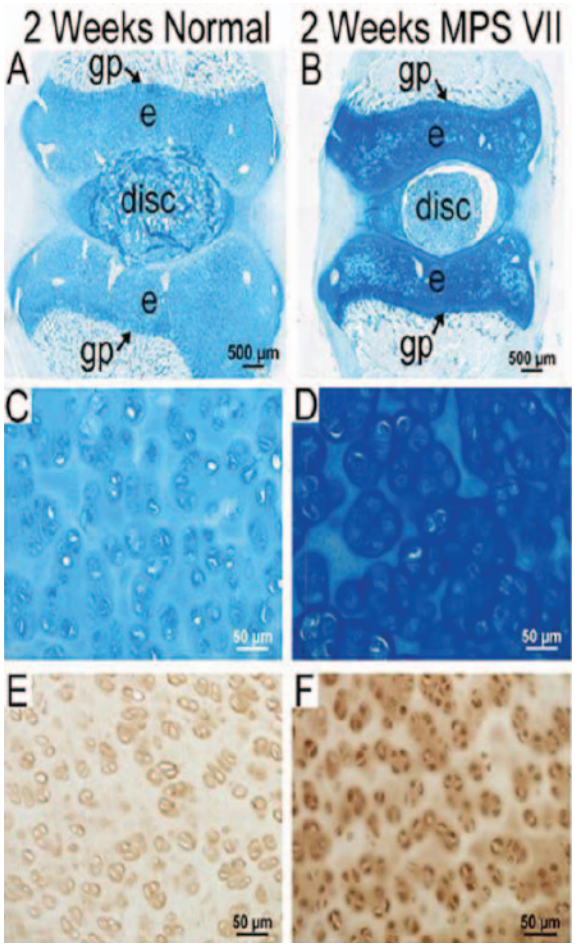

Figure 1. Abnormal GAG accumulation in the vertebral epiphyseal cartilage of MPS VII dogs compared to normals is striking even at 2 weeks-of-age. A-D) Alcian blue stain for total GAG. E-F) Chondroitin sulfate; e = epiphysis, gp = growth plate.

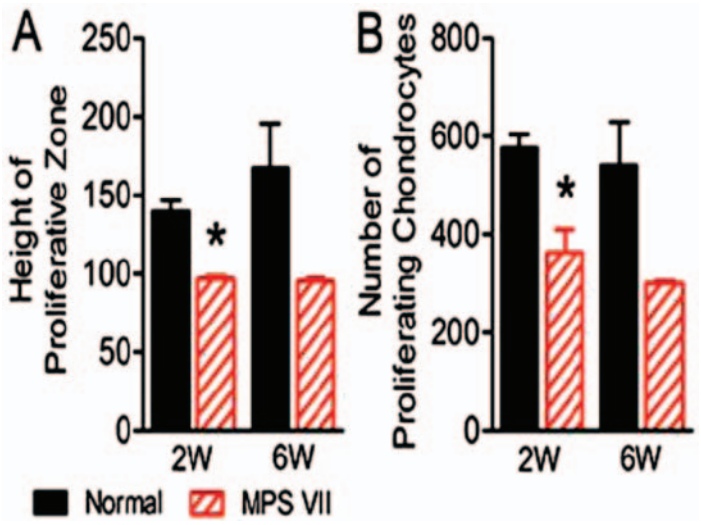

Figure 2. Differences in (A) Proliferative zone height and (B) Number of proliferating chondrocytes between normal and MPS VII vertebral growth plates at 2 and 6 weeks of age. *p<0.05 vs normal.

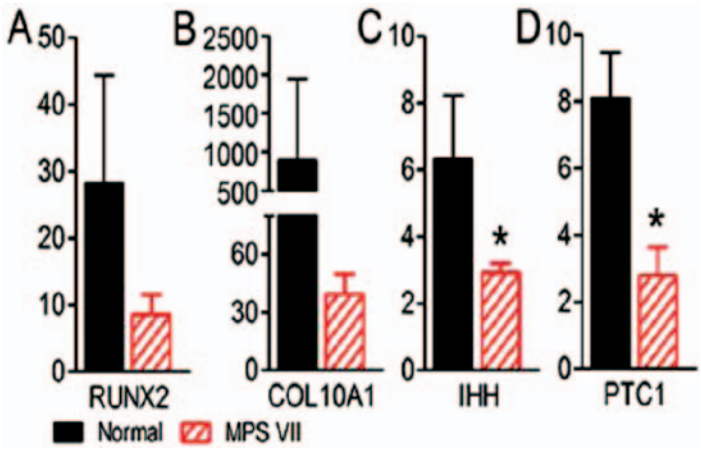

Figure 3. mRNA expression of hypertrophic markers and IHH pathway genes at 2 weeks-of-age. A. RUNX2. B. COL10A1. C. IHH. D. PTC1. *p<0.05 vs normal.

was detected in MPS VII vertebral epiphyses compared to normals (Figure 2). The mRNA expression levels of IHH and PTC1 were significantly lower for MPS VII animals (46% and 34% of normal respectively, both $p<0.05$, Figure 3). Expression of hypertrophy markers COL10A1 and RUNX2 was also lower, although not significantly (4% and 30% of normal respectively, Figure 3).

Discussion

In this study, we investigated mechanisms of failed cartilage-to-bone conversion in MPS VII vertebrae. Key findings include striking, abnormal GAG accumulation within the epiphyseal cartilage of MPS VII vertebrae as early as 2 weeks of age, morphological abnormalities of the growth plate at 2 and 6 weeks of age, and decreased mRNA expression of hypertrophic markers at 2 weeks of age, all indicative of delayed chondrocyte differentiation. The IHH signaling pathway plays a critical role in endochondral ossification, both through direct induction of chondrocyte differentiation and indirectly through activation of other signaling pathways, such as parathyroid hormone-related peptide signaling.[8,9] Here we demonstrate significantly decreased mRNA expression of both IHH and PTC1 in MPS VII vertebral epiphyseal cartilage at 2 weeks of age, and decreased and aberrant protein expression of the IHH receptor Patched-1 at 6 weeks of age. Our data support that the IHH pathway is a promising therapeutic target for normalizing bone formation in MPS VII. These results also highlight the importance of early therapeutic intervention to prevent progression of bone disease in MPS VII.

Significance

MPS VII is associated with severe spine disease, which significantly impacts patient quality of life, and for which there are currently no effective treatments. This work elucidates mechanisms of failed bone formation in MPS VII vertebrae and implicates the IHH pathway as a potential therapeutic target.

Acknowledgments

This work was funded by grants from the Penn Center for Musculoskeletal Disorders and the NIH.

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Deep Sequencing of Notochord-Derived Cells During Embryonic Formation of the Nucleus Pulposus: Preliminary Findings

[1]Lachlan J. Smith, PhD
[1]Joseph A. Chiaro, BS
[2]Kendra K. McKee, BS
[1]Neil R. Malhotra, MD
[1]Robert L. Mauck, PhD
[2]Brian D. Harfe, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]University of Florida, Gainesville, FL, USA

Introduction

Intervertebral disc degeneration is strongly implicated as a cause of low back pain.[1] Current surgical and conservative treatments for discogenic low back pain only treat the symptoms, and there is a pressing need for new therapeutic strategies to restore native disc structure and mechanical function by potentiating native tissue regeneration. Identification of such strategies may be achieved by studying aspects of intervertebral disc development. During embryonic development, the mesoderm-derived notochord undergoes a transformation from a rod-like structure that acts as signaling center involved in patterning the axial skeleton, to form the disc nucleus pulposus (NP), the proteoglycan-rich structure at the center of the disc that performs a crucial role in resisting compressive loads.[2] While previous studies have shown that all cells comprising the adult mouse NP are notochord-derived,[3,4] little is known about the molecular mechanisms which drive the transformation from notochord to NP. The objective of this study was to use whole transcriptome deep sequencing (RNA-Seq) to define differences in the global mRNA expression profiles of notochord-derived cells during embryonic formation of the NP, and to identify the key anabolic factors driving this process. We hypothesized that differences between the global mRNA expression profiles of embryonic notochords and postnatal discs would reflect a transformation from a signaling center (notochord) to an extracellular matrix-rich and functional load-bearing tissue (NP).

Methods

Animal studies were performed following IACUC approval. Mice used in this study were Shh-cre;ROSA:YFP.[3] This system takes advantage of the fact that all cells of the notochord express the morphogen sonic hedgehog (SHH), whereas those of the surrounding mesenchyme do not. This allows for FACS isolation of pure populations of notochord-derived cells. Two developmental stages were examined in this study: embryonic day 12.5 (E12.5), immediately before the notochord-NP transformation commences (Figure 1, top); and postnatal day 0 (P0), when the transformation is complete and the NP is fully formed (Figure 1, bottom). Each biological replicate (E12.5: n=3; P0: n=1) was comprised of cells pooled from all embryos/pups in a litter (average of n=6 per litter). For E12.5, discrete notochords were dissected from embryos for immediate RNA isolation. For P0 samples, spines, were dissected free of posterior elements, including dorsal root ganglia, minced and digested for 2 hours in collagenase. YFP-

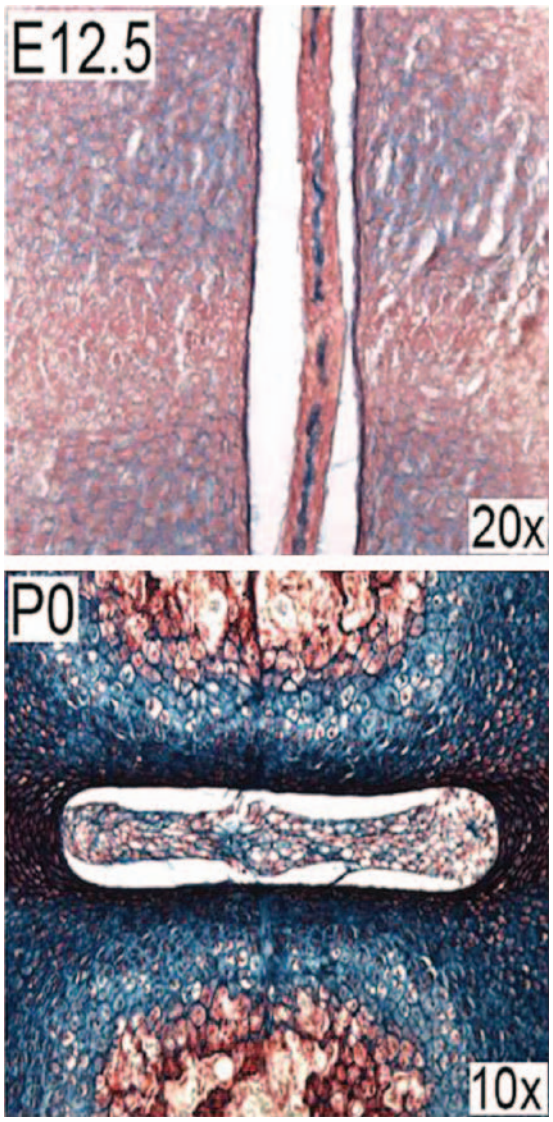

Figure 1. Histological appearance of the embryonic spine at E12.5 showing intact notochord (top), and at P0 showing fully formed NP (bottom).

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lachlans@mail.med.upenn.edu

positive (notochord-derived) cells were collected using FACS (Figure 2), and RNA isolated. RNA was converted to RNA-Seq libraries, sequenced (Illumina HiSeq, ~50 million reads/transcript) and aligned to the mouse genome. Fold changes (E12.5=>P0) in extracellular matrix molecules, signaling factors and known notochordal/NP markers were assessed. Analysis was limited to the top 5000 expressed genes for each group. Pathway analysis was performed using Ingenuity Pathway Analysis software. Specifically, upstream analysis was used to predict those growth factors potentiating cell differentiation and driving embryonic formation of the NP.

Results

Analysis of fold changes revealed increased expression of extracellular matrix molecules at P0 relative to E12.5 (Figure 3A). Specifically, this included proteoglycans (ACAN: +3; LUM: +5; FMOD; +8; BGN: +42; DCN: +11; ASPN: +31; and PRG4: +76), and collagens (COL2A1: +2; COL1A1: +5 and COL6A1: +7). Expression of the morphogen SHH was dramatically decreased at P0 relative to E12.5 (−164). With respect to putative NP cell markers, some were decreased (KRT8: −5; KRT18: −11; HBB: −54), and others were unchanged (VIM, KRT19, PAX1) (Figure 3B). Several chondrogenic markers also showed increased expression, including COMP (+72) and TNC (+10). Upstream analysis of global fold changes in mRNA expression predicted that the anabolic cytokines most likely driving embryonic formation of the NP include TGFB1, TGFB3, BMP6, CTGF and EGF.

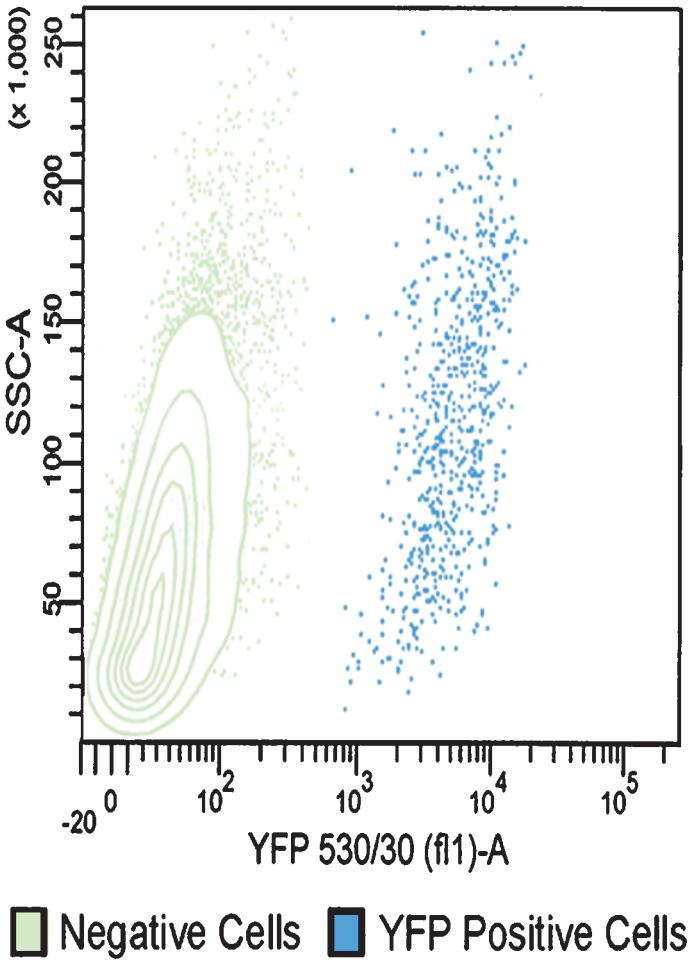

Figure 2. Representative cell sorting result showing a distinct population of YFP-positive cells from Shh-cre;ROSA:YFP embryos.

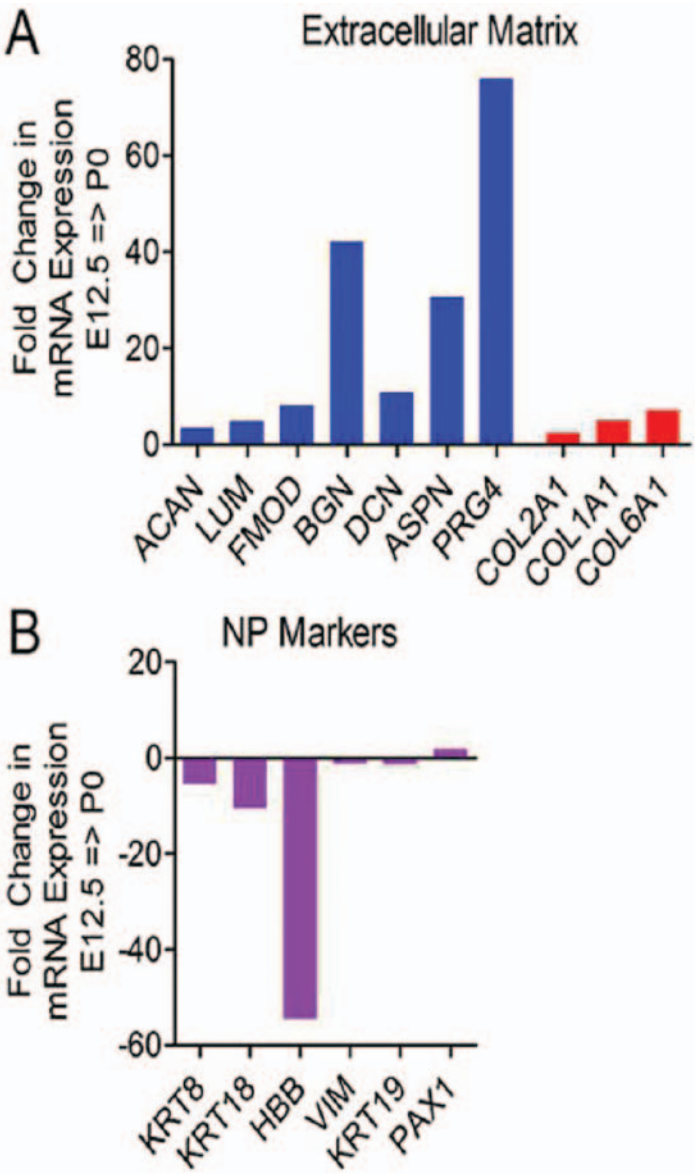

Figure 3. A) Fold changes in mRNA expression of key extracellular matrix components, and B) NP cell markers, from E12.5 to P0.

Discussion

These results, while preliminary, support the conclusion that during embryonic formation of the NP, notochord cells differentiate toward a more chondrogenic phenotype, adopting a molecular expression profile necessary to synthesize and maintain an extracellular matrix-rich, functional, load-bearing tissue. Reduction in SHH expression is consistent with a diminished postnatal signaling role for the NP. Ongoing work will confirm these findings with

additional biological replicates and complementary assays (including verification by real time PCR, in situ hybridization and immunohistochemistry). Identification of key anabolic factors responsible for notochord-derived cell differentiation and embryonic formation of the NP may lead to novel growth factor regimens to direct stem cell differentiation towards the NP phenotype or be injected therapeutically to promote intervertebral disc regeneration.

Significance

Low back pain resulting from intervertebral disc degeneration is a significant socio-economic burden. The results of this study may lead to new biological therapies for structural and functional regeneration of the disc.

Acknowledgments

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U·P·O·J

Changes in the Trabeculae-Vessel Function Unit in Response to Estrogen Deficiency-Induced Bone Loss and Intermittent Parathyroid Hormone-Induced Bone Gain

Wei-Ju Tseng, MSE
Tiao Lin, MD
Chantal MJ de Bakker
L. Scott Levin, MD, FACS
Ling Qin, PhD
X. Sherry Liu, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

The bone remodeling process is required to repair damaged bone tissue and more importantly, to regulate calcium and phosphate homeostasis in conjunction with the microvascular network within bone marrow. However, simultaneous visualization of the trabecular and vascular microstructures remains challenging, and thus the precise relationship between blood vessel formation and trabecular remodeling, as well as the impact of this relationship on metabolic bone diseases such as osteoporosis, remains unclear. In our recent study, we observed a trend of positive correlation between blood vessel number and trabecular number in rats. Therefore, we hypothesized that the volume and number of blood vessels are associated with those of trabeculae. We used a well-described bone loss model by inducing estrogen deficiency in ovariectomized (OVX) rats[1] and a bone gain model by administering intermittent parathyroid hormone (PTH) in intact rats.[2] Together with vehicle-treated intact rats, we aimed to generate samples with a wide spectrum of trabecular bone and vessel densities. Critical to the advancement of bone vasculature research is the development of a 3-dimensional (3D) simultaneous visualization of the trabecular and vascular microstructures. In this study, we developed a novel vascular network perfusion technique combining standard μCT and image processing techniques to simultaneously visualize and quantify the 3D trabecular and vascular microstructures in the rat tibia. The objective of this study was to investigate the changes in the trabeculae-vessel function unit in response to estrogen deficiency-induced bone loss and intermittent PTH-induced bone gain models.

Methods

Study Design

Six intact and three ovariectomized female Sprague-Dawley rats (90 days old) were purchased and housed at the animal facility for 60 days prior to the experiment (IACUC approved). The six intact rats were divided into saline-treated (VEH) and PTH-treated groups at 150 days old. Both VEH (saline) and PTH (PTH 1-34, 60μg/kg/day, Bachem) groups received subcutaneous injections 5 days/week for 2 weeks.

In Vivo μCT Scans

At the end of treatment, the left tibiae from rats in all three groups were scanned using the vivaCT 40 scanner (Scanco Medical AG) while the rats were under anesthesia. A 10-mm region located distal to the proximal growth plate was scanned for each tibia at 10.5μm resolution.

Perfusion

Following *in vivo* scans, a catheter was inserted into the abdominal aorta, and an incision was made in the right atrium. A three-step perfusion protocol was used. Using a perfusion pump, 50 mL of heparin sodium (30 units/mL) followed by 100 mL of 0.9% saline were infused at 4.4 mL/min through the rat. Next, using a syringe pump, 4.5 mL of freshly mixed Microfil (MV122, Flow Tech) was injected 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 perfusion mixture was prepared by diluting a silicone rubber injection compound 4:1 with medium-viscosity diluent and mixing the result with 4.5% curing agent. The perfused animals were stored at 4 °C for 24 hours. Tibiae were harvested and fixed in 4% formalin.

Post-Perfusion Scans

A 10mm-thick region located distal to the proximal growth plate was scanned at a 6μm resolution using the μCT 35 scanner (Scanco Medical AG).

Image Registration

A registration procedure at 10.5 μm resolution was employed using a landmark-initialized, mutual-information-based registration kit (ITK,

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NLM). Post-perfusion scans (containing both bone and blood vessel) were registered to pre-perfusion scans (containing bone only), which allowed the same region of interest to be analyzed in both scans. A custom program was used to separate the vessels from the registered scans. Trabecular and vasculature structures were quantified in a 6 mm region distal to the growth plate. Trabecular and vessel volume fraction (Tb.BV/TV and Ves.V/TV), trabecular and vessel number (Tb.N and Ves.N), trabecular and vessel thickness (Tb.Th and Ves.Th), and trabecular and vessel spacing (Tb.Sp and Ves.Sp) of each group were measured.

Statistics

Comparisons between VEH and PTH groups and between VEH and OVX groups were made using 2-tailed student's *t*-tests with $p<0.05$ indicating significance and $p<0.1$ indicating trends.

Results

OVX vs. VEH

As expected, trabecular bone in the OVX group had 69% lower Tb.BV/TV ($p<0.05$), 75% lower Tb.N ($p<0.05$), 400% higher Tb.Sp ($p<0.05$), and trends toward a lower Tb.Th (11%, $p<0.1$) compared to that of the VEH group (Figure 1). Vessels in the OVX group were 82% thicker than those in the VEH group ($p<0.05$, Figure 2). There was no measurable difference in Ves.BV/TV, Ves.N or Ves.Sp between the VEH and OVX groups.

PTH vs. VEH

There was no significant difference in Tb.BV/TV, Tb.N or Tb.Sp between PTH and VEH groups, with a trend of increase in Tb.Th in the PTH group (8%, $p<0.1$, Figure 1F). 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% in Tb.Th ($p<0.05$) due to a 2-week PTH treatment. Moreover, compared to the VEH group, the PTH group had trends toward higher Ves.V/TV (53%, $p<0.1$, Figure 2D), Ves.N (38%, $p<0.1$, Figure 2E), and 34% lower Ves.Sp ($p<0.1$, Figure 2G). There was no significant difference in 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 PTH-treated rats (Figures 1 and 2). Following an 8-week development of osteoporosis, OVX rats showed systemic deteriorations in trabecular bone microstructure and a significant increase in vessel thickness compared to the VEH rats. This result did not support our hypothesis, suggesting that estrogen-induced

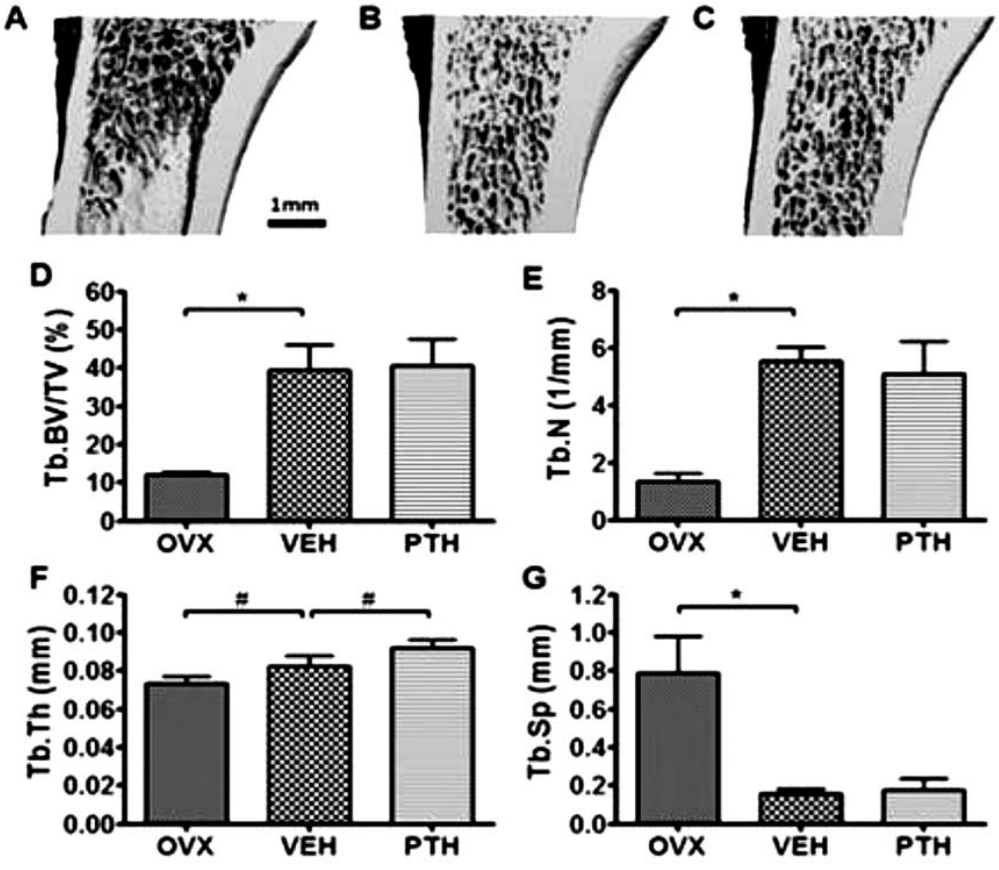

Figure 1. 3D representative bone images of (A) OVX, (B) VEH, (C) PTH groups; 3D microstructure analysis of trabecular bone: (D) Trabecular Volume Fraction (E) Trabecular Number, (F) Trabecular Thickness, (G) Trabecular Spacing, Mean ± SD, *: $p<0.05$, #: $p\leq0.01$.

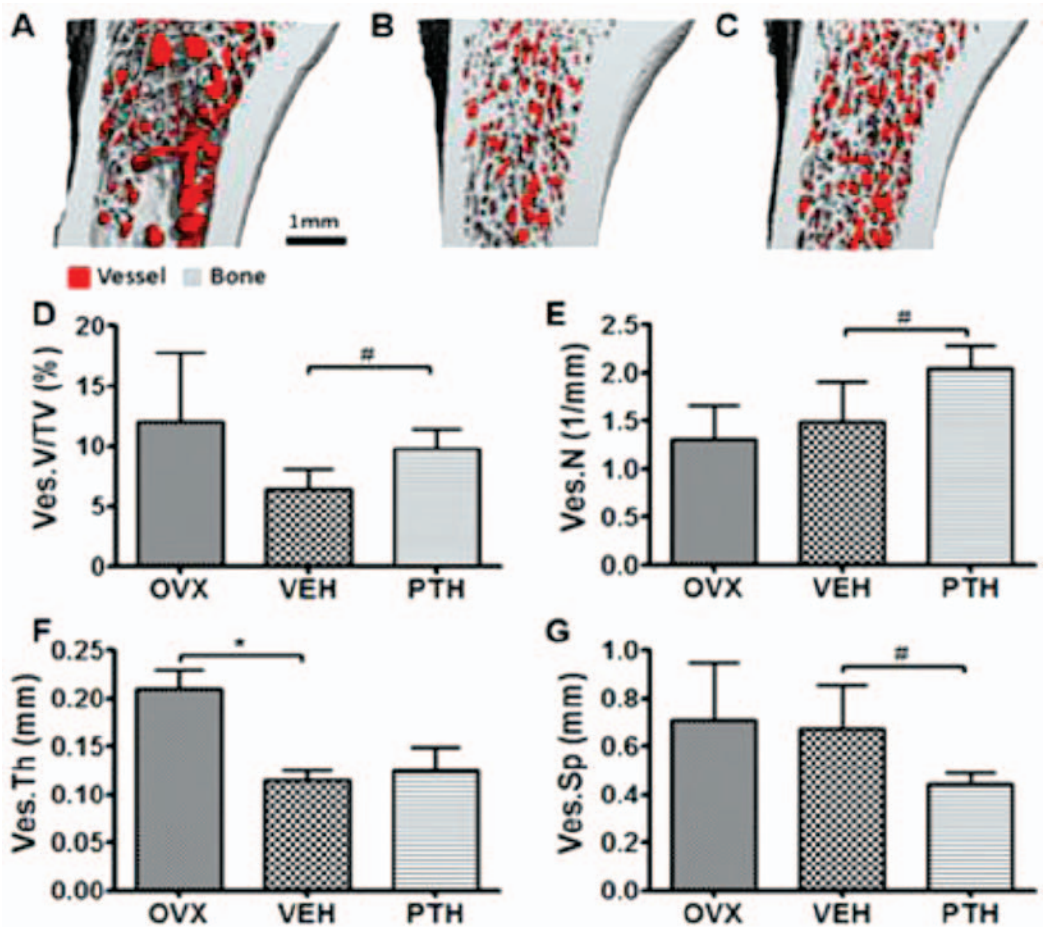

Figure 2. 3D representative bone and vessel images of (A) OVX, (B) VEH, (C) PTH groups; 3D microstructure analysis of vasculature: (D) Vessel Volume Fraction, (E) Vessel Number, (F) Vessel Thickness, (G) Vessel Spacing, Mean ± SD, *: $p<0.05$, #: $p\leq0.01$.

bone loss is not necessarily associated with reduced blood vessels. Compared to VEH-treated rats, PTH-treated rats tended to have greater vessel volume and number and reduced vessel spacing, which is consistent with Kang *et al's* recent report in a murine mandubular model of distraction osteogenesis and angiogenesis following 21 days intermittent PTH treatment.[3] On the other hand, our results were inconsistent with Prisby *et al's* report,[4] which did not find improved angiogenesis after PTH treatment. However, the discrepancy may be due to use of different PTH analogues (1-34 versus 1-84) and rat sex (female versus male). Both PTH treatment and OVX result in accelerated bone remodeling, but with opposite net balance towards formation and resorption, respectively. Interestingly, our results showed increases or trends toward increase in blood vessels in both PTH and OVX rats, suggesting a possible association between angiogensis and bone remodeling rate. 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 in both an OVX rat model and an intermittent PTH-treated rat model, resulting in an improved understanding of the effects of OVX and intermittent PTH on the bone-blood vessel function unit.

Acknowledgments

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Alendronate and PTH Combination Therapy Stimulates Bone Formation While Inhibiting Bone Resorption Activities in the Rat Tibia: A Longitudinal, In Vivo, Dynamic Bone Histomorphometry Study

Chantal M. de Bakker
Allison Altman, PhD
Connie Li
Wei-Ju Tseng
Mary Beth Tribble
Beom Kang Huh
Abhishek Chandra, PhD
Ling Qin, PhD
X. Sherry Liu, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Osteoporotic bone loss is characterized by a shift in bone remodeling such that resorption outpaces formation. Treatments improve bone mass by increasing net formation: anti-resorptive drugs such as alendronate (ALN) block osteoclast activity, while anabolic agents such as PTH increase bone remodeling, with a greater effect on formation. Although these drugs are widely used, their role in modulating formation and resorption is not fully understood, due in part to technical limitations in the ability to longitudinally assess bone remodeling. Importantly, it is not known whether or not PTH-induced bone formation is independent of resorption, resulting in controversy over the effectiveness of combination therapies that use both PTH and ALN.[1,2] Although formation can be assessed using dynamic histology, this technique is destructive, imprecise, and cannot assess bone resorption. Methods for improved quantification of bone formation and resorption have been developed,[3,4] but are limited by their destructive nature or low temporal resolution, making it difficult to monitor drug effects over clinically relevant treatment times. We developed an *in vivo* dynamic bone histomorphometry technique for rat tibiae, and applied this method to longitudinally track changes in bone resorption and formation as a result of treatment with ALN, PTH, or combination therapy. We hypothesized that adding ALN to PTH treatment would inhibit bone resorption activities while maintaining the elevated bone formation activities induced by PTH treatment, thus resulting in an additive, beneficial effect on trabecular bone.

Methods

Animal Protocol

3 month-old, female, Sprague Dawley rats were assigned to Veh (n=5), PTH (n=8), ALN (n=6), and PTH+ALN (n=7) treatment groups (IACUC approved). Starting on day 0, rats were treated with daily 60 μg/kg PTH (PTH and PTH+ALN), 50 μg/kg alendronate every three days (ALN and PTH+ALN), or daily saline (Veh) through subcutaneous injections over 12 days. Calcein was injected on days 3 and 11 to allow for dynamic histomorphometry. The right proximal tibia of each rat was scanned by μCT at 10.5μm resolution on days -8, 0, and 12 (vivaCT 40, Scanco Medical, Brüttisellen, Switzerland). Rats treated with PTH and PTH+ALN had an additional scan at day 4, as our previous study suggested that PTH can prevent radiation damage.[5] All rats were sacrificed on day 12, and serum and tibiae were harvested from a subset of rats to measure standard histological parameters of bone formation, measure osteoblast and osteoclast surface (Ob.S/BS and Oc.S/BS), and assess serum resorption marker TRAP.

Image Processing

μCT images from day -8 to 0 and day 0 to 12 (day 4 to 12 in PTH and PTH+ALN groups) were registered using mutual-information-based, 3D image registration software (ITK, NLM) to precisely align the trabeculae in the secondary spongiosa. Following registration, images were Gaussian filtered, thresholded, and subtracted to obtain a map of the locations of bone formation and resorption. Formation and resorption parameters analogous to histology-based measurements were calculated as follows: bone formation rate (BFR/BS) = volume of bone formed/(# of days*bone surface), bone resorption rate (BRR/BS) = volume of bone resorbed/(# of days*bone surface), mineral apposition rate (MAR) = thickness of formed bone/# of days, and mineral erosion rate (MER) = thickness of resorbed bone/# of days.

Statistics

Correlations between μCT- and histology-based measures of BFR/BS and MAR and between μCT-based BRR/BS and serum levels of TRAP were assessed using linear regression. Comparisons among treatment groups and over time were made using a two-way ANOVA with Bonferroni correction (NCSS, LCC, Kaysville UT).

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xiaoweil@mail.med.upenn.edu

Results

The locations of bone formation identified through μCT yielded excellent agreement with calcein-labeled regions identified through histology, and μCT-based measures of BFR/BS ($r=0.78$), MAR ($r=0.60$), and BRR/BS ($r=0.91$) correlated strongly with histology-based measures of bone formation and serum levels of TRAP (Figure 1). The longitudinal design of this study allowed us to assess drug effects within each rat over time as well as compare bone formation/resorption parameters among treatment groups. Over the treatment period, changes in bone volume fraction (BV/TV) indicated an additive effect of combination therapy over treatment with PTH or ALN alone (Figure 2). Measurements derived through *in vivo* dynamic bone histomorphometry demonstrated an increase of 220% in BFR/BS and 30% in MAR over time in specimens treated with PTH and an increase of 378% in BFR/BS and 37% in MAR in rats treated with PTH+ALN ($p<0.05$, Figure 2). In specimens treated with PTH, MER increased 27% ($p<0.05$), while specimens treated with ALN and PTH+ALN showed 37% decreased MER ($p<0.05$) and 65% decreased BRR/BS ($p<0.05$), respectively (Figure 2). At the end of the treatment period, both CT-based BFR/BS and histology-based osteoblast surface were elevated in rats treated with PTH and PTH+ALN as compared to those treated with Veh and ALN (Figure 3, $p<0.05$). CT-based BRR/BS indicated that resorption was lower in rats treated with PTH+ALN ($p<0.05$), and tended to be lower in rats treated with ALN ($p<0.1$) than in PTH-treated rats, while histology-based osteoclast surface showed no difference among groups.

Discussion

In this study we developed an *in vivo* dynamic bone histomorphometry technique to monitor changes in bone remodeling activities in response to anti-resorptive and anabolic treatment. The strong correlations between μCT-based and traditional measures of bone remodeling, and the qualitative agreement between μCT- and histology-based localization of bone formation sites, indicate that the *in vivo* dynamic bone histomorphometry technique developed in this study allows for accurate assessment of bone formation and resorption. Application of this method resulted in a non-invasive, 3D evaluation of the bone formation and resorption events taking place as a result of treatment with PTH, ALN, or combined PTH+ALN. Additionally, the longitudinal nature of this technique allows for pre-treatment measurements, so that each rat can serve as its own control. Compared to pre-treatment, rats had decreased bone resorption rate and increased bone formation and mineral apposition rates during the period of treatment with PTH+ALN, which partially explains the additive effect of combined therapy with

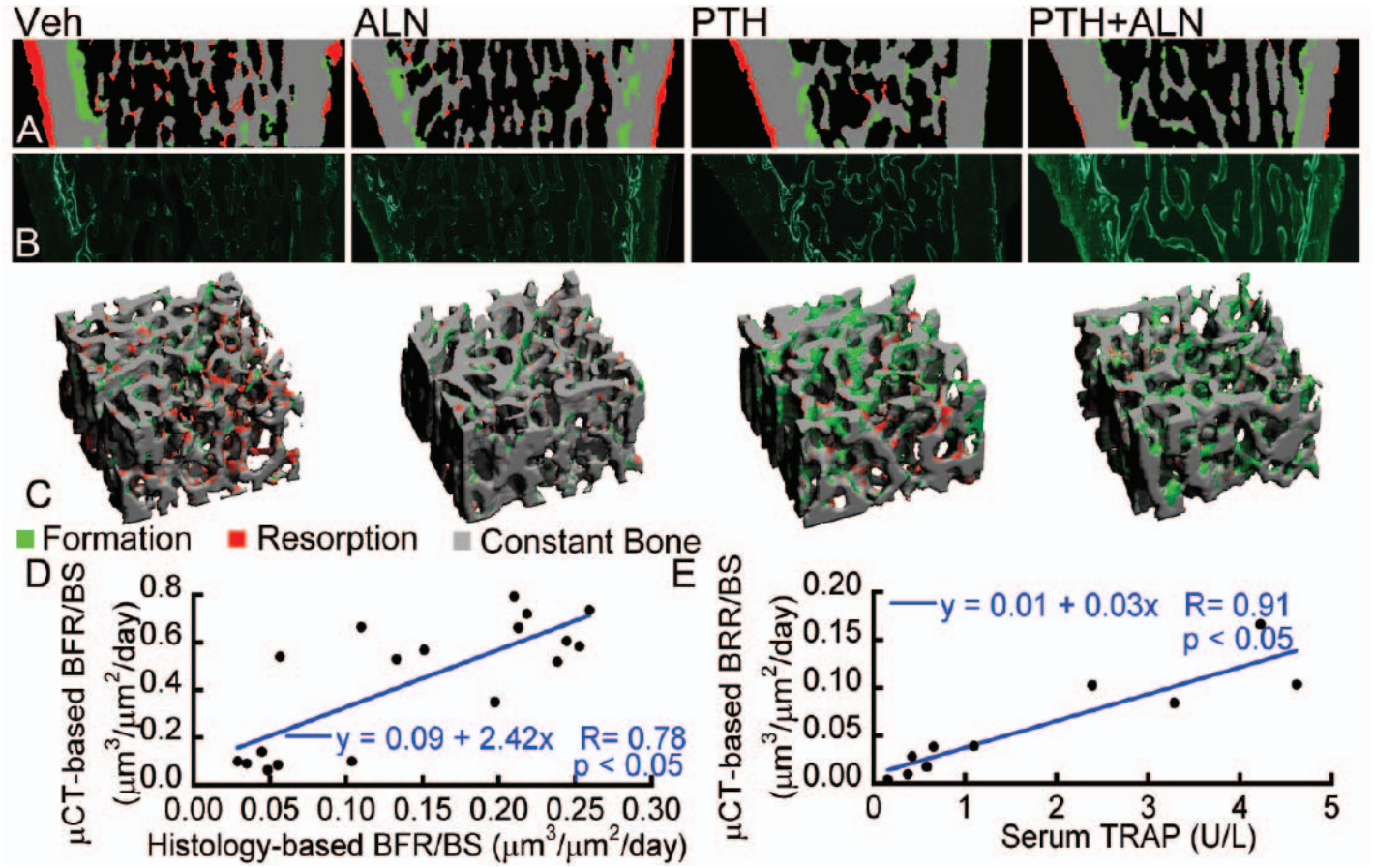

Figure 1. Validation of μCT method: Paired comparisons were made of (A) *in vivo*, μCT-based bone formation/resorption map to (B) calcein-labeled histology section for a representative Veh, ALN, PTH and PTH+ALN tibia. (C) A 3D rendering of bone resorption and formation within the analyzed trabecular region is also shown. Significant correlations were found (D) between μCT- and histology based measure of BFR/BS and (E) between μCT-based BRR/BS and serum TRAP.

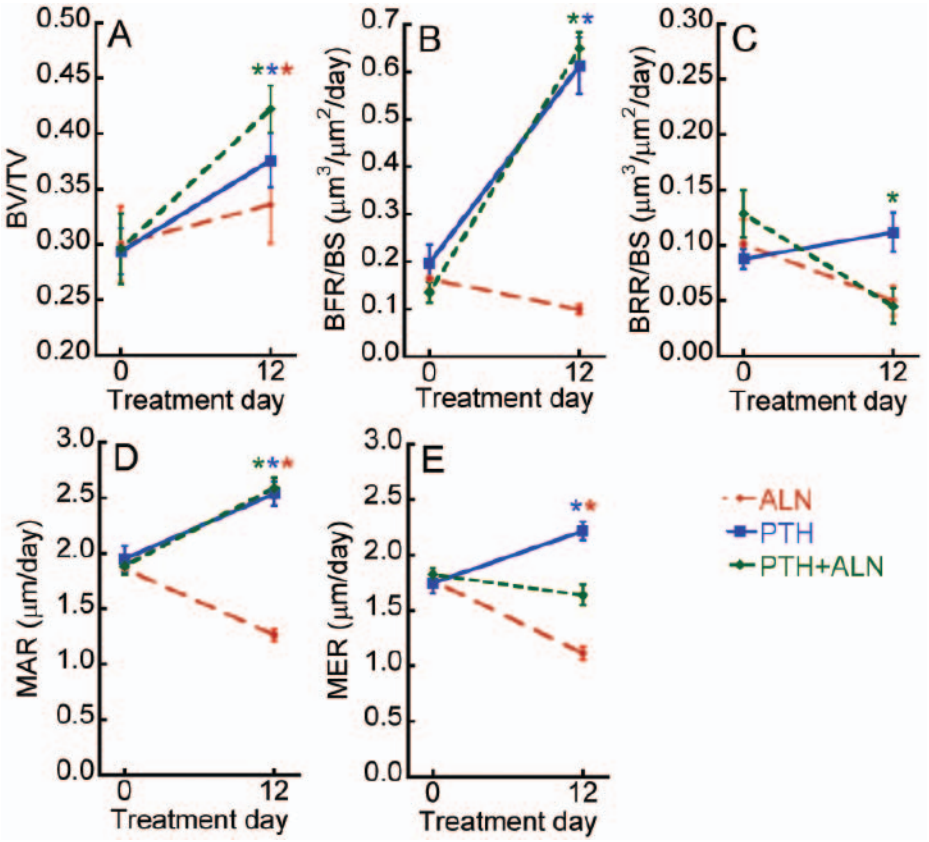

Figure 2. Effects of ALN, PTH, and PTH+ALN treatment on (A) BV/TV, (B) BFR/BS, (C) BRR/BS, (D) MAR, and E MER. *:significant differences from day 0 ($p<0.05$).

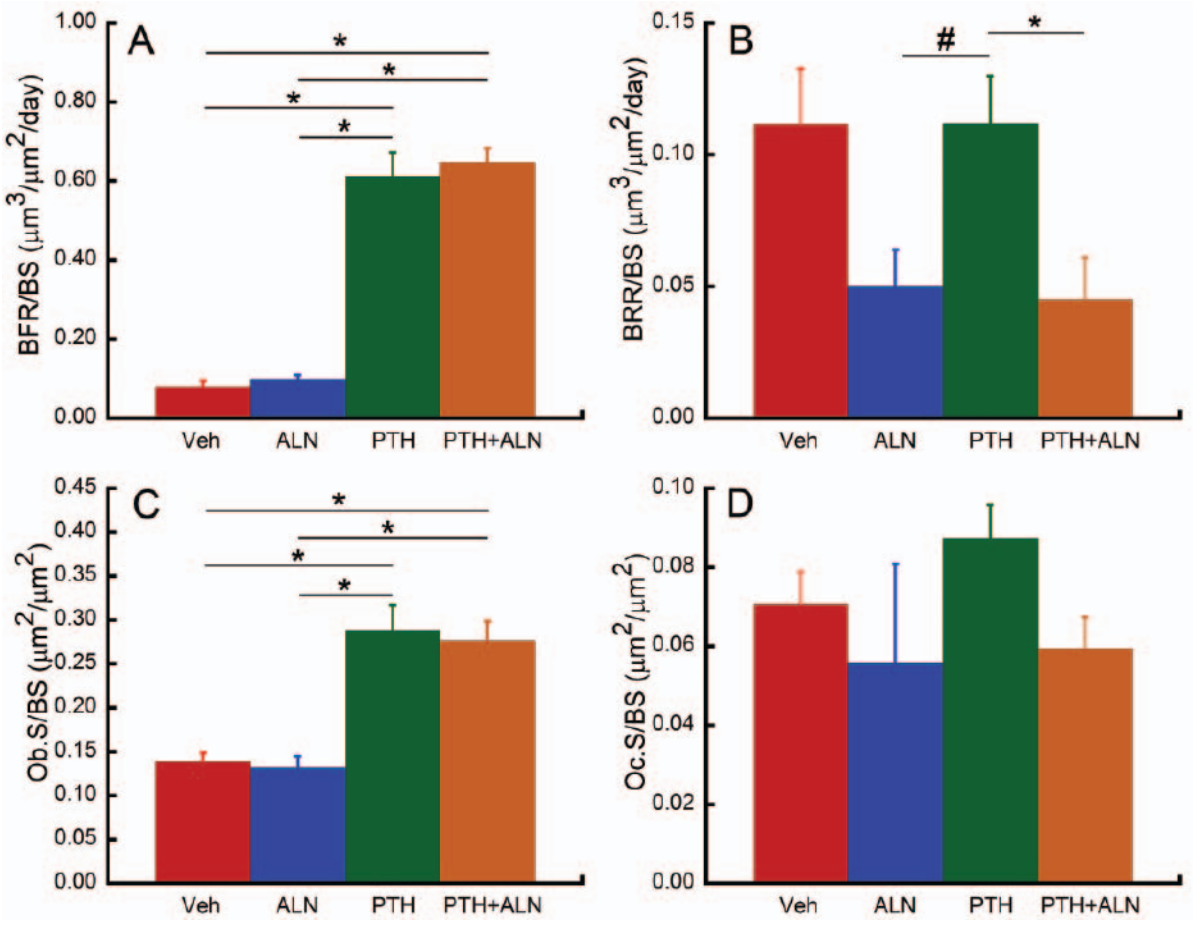

Figure 3. Cross-sectional comparison of CT-based (A) BFR/BS and (B) BRR/BS and histology-based (C) Ob.S/BS and (D) Oc.S/BS among the four groups after 12 days of treatment *: $p<0.05$, #: $p<0.1$.

PTH+ALN over monotherapy. This provides *in vivo*, direct evidence, suggesting that PTH's anabolic effect on stimulating bone formation is independent of resorption. In clinical applications, this suggests that co-treatment of PTH with an anti-resorptive is beneficial as the anti-resorptive may enhance the anabolic effect of PTH.

Significance

Non-invasive, longitudinal assessment of bone formation and resorption would allow for precise measurements of changes in bone remodeling, resulting in an improved understanding of the mechanisms of bone disorders and drug treatments. Application of this technique elucidated the effects of combination therapy of PTH and an anti-resorptive, suggesting that the anabolic effect of PTH is independent of resorption and thus combination therapy may provide greater improvements in bone quality over monotherapy.

Acknowledgments

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Alleviation of Radiotherapy-Induced Local Trabecular Bone Loss by PTH(1-34) is Associated with Improved DNA Repair and Cell Survival in Osteoblasts

[1]Abhishek Chandra, PhD
[1]Tiao Lin
[1]Ji Zhu
[1]Beom Kang Huh
[2]Allison Altman, PhD
[1]Sarah Hagan
[1]Keith Cengel
[1]X. Sherry Liu, PhD
[1]Ling Qin

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]McKay Orthopedic Research Laboratory, Philadelphia, PA, USA

Introduction

Radiotherapy is a common therapeutic for cancers, but it has inevitable adverse effects on bones within irradiated region and causes problems, such as osteoporosis, osteoradionecrosis, and fractures. To date, there is no preventive or curative treatment for radiation-induced bone damage. We have previously reported that parathyroid hormone (PTH, 1-34), an anabolic treatment for osteoporosis, prevents the adverse effects of radiation generated from multiple longitudinal micro-computed tomography (μCT) scans on the trabecular bone architecture in young rats.[1] However, μCT scan does not mimic clinical radiator due to its low and fixed dosage. Furthermore, the mechanism by which PTH reverses radiation-induced bone loss has not been elucidated. In this study, we investigated the effectiveness of PTH in a clinically relevant radiation model using skeletally mature rats. The mechanisms of PTH's rescue effects on bone loss were studied at structural, cellular, and molecular levels.

Methods

Animal protocols- 3-month-old female Sprague Dawley rats (n=5/group) were radiated by SARRP at their right tibial metaphyseal region at a dose of 8 Gy twice (day 1 and 3). This radiation protocol mimics the dose to the hip during hypofractionated radiotherapy for prostate cancer. The contralateral non-radiated tibiae served as paired controls. Rats were then separated into two groups receiving either vehicle or rhPTH(1-34, 60 μg/kg/day) treatment for 4 weeks. In vivo μCT and analysis- To avoid the bone growth issues in rats,we developed a unique 3D μCT registration method to identify the same trabecular structure at day 28 that matches the metaphyseal area at 2.5-4 mm below the growth plate at day 0 in the same tibia. The structural parameters and mechanical competence of the same block of trabecular bone before and after radiation were then calculated based on standard image analysis and finite element analysis (FEA). Histology- Tibiae were harvested at 4 weeks for measuring osteoblast numbers using H&E staining or at 2 weeks for paraffin sections with TUNEL assay for detecting apoptotic osteoblasts. Apoptosis assay of UMR-106 cells after radiation and PTH treatment- UMR cells were radiated at 8 Gy followed by 10 nM PTH treatment in presence or absence of a PKA inhibitor (H89)or WNT-inhibitor (IWR. Ethidium Bromide (EB)/Acridine Orange (AO) staining was performed 2 days later to count apoptotic cells cells. Single cell gel electrophoresis- Comet assay was performed under alkaline conditions to measure the extent of DNA damage at a single cell level. Immunocytochemistry- Cells were immunostaining with antibodies against γ-H2AX, caspase 3, or β-catenin to detect their cellular localization.

Results

3D registration of the same trabecular bone before and after radiation demonstrated that trabecular bone volume fraction (BV/TV) in non-radiated tibiae of vehicle-treated rats at day 28 increased significantly (69%) with increased trabecular thickness (Tb.Th, 36%) and unchanged trabecular number (Tb.N) compared to its own at day 0. However, BV/TV in radiated tibiae of vehicle-treated rats only increased slightly (36%) compared to its own at day 0 but it was 19% significantly less than that in non-radiated contralateral tibiae at day 28 (Figure 1A). This was mainly due to an 18% decrease in Tb.N and a 26% decrease in connective density (Conn.D). Carefully examining the reconstructed 3D μCT images reveals that, while almost all trabecular elements were preserved in non-radiated samples during 4 weeks of growth, some small trabecular elements were apparently lost after radiation (red circles in Figure 1B), implicating that radiation shifts the balance of bone remodeling toward more resorption. FEA revealed a 57% decrease in trabecular bone stiffness in radiated bones compared to non-radiated controls (Figure 1C), suggesting that the mechanical strength is severely impaired after radiation. Interestingly, PTH(1-34) treatment had a great anabolic effect on trabecular bone and remarkably stimulated bone mass in both non-radiated and radiated tibiae to a similar level (Figure 1A).A close look at the 3D registered μCT images uncovered that PTH not only thickened the trabecular elements but also preserved them

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from radiation-induced loss (Fig. 1B).Trabecular bone strength was also maintained in radiated bones by PTH treatment (Figure 1C).

Further histological analysis indicated that radiation caused apoptosis in osteoblasts, leading to few viable and functional osteoblasts (30% of non-radiated control) on the trabecular bone surface (Figure 2A-C), while PTH injections increased their number and protected them from cell death (Figure 2C).To confirm and expand these in vivo findings, we radiated osteoblast-like UMR106-01 cells followed by vehicle or PTH (1-34) treatment. Radiation greatly stimulated the percentage of apoptotic cells from 1.0% to 12.6% and 10 nM PTH diminished this increase to 2.6% (Figure 2D). Inhibitor assays revealed that the survival action of PTH is mediated by PKA and β-catenin. Indeed, PTH enhanced β-catenin amount and its nuclear translocation in osteoblasts after radiation via PKA pathway (Figure 2E and data not shown). Radiation induces highly lethal DNA damage, among which double-strand breaks (DSBs) is the major factor responsible for cell death. A sensitive method to detect DSBs is the immunofluorescence staining of γ-H2AX. We found that PTH reduced the radiation-induced γ-H2AX foci number as early as 2 h (Figure 3A). Comet assay further confirms that PTH treatment blocks radiation-induced DNA damage (represented by comet tails) in a PKA- and β-catenin-dependent manner (Figure 3B). The occurrence of DSBs invokes the repair pathway. Interestingly, we found that 30 min of PTH treatment significantly increased the amount of Ku70, a critical component of repair complex, regardless of radiation (Figure 3C). If DNA lesions induced by radiation cannot be resolved in a timely fashion, cells will begin the process of programmed cell death. Western blot showed that radiation reciprocally regulated anti-apoptotic Mcl1 and pro-apoptotic Bim for cell death and that PTH had opposite effects (Figure 3D). At last, radiation activated the downstream protein of apoptotic pathway, caspase 3 while PTH suppressed it (data not shown).

Discussion

Our ability to accurately trace the same bone before and after radiation provides strong and direct evidence that PTH treatment is able to alleviate radiotherapy-induced local loss

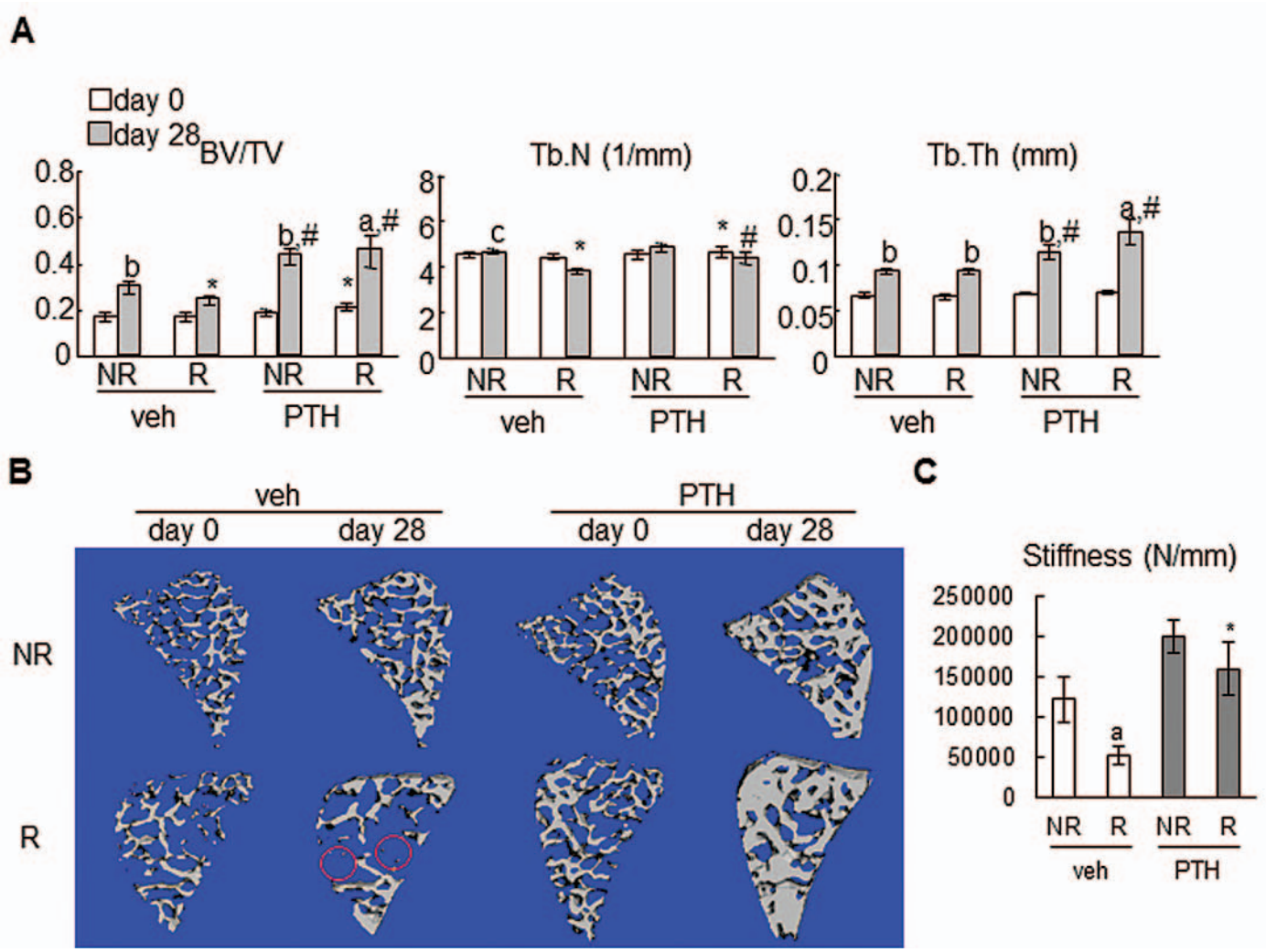

Figure 1. (A) PTH reverses SARRP radiation-induced bone loss and damage. (B) μCT images of the rat proximal metaphyseal region of radiated (R) and non-radiated (NR) tibiae of vehicle or PTH treated animals. (C) Measure of bone strength by finite element analysis. a<0.05; b: p<0.01; c: p<0.001, d 28 vs. d 0. *: p<0.05, R vs. NR. #: p<0.05, PTH vs. veh.

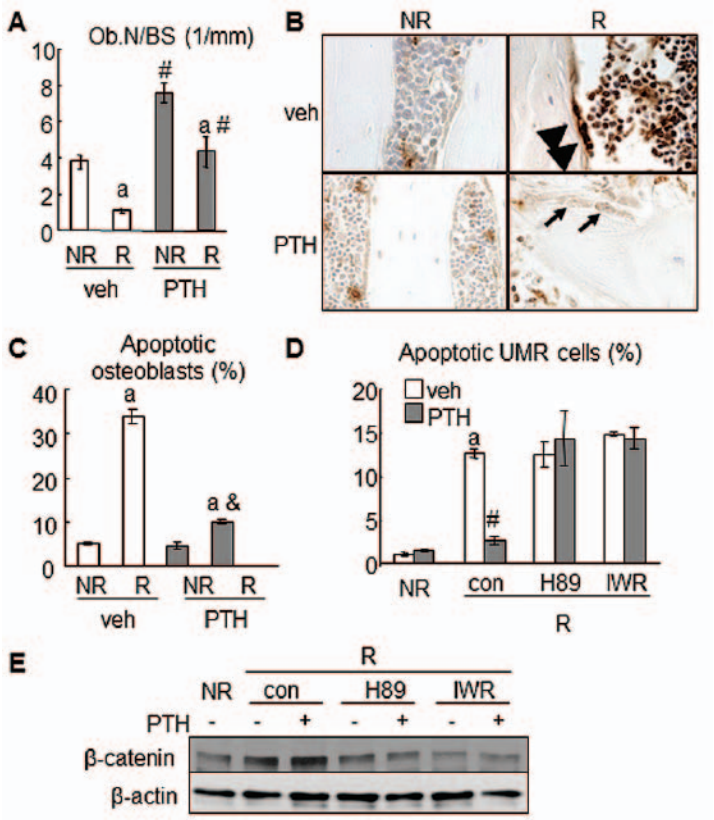

Figure 2. PTH alleviates radiation-induced apoptosis in osteoblasts. (A) Bone histomorphometry to measure osteoblast number and (B,C) TUNEL staining (arrowheads indicate apoptotic cells and arrows indicate healthy osteoblasts of tibiae sections and its quantification (D) Apoptotic assay in UMR cells after radiation and PTH treatment (E) β-catenin immunoblots after radiation and PTH treatment. a: $p<0.01$, R vs. NR, #: $p<0.01$, PTH vs. veh.

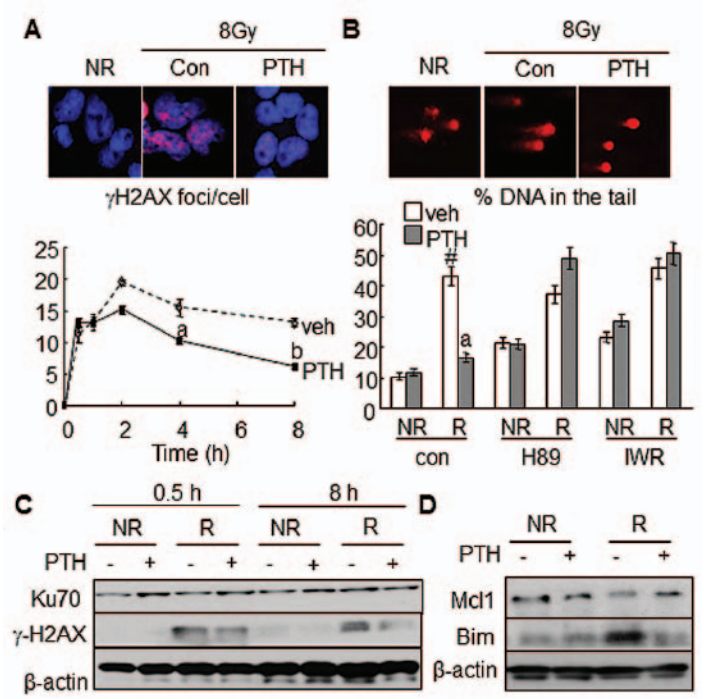

Figure 3. PTH promotes DNA repair and subsequently survival in osteoblasts (A) immunofluorescence assay detecting γ-H2AX post-radiation and PTH treatment. (B) Comet assay to determine DNA damage. (C) Immunoblot for Ku70 and γ-H2AX(D) Immunoblot of Mcl1 and Bim. a: $p<0.01$; b: $p<0.001$, PTH vs veh, #: $p<0.01$, R vs NR.

of trabecular elements and deterioration in bone strength. Using in vivo and in vitro approaches, we report that PTH achieves its therapeutic effect by accelerating DNA repair and stimulating anti-apoptotic signals via a PKA/β-catenin pathway in mature osteoblasts, which leads to their preservation against radiation-induced cell death.

Significance

The improved survivorship rate and the increased age of cancer patients receiving radiotherapy emphasize the importance of understanding the mechanism of radiation-induced osteoporosis and identifying a treatment for this disease. Our studies showing that PTH(1-34) can effectively prevent radiation-induced bone damage in rats is a major and unique step ahead, promising to pave the way toward effective treatments to reduce radiation damage on bone and thereby maximize the therapeutic index for radiotherapy.

Acknowledgments

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Comparison Between Ovariectomy and Lactation Induced Bone Loss: A Dynamic Imaging Study

Connie Li
Carina Lott
Allison R. Altman, PhD
Chantal M. de Bakker
X. Sherry Liu, PhD

University of Pennsylvania, Philadelphia, PA, USA

Introduction

Lactation and postmenopausal osteoporosis are two hypoestrogenic physiological states that induce substantial changes in the bone mass and microarchitecture of women. During lactation, the body draws on calcium stores in the skeleton for milk production, resulting in substantial bone loss. In postmenopausal osteoporosis, ovarian hormone deficiency is responsible for bone loss.[1,2] What is remarkable about lactation-induced bone loss is that bone mineral density and structure are rapidly restored after weaning when estrogen levels return to normal.[1] In contrast, estrogen replacement post menopause can no longer reconstitute the deteriorated skeleton[3] in the manner that occurs in lactating women after weaning. Therefore, reversible changes in bone during lactation and weaning may provide important insight into pathogenesis and treatment of estrogen-deficiency induced bone diseases. A past study comparing lactating and ovariectomized (OVX) rats found that the resulting loss of bone in both groups followed similar patterns; however, lactation had a greater effect on trabecular bone loss than ovariectomy.[4] The purpose of this study was to explore the differences in structural mechanisms of bone loss and bone remodeling activities during lactation and postmenopausal osteoporosis in a rat model using high resolution *in vivo* micro computed tomography (μCT). We hypothesized that both types of bone loss would be caused by increased resorption, leading to rapid structural deterioration.

Methods

Eleven 4-month-old female Sprague Dawley rats were divided into two groups: OVX (n=5) and lactating rats (LAC, n=6). The LAC group underwent mating, pregnancy, delivery, and lactation, with litter size normalized to nine pups per dam. OVX rats were ovariectomized to simulate post-menopausal osteoporosis. A region 4.3 mm distal to the proximal tibia of each rat was scanned using an *in vivo* μCT system (VivaCT 40; SCANCO Medical AG) at an isotropic voxel size of 10.5 μm. LAC rats were scanned at days 0, 7, 14, and 21 after beginning lactation and OVX rats were scanned at days 0, 7, 14, and 28 after surgery. To track longitudinal changes, sequential *in vivo* μCT images were registered via landmark-initialized, mutual-information-based registration.[5] Trabecular bone volume fraction (BV/TV), number (Tb.N), thickness (Tb.Th), spacing (Tb.Sp), structure model index (SMI), connectivity density (Conn.D), and degree of anisotropy (DA) were calculated using Scanco software. A 1.58x1.58x1.05 mm^3 sub-volume corresponding to 150x150x100 voxels was selected from the primary spongiosa region of each μCT scan at days 0 and 7 for further analyses. Each pair of sub-volumes for days 0 and 7 further underwent a multi-step, precise registration procedure.[6] The aligned sub-volumes were then binarized and subjected to 3D *in vivo* dynamic bone histomorphometry to calculate bone formation rate (BFR/BS), bone resorption rate (BRR/BS), mineral apposition rate (MAR), and mineral erosion rate (MER).[6] Furthermore, the precisely registered sub-volumes were also subjected to an Individual Trabecular Dynamics (ITD) analysis to quantify incident rates of trabecular rod disconnection and plate perforation. Two-way repeated measures ANOVA tests were performed to compare the relative changes in 3D microstructure and ITD between LAC and OVX rats using baseline measures as covariates. Student's t-tests were used to compare bone histomorphometry and ITD measurements between LAC and OVX rats. For all tests, $p<0.05$ was considered a significant difference.

Results

3D microstructural analysis indicated significant trabecular deterioration in both OVX and LAC groups, in which OVX rats displayed a greater degree of bone loss (Figure 1). OVX rats experienced decreases in BV/TV, Tb.N, Tb.Th, Conn.D, and DA and increases in Tb.Sp and SMI over time (Figure 1 and Table 1). LAC rats experienced decreases in BV/TV, Tb.N, and Tb.Th, increases in Tb.Sp and SMI, with no significant changes in Conn.D and DA (Table 1). Comparisons of microstructural parameters between OVX and LAC groups indicated that OVX rats presented a 10% greater loss in BV/

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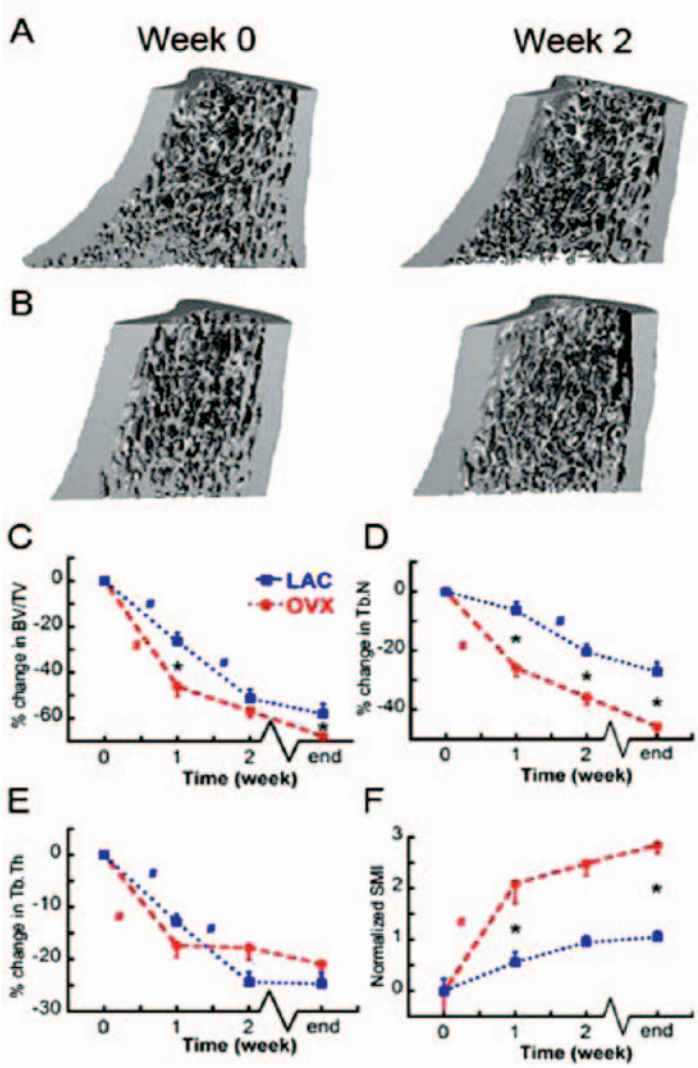

Figure 1. (A) Registered μCT images of the proximal tibia of an OVX rat on days 0 and 14. (B) Registered μCT images of the proximal tibia of a LAC rat on days 0 and 14. (C) % change of BV/TV (D) % change of Tb.N (E) % change of Tb.Th (F) Normalized SMI over time. # indicates differences between time point and * indicates differences between groups.

TV ($p=0.004$), 19% greater loss in Tb.N ($p<0.001$), 54% greater increase in Tb.Sp ($p<0.001$), and a greater increase in SMI by 1.8. There were no significant differences in Tb.Th, Conn.D, and DA between groups. ITD analysis suggests that rod disconnection was primarily responsible for changes in bone microarchitecture in both groups. From days 0 – 7, 9.0% and 10.5% of trabeculae underwent rod disconnection in the OVX and LAC groups, respectively, and 1.5% and 1.1% underwent plate perforation, respectively. There was no significant difference in any ITD parameters between the two groups. From 3D *in vivo* dynamic bone histomorphometry, we found that OVX rats experienced a greater degree of bone resorption from days 0 – 7 than did LAC rats (Figure 2). Specifically, the BRR/BS in OVX rats was 45% greater than in LAC rats ($p=0.02$) and the MER in OVX rats was 26% greater than in LAC rats ($p<0.001$). There were no differences in BFR/BS and MAR between the two groups.

Discussion

Both OVX and LAC rats displayed similar overall patterns of bone loss that were most pronounced in the OVX group. OVX surgery leads to significantly fewer, thinner, more spread out and rod-like trabecular bone network, with less connections and lower anisotropy. Changes in post-lactation bone share many similar structural mechanisms that lead to rapid bone volume loss, except for non-detectable changes in Conn.D and DA. At the end of the study, the loss of volume and number of trabeculae and the increase in trabecular spacing occurs to a greater extent in the OVX group. Furthermore, ITD analysis suggests that rod disconnections and plate perforations are critical mechanisms causing reduced integrity of the trabecular network, to a similar degree in both OVX and LAC rats. Interestingly, *in vivo* dynamic bone histomorphometry indicates a significantly greater bone resorption in OVX rats than in LAC rats. Although there was no statistical difference in bone formation rate between two groups, which may be due to highly variable data in the OVX group, the mean value of BFR/BS of OVX group is double that of the LAC group. These results suggest that there was a higher bone turnover rate

Table 1. Standard microstructural variables of interest represented as mean ± SEM. * indicates significant differences from baseline to end for % change, while a significant p-value indicates differences between groups ($p<0.05$).

	OVX			LAC			p-value
	baseline	end	%change	baseline	end	%change	
BV/TV	0.45±0.06	0.15±0.03	−68±4*	0.30±0.13	0.13±0.06	−58±−26*	0.004
Conn.D	202±24	44±8	−76±6*	114±50.8	49±22	−58±−26	0.97
SMI	−0.23±0.73	2.62±0.17	N/A	1.52±0.68	2.58±1.15	N/A	0.08
Tb.N*	6.56±0.22	3.56±0.26	−46±3*	5.18±2.32	3.77±1.69	−27±-12*	<0.001
Tb.Th*	0.092±0.009	0.072±0.005	−21±3*	0.082±0.037	0.061±0.027	−25±11*	0.11
Tp.Sp*	0.133±0.011	0.274±0.027	106±12*	0.167±0.074	0.253±0.113	52±23*	<0.001
DA	1.414±0.021	1.540±0.026	9±3*	1.602±0.716	1.695±0.758	6±3	0.03

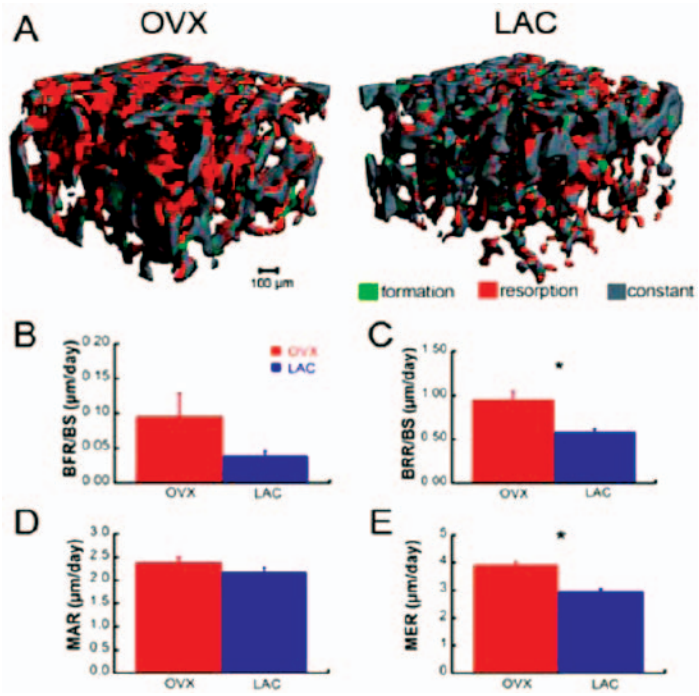

Figure 2. Results from 3D *in vivo* dynamic bone histomorphometry. (A) Representative 3D renderings of sub-volumes of trabecular region illustrating bone formation and resportion from days 0-7 in an OVC rat and LAC rat. (B) Comparison of BFR/BS. (C) Comparison of BRR/BS. (D) Comparison of MAR. (E) Comparison of MER. * Indicates significant difference between groups.

due to OVX than due to lactation. The inconsistency of this study's results with the previous literature may have resulted from excluding pregnancy from the study. Prior to pregnancy and ovariectomy, the rats shared similar microstructural parameters (data not shown). At the onset of lactation (d0) however, LAC rats had reduced trabecular bone volume and structural integrity (Table 1). The difference in baseline values between LAC and OVX rats seems to suggest that bone loss also occurred during pregnancy, which was not accounted for in this study. The results from this study suggest that both lactation-associated bone loss as well as estrogen deficiency-induced bone loss occur through similarly increased bone resorption and structural deterioration mechanisms.

Significance

Bone undergoes similar structural changes during these two physiological events, encouraging future study of post-lactation bone recovery which may be applicable to post-menoapausal osteoporosis treatment.

Acknowledgments

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Increased Endocortical Formation and Periosteal Resorption in Premenopausal Women with Idiopathic Osteoporosis Treated with Intermittent Parathyroid Hormone

[1]Mary Beth Tribble
[2]Adi Cohen, MD
[1]Chantal M. de Bakker
[2]Kyle Nishiyama, PhD
[2]Elizabeth Shane, MD
[1]X. Sherry Liu, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Columbia University, New York, NY, USA

Introduction

Idiopathic osteoporosis (IOP) in premenopausal women is characterized by low bone mineral density (BMD) and/or low trauma fractures, abnormal bone microarchitecture, and reduced bone strength, without an underlying secondary cause.[1] While intermittent parathyroid hormone (PTH) has been shown to be an effective treatment for osteoporosis in men and postmenopausal women, the response of premenopausal women with IOP to PTH remains unclear. We recently reported that daily injection of 20 μg of PTH 1-34 for 18-24 months improves bone density and quality at central skeletal sites.[2] Recently, using high-resolution peripheral quantitative computed tomography (HR-pQCT), we found that daily PTH injection also improves trabecular microarchitecture at the distal radius and tibia. However, little work has been done to determine how PTH affects cortical bone. Based on a standard cortical bone analysis, we observed no changes in cortical bone geometry at both the distal radius and tibia, and a significant increase in cortical porosity at the radius, but not at the tibia.[3] However, previous studies suggest that PTH causes significant changes in bone remodeling at cortical bone surfaces.[4,5,6] To further study the effect of PTH on cortical bone remodeling, we aimed to delineate the local bone resorption and formation activities in different envelopes of cortical bone over time. Therefore, in this study we developed an image analysis framework based on longitudinal HR-pQCT scans to quantify changes in BMD at cortical surfaces. We hypothesized that significant bone remodeling occurs at both the periosteal surface (PS) and endosteal surface (ES) in IOP patients in response to PTH.

Methods

Premenopausal women (n=17, age ± years) with a history of fragility fractures and/or low areal BMD received 20 μg of PTH 1-34 daily for 18 months. The distal tibia was scanned using HR-pQCT (XtremeCT, Scanco) at baseline and 18 months. A 110-slice region at a voxel size of 82 μm was scanned 22.5 mm proximal to the endplate of the nondominant distal tibia. Standard HR-pQCT 2D-area matching image registration may limit the detection of changes in structure or density near cortical surfaces. Therefore, landmark-initialized mutual information-based 3D image registration (ITK, NLM) of the trabecular compartment was used to align the grayscale baseline and follow-up scans. During image registration, the image from one time point (moving image) is resampled and transformed to align with the image from another time point (fixed image). Resampling the moving image leads to a reduction in image quality, while the fixed image is unaffected. Unequal amounts of artifact in the images may affect results obtained during image analysis. Thus, mutual moving registration (MMR) was developed. Briefly, the amount of 3D rotation needed to align the moving image with the fixed image is determined, divided equally, and used to mutually transform the images into a new coordinate system. By using MMR, comparable artefacts are induced, reducing the imbalance in image quality which occurs with standard image registration. Subsequent registration of a subvolume ensured precise alignment of the trabeculae (Figure 1), allowing for localized mineralization changes to be quantified. Once registered, contours were drawn semi-automatically to identify the PS and ES at both time points. The PS and ES voxels were isolated and then dilated to create surface masks which capture bone remodeling occurring adjacent to the cortical surfaces. The registered scans were subtracted to generate a BMD differential map (Figure 2), and the masks were used to isolate envelopes corresponding to the PS, ES, and intracortical area. Regional differences in bone mineral density (ΔBMD), and total mineral content (TMC) were derived from the BMD differential map. Based on the thresholded baseline and 18-month scans, structural parameters such as cortical thickness (Ct.Th),

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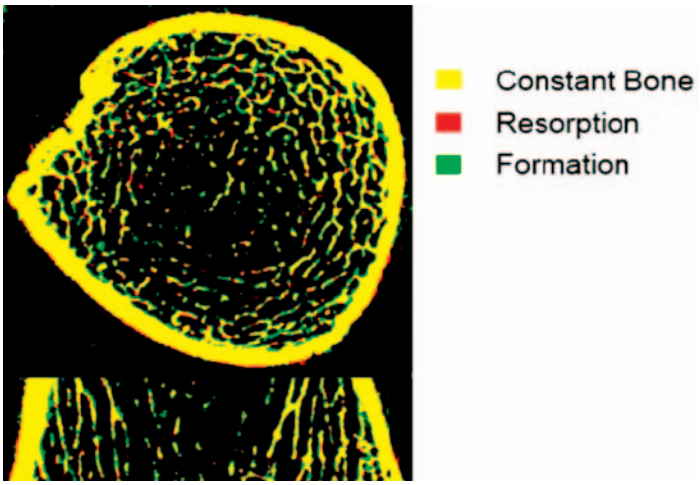

Figure 1. Registered segmented images indicating changes in bone over 18 months.

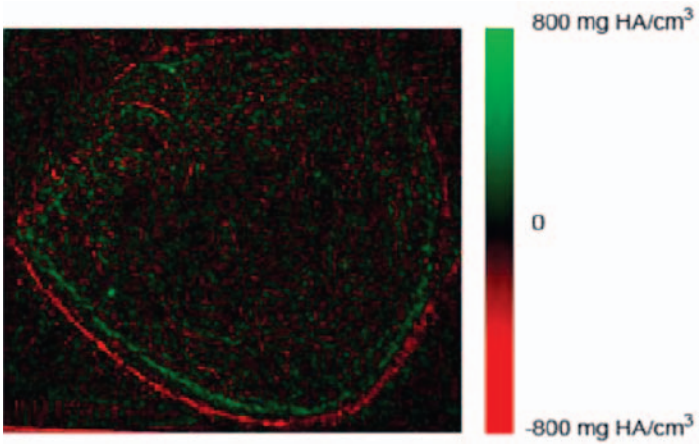

Figure 2. Differential map indicating ΔBMP at the PS and ES; there was minimal change at the intracortical area.

cortical area (Ct.Area), PS perimeter, ES perimeter, and polar moment of inertia (pMOI) were quantified. Paired student's *t*-tests were used for all comparisons, with $p<0.05$ considered a significant difference.

Results

After 18 months of PTH treatment, significant bone remodeling was observed. A 14% ($p<0.001$) decrease in TMC at the PS and a 6% ($p<0.001$) increase in TMC at the ES were observed over 18 months. There was no significant change within the intracortical area. Compared to ΔBMD of the intracortical area (-2.4 ± 19.8 mg HA/cm^3), ΔBMD at the PS (-53.9 ± 41.2 mg HA/cm^3) indicates significant mineral loss ($p<0.001$), and ΔBMD at the ES (44.6 ± 28.8 mg HA/cm^3) indicates significant mineral apposition ($p<0.001$, Figure 3)). While there was no significant change in pMOI over time, there were significant decreases in PS (0.2%, $p<0.01$) and ES perimeters (0.3%, $p<0.05$), a significant increase in Ct.Area (0.9%, $p<0.05$), and a 0.8% increase in Ct.Th trended towards significance ($p=0.1$).

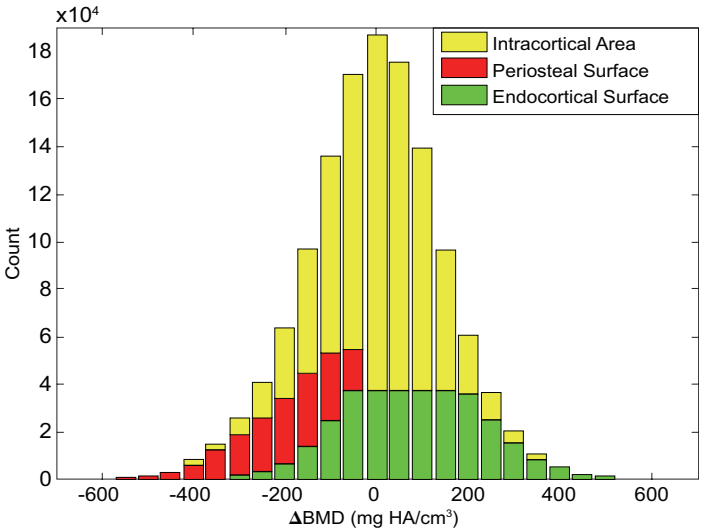

Figure 3. Histogram of ΔBMP within the three envelopes: periosteal surface, endosteal surface, and intracortical area.

Discussion

By using longitudinal HR-pQCT imaging and advanced 3D image registration, we were able to delineate regional changes in cortical BMD over time. Premenopausal women with IOP treated with PTH experienced significant decreases in BMD at the periosteum and increases at the endosteum, possibly due to excessive bone resorption at the PS and net bone formation at the ES. The effect of PTH on cortical bone remodeling at the iliac crest has been studied previously in postmenopausal osteoporosis. Short-term (<6 months) administration of PTH has been shown to increase bone formation at the ES and PS of the iliac crest.[4,5] However, a study of the effects of 18 months of PTH treatment found increased bone formation at the ES and little formation at the PS, thus supporting our findings.[6]assessed by DXA, by different mechanisms of action, supported by changes in biochemical markers of bone turnover. The purpose of this cross-sectional study was to explore the differential effects of these two osteoporosis treatments at the bone tissue level by examining bone histomorphometric parameters of bone turnover after either 6 or 18 months of treatment.\nMATERIALS AND METHODS: Patients were a cohort from a randomized parallel double-blind study conducted to compare the effects of once-daily teriparatide 20 microg and alendronate 10 mg in postmenopausal women with osteoporosis. Transiliac crest bone biopsies were obtained after tetracycline double labeling from 42 patients treated for 6 months (n = 23 Several factors confound the interpretation of this study within the context of previous research. Since the levels of bone remodeling differ between the peripheral and central skeleton, conclusions drawn from studies of bone remodeling at the iliac crest may not be applicable to the distal tibia. Also, due to the differing pathologies between postmenopausal osteoporosis and premenopausal IOP in women, observations relating to bone remodeling for postmenopausal osteoporosis may not translate to premenopausal IOP. In summary, our results

indicate that after 18 months of treatment, PTH preferentially improves new bone deposition at the endosteum and accelerates bone resorption at the periosteum of the distal tibia in premenopausal women with IOP. Although both ES and PS perimeters decrease, there is a significant increase in cortical area and a trend toward an increase in cortical thickness. Taken together, these changes in cortical structure did not alter the cortex's mechanical resistance to bending, as indicated by the lack of change in pMOI. Moreover, the preferential mineral deposition at the endosteum may help to improve bone's resistance to endocortical trabeculation, a major bone loss mechanism after menopause.

Significance

By using HR-pQCT and advanced image registration, we noninvasively examined the effects of PTH on cortical bone remodeling at the distal tibia in premenopausal women with IOP. PTH causes significant endocortical formation and periosteal resorption. As mechanical function of the cortex was maintained and endocortical BMD was improved, we conclude that PTH is a viable treatment option for premenopausal IOP.

Acknowledgments

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U·P·O·J

Development of a Large Animal Model of Osteochondritis Dissecans (OCD) of the Knee

[1,2]Christian G. Pfeifer, MD
[1,2]Stuart D. Kinsella, MD/MTR Candidate
[1]Andrew H. Milby, MD
[1]Matthew B. Fisher, PhD
[1]Nicole S. Belkin, MD
[1,2]Robert L. Mauck, PhD
[1]James L. Carey, MD, MPH

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

Introduction

OCD is a disorder of bone and cartilage in young persons that can engender disabling pain and precipitate the early onset of osteoarthritis (OA).[1] While OCD lesions can manifest in any joint,[2] 77-85% of lesions occur in the lateral aspect of the medial femoral condyle.[3,4] OCD lesions are typified by a disruption of the continuity of the subchondral trabecular architecture, with this discontinuity sometimes extending to the articular cartilage surface. OCD can progress across a continuum, from stable 'progeny' lesions with intact cartilage to completely dislocated progeny fragments of cartilage and associated underlying bone.[5] The etiology of OCD is not well understood, with studies suggesting causative factors such as repetitive microtrauma, vascular insufficiency, primary osteonecrosis, and genetic/developmental abnormalities, though the pathophysiology is most likely multifactorial.[6] Current practice for OCD treatment is lesion specific, depending on many factors including stability, location, and bone/cartilage quality, but lacks evidence-based criteria. While spontaneous OCD-like lesions have been investigated and experimental models in small animals have been attempted,[7] there is currently no large animal model of OCD in which to evaluate novel surgical treatments. In this study, we developed a large animal model of OCD in the stifle joint of the Yucatan minipig. We hypothesized that by surgically creating an osteochondral defect and repairing it with a biodegradable membrane interposed between the 'progeny' fragment and the 'parent' bone/cartilage, an OCD-like lesion would develop. To test this hypothesis, we evaluated short-term bone and cartilage changes when two different degradable materials (with or without fenestrations) were placed in the defect.

Methods

Bilateral osteochondral lesions (9.5 mm x 12.5 mm) were created in the medial femoral condyles of nine 6-month old Yucatan minipigs. Before replacing the 'progeny' fragment, a biodegradable membrane was sandwiched between the progeny and parent bone (Figure 1). Five different treatment groups were evaluated at 2 weeks: a slowly degrading nanofibrous poly(ε-caprolactone)(PCL) membrane (n=4), a fenestrated PCL membrane (fenPCL, with 1.5 mm holes covering 25% of surface area, n=4), a commercially available collagen membrane (Biogide®, BG, n=3), and a fenestrated BG membrane (fenBG, n=3). Additional defects were created as controls (Ctrl, n=4), where the progeny was reinserted into the defect without an interposed layer. Six 6-0 sutures were placed at the defect boundary to provide initial stability. Animals were sacrificed at postoperative day 14 and the lesion was evaluated by gross inspection, fluoroscopy, micro-CT, and histology. To quantify changes between groups, a scoring system based on gross appearance (0-2), fluoroscopy (0-2), and micro-CT (0-6) was established, where lower numbers indicated 'normal' and scores of 4-7 indicated an 'OCD-like' appearance. We additionally quantified bone volume per total volume (BV/TV) in a defined region surrounding and inclusive of the defect using micro-CT. Statistical analysis was carried using one-way ANOVA with Bonferroni post-hoc test for micro-CT and a Kruskal-Wallis test with Dunn's multiple comparison post-hoc for the OCD Score.

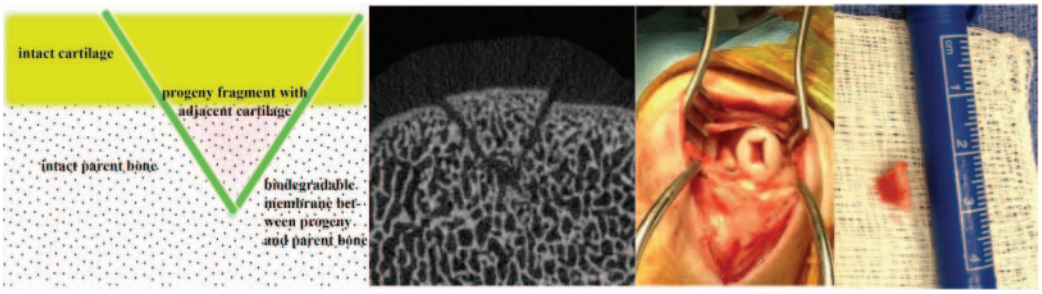

Figure 1. Left to right: schematic of OCD lesion, micro-CT in coronal plane of lesion on day 0, intraoperative surgical site after creation of the lesion (before insertion of progeny fragment), and higher magnification view of progeny fragment (with scale bar).

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dr.christianpfeifer@gmail.com

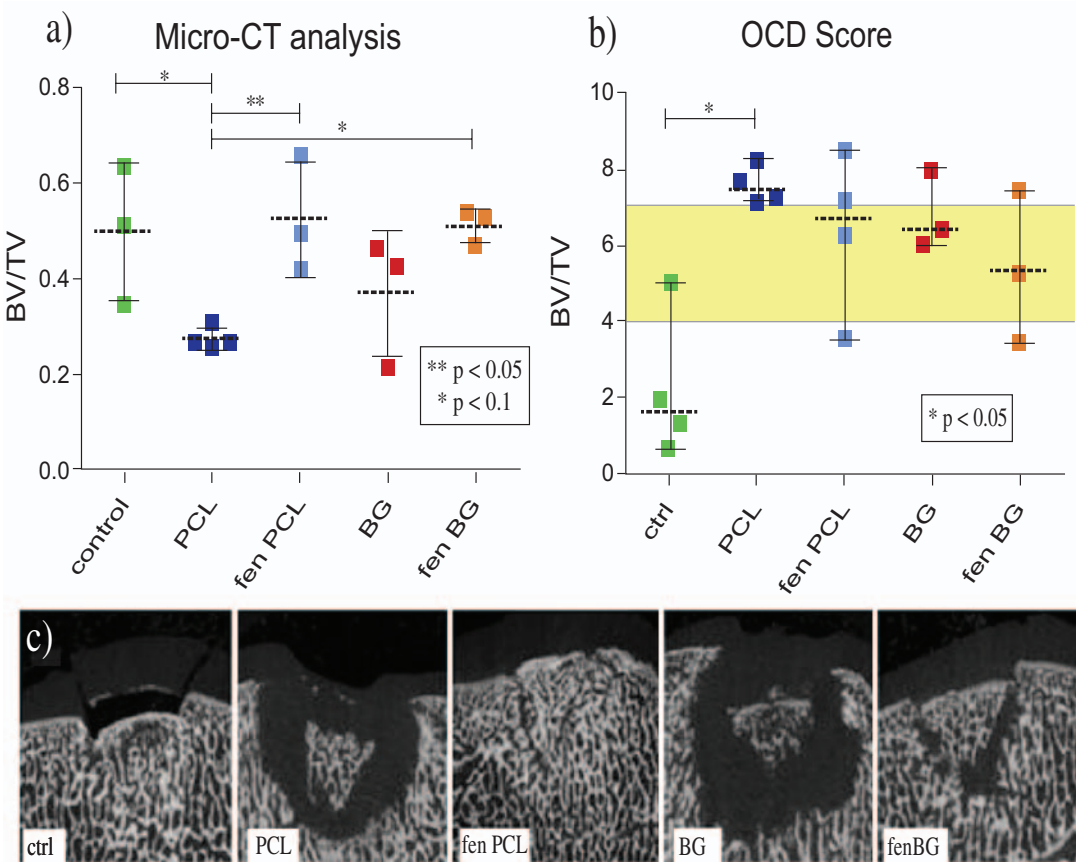

Figure 2. a) Micro-CT analysis of bone volume per total volume in a defined region including the lesion. b) Total 'OCD score' for each condition. An ideal range (between completely stable/connected (7 points) is indicated by the shaded region. c) Ex vivo micro-CT images from the center of the lesion on postoperative day 14 for each group (coronal view).

Results

Surgical creation of an osteochondral defect on the femoral condyle proceeded without complication, and animals recovered to normal ambulation within 2 days of surgery. On day 0, there was clear separation between parent and progeny fragment when the interpositional membrane was placed (Figure 1). After 14 days, control groups showed marked healing of the subchondral bone, though some lesions were slightly depressed relative to the articular surface (Figure 2c). Condyles treated with PCL or BG membranes showed substantial remodeling at this time point, with clear loss of bone in both the progeny fragment and surrounding parent bone. Conversely, both fenestrated groups (fenPCL and fenBG) showed less bone loss and in some instances, small trabecular bridges forming between the parent and progeny (Figure 2c). From histological sections, there was no evidence of integration in the cartilage layer in any group, and some fibrous tissue was observed between the parent and progeny

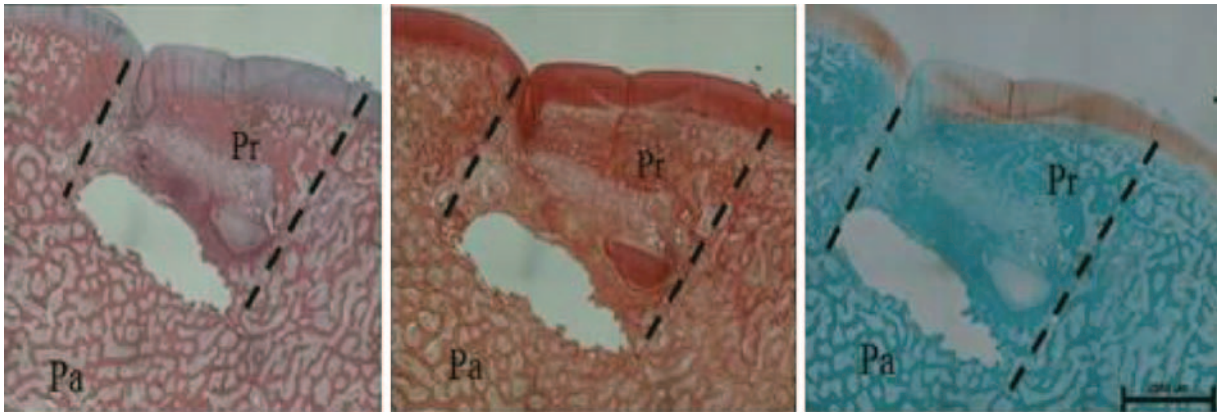

Figure 3. Histological sample of an OCD-like lesion created after placement of a PCL membrane between the Parent (Pa) and Progeny (Pr) fragment (sagittal view). Evidence of remodeling in both progeny and parent bone is apparent, as is fibrous tissue in the defect. Osteotomy sides are marked by dotted lines. Scale bar: 2mm. Stains left to right: Hematoxylin & Eosin, Picrosirius Red, Safranin O & Fast Green.

fragments (Figure 3). Micro-CT quantification showed significant differences in BV/TV between the PCL and fenPCL groups, control and PCL groups, and PCL and fenBG groups, but no differences between any other group pairs (Figure 2a). Grading by six blinded reviewers (using the 'OCD-like' scoring system) showed a significant difference between Control and PCL groups ($p<0.05$) and indicated that several groups (fenPCL and fenBG) fell within the target window (Figure 2b).

Discussion

In this pilot study, we successfully produced an osteochondral lesion with hallmarks of OCD in a large animal model by situating a semi-permeable membrane between the parent bone and progeny fragment. Control groups showed evidence of bony apposition in the subchondral trabecular space, while inclusion of either biodegradable membrane instigated significant bony remodeling of the progeny fragment and the parent bone. Fenestrations within the membrane decreased the extent of this remodeling. Quantitative data and semi-quantitative grading of samples provided outcome parameters that were able to distinguish treatment groups from controls. While these results suggest that an 'OCD-like' state is present at this early time point, additional animals are now being investigated over longer periods of time to determine whether this is a transient phenomenon or whether placement of these interpositional membranes promotes fibrous non-union over a longer duration. Overall, our results suggest that it will be possible to generate an OCD-like model in the minipig, opening the door for the future development of novel surgical strategies.

Significance

This large animal model may serve as reliable basis for the development of novel surgical approaches for the treatment of OCD lesions.

Acknowledgments

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Healing Response and Subchondral Bone Remodeling with Treatment of Focal Cartilage Lesions in a Porcine Model

[1,2]Matthew B. Fisher, PhD
[1,2]Nicole S. Belkin, MD
[1,2]Andrew H. Milby, MD
[1,2]Elizabeth A. Henning, BS
[1,2]George R. Dodge, PhD
[1,2]David R. Steinberg, MD
[1,2,3]Robert L. Mauck, PhD

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

[2]Translational Musculoskeletal Research Center, Philadelphia VA Medical Center, Philadelphia, PA, USA

[3]Department of Bioengineering, University of Pennsylvania, Philadelphia, PA, USA

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fishmatthew@gmail.com

Introduction

Intrinsic repair of articular cartilage is unsatisfactory, and untreated focal defects (without extensive damage to the subchondral bone) impair quality of life to the same extent as do more widespread osteoarthritic (OA) changes to the joint.[1] As such, there is substantial interest in treating localized defects in certain patient populations.[2,3] Pre-clinical large animal models, such as the goat, sheep, and pig, have provided a wealth of information on the efficacy of potential treatments.[4-8] Some studies have noted a marked remodeling of the subchondral bone following the creation of a purely chondral defect; however, the mechanisms underlying this response have not been well characterized.[9] One hypothesis is that the surgical procedure creates microscopic damage to the underlying bone, instigating a remodeling response. Alternatively, the lack of mechanical function in the repair tissue or implant material could lead to subchondral remodeling due to decreased load transfer to the bone. To gain further insight into this issue, the objective of this study was to compare the healing response and subchondral remodeling in models of cartilage injury that do and do not create microdamage to the bone, both in the context of naturally forming repair tissue and with treatment using a cartilage autograft that provides functional load transfer to the subchondral bone.

Methods

In seven Yucatan minipigs, chondral defects (4 mm diameter) were created bilaterally in the trochlear groove of the stifle joint. Five experimental groups were compared: 1) an untreated full thickness defect (untreated FTD, n=14), 2) a full thickness defect treated with microfracture (FTD-MF) (n=6), 3) a full thickness defect treated with transfer of autologous cartilage (FTD-ACT) (n=7), and 4) an untreated partial thickness defect (untreated-PTD, n=3). Normal cartilage served as a positive control (n=14). Other groups not reported here were also performed, giving rise to the unequal sample sizes. At 6 weeks, animals were euthanized. Bone morphometry under the defect site was determined using microcomputed tomography (μCT). Bone volume per total volume (BV/TV) was calculated for the first 2 mm and for a region 3-5 mm beneath the original defect. Histological evaluation included cell morphology (hematoxylin & eosin) and matrix staining (proteoglycan and collagen via Safranin O/fast green). Samples were scored using a modified ICRS-II system (7). BV/TV and histological scores between groups was compared via ANOVA with Games-Howell post-hoc tests to account for the unequal variances between groups ($p<0.05$).

Results

At the time of surgery, a small amount of bleeding from the subchondral bone was noted following the creation of all full thickness defects, while no bleeding was observed when creating the partial thickness defects. Six weeks after surgery, bone morphology of the groups involving a full thickness cartilage defect showed evidence of bone remodeling and resorption beneath the defects, with regional differences (Figure 1A). Quantitatively, within 2mm of the cartilage/bone interface the BV/TV for these groups were 55-61% lower than normal ($p<0.05$) and 56-62% (p0.05). In terms of histologic appearance (Figure 2A), the untreated FTD group filled incompletely with a mostly fibrous tissue. MF treatment led to a similar appearance, with some samples showing more robust staining for proteoglycans. ACT treatment resulted in fill of the vast majority of the defect space with tissue that stained well for proteoglycans; however, these constructs were quite variable in their ability to integrate with the surrounding tissue. From ICRS-II scoring (Figure 2B), the mean overall values for the FTD groups were 12-57% lower than normal ($p<0.05$). Additionally, the untreated FTD group was 48% and 51% lower than the untreated PTD and FTD-ACT groups, respectively ($p<0.05$). In terms of matrix staining, the untreated FTD and FTD-MF groups were 57% and 43% lower than normal, respectively ($p<0.05$). Additionally, the untreated group was 55% lower than the FTD-ACT group ($p<0.05$). Finally, in terms of cellular morphology, the full thickness defect groups were 12-65% lower than normal, and the untreated group was 60% lower than the FTD-ACT group ($p<0.05$). Additionally, no differences

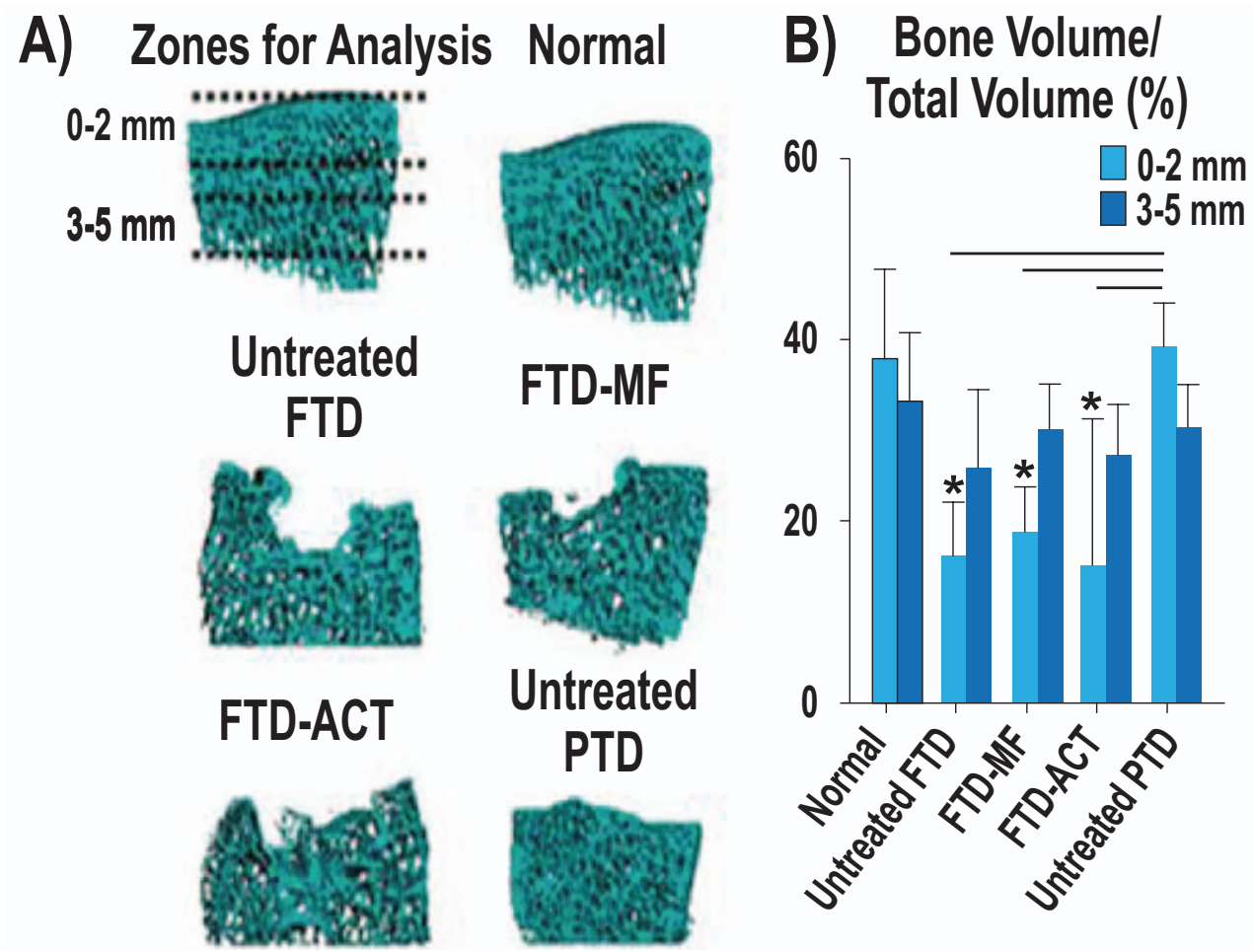

Figure 1. Typical 3D μCT reconstructions of bone (A) (centered under defect, scale bare = 2mm). Bone Volume/Total Volume in regions adjacent to (0-2mm) and further removed (3-5mm) from the cartilage interface (B) (*$p<0.05$ vs. normal, bars −$p<0.05$ between groups). (FTD = full thickness defect; PTD = partial thickness defect; MF = microfracture; ACT = autologous cartilage transfer).

were found between the untreated PTD and any of the full thickness defect groups for matrix staining and cellular morphology ($p<0.05$).

Discussion

In this study, we quantitatively assessed the role of the severity of a focal cartilage injury as well as potential treatments on the healing response of cartilage as well as the remodeling of the subchondral bone in a porcine model. Interestingly, substantial bone remodeling occurred when a full thickness defect was created. This effect was independent of treatment group, as similar levels of bone remodeling occurred if the defect was left untreated, was treated with microfracture, or was treated with an autologous cartilage plug. On the other hand, creation of a partial thickness chondral defect had no impact on the underlying bone. Together, these results suggest that the bony remodeling observed is a result of the injury to the subchondral bone surface and not treatment (or capacity for load trans mission). Indeed, even filling the defect with an autologous cartilage plug, which should allow transfer of mechanical loads to the bone,[10] could not prevent remodeling, while the partial chondral injury (which did not allow for mechanical load transmission) showed little bony remodeling. One limitation of this study is the use of an adolescent porcine model, which lacks a layer of calcified cartilage in the trochlear groove. Thus, creation of a full thickness defect resulted in unavoidable microscopic damage to the subchondral bone and bleeding within the defect.[5] Other animal models with a layer of calcified cartilage may allow the creation of full thickness defects without bony remodeling, although some studies in the skeletally mature goat model suggest otherwise.[9] Despite the remodeling, transfer of autologous cartilage was able to restore the histological appearance of the native cartilage, with histological scores substantially higher than the untreated or MF groups, which filled with a fibrocartilaginous tissue. These data indicate that the type of cartilage injury should be carefully controlled in future studies to evaluate tissue engineering or regenerative medicine approaches. Longer-term studies are also warranted to determine whether such subchondral abnormalities resolve towards the reestablishment of patent subchondral architecture if provided a longer time course for healing and remodeling.

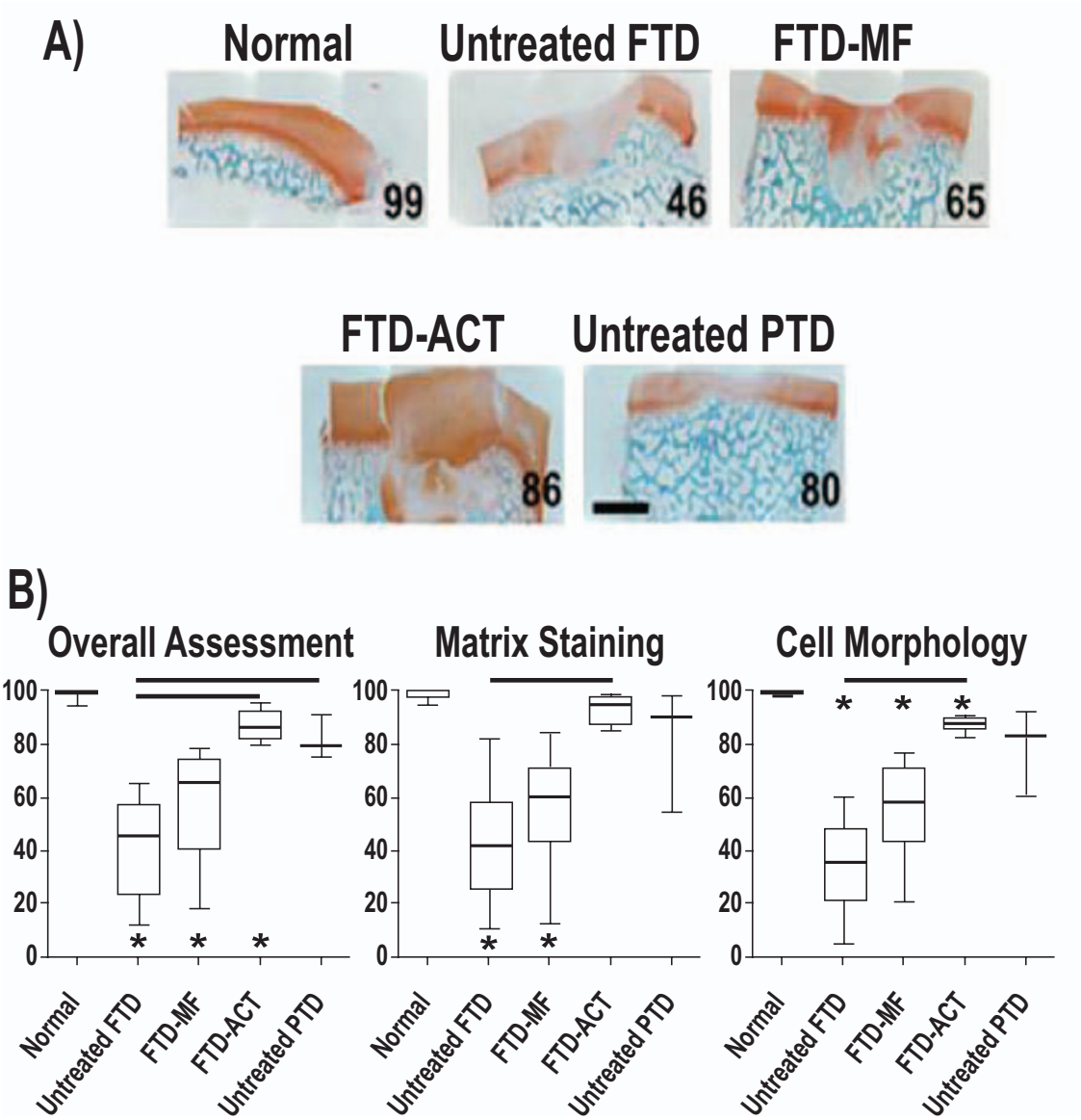

Figure 2. (A) Histological staining for proteoglycans (red) and collagen (green) following 6 weeks in vivo (scale = 2mm, overall score shown). (B) Histologic scoring: Overall assessment, matrix staining, and cellular morphology (*$p<0.05$ vs. normal, bars-$p<0.05$ between groups).

Significance

The severity of a focal chondral defect dictates the amount of bony remodeling in the porcine model. These data will guide future work in the evaluation of tissue engineering and regenerative medicine strategies for cartilage repair using this animal model.

Acknowledgments

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U·P·O·J

Percutaneous Delivery of Chondroitinase ABC Induces Moderate Disc Degeneration in a Goat Model

[1]Andrew H. Milby, MD
[1,2]Brent L. Showalter, BS
[1]Joanne Haughan, VMD
[1,3]Robert L. Mauck, PhD
[2]Dawn M. Elliott, PhD
[1]Neil R. Malhotra, MD
[1]Thomas P. Schaer, VMD
[1,3]Lachlan J. Smith, PhD

[1]University of Pennsylvania, Philadelphia, PA, USA

[2]University of Delaware, Newark, DE, USA

[3]Philadelphia VA Medical Center, Philadelphia, PA, USA

Introduction

Low back pain is highly prevalent, substantially impairs quality of life and is a leading cause of healthcare expenditures.[1] Low back pain leads to 15 million physician visits annually with only 500,000 patients meeting criteria for surgical intervention.[2] Four million patients will not meet surgical criteria, have moderate disc degeneration, and remain unresponsive to long term conservative treatment. Without an effective treatment paradigm for this large population, the community of spinal therapeutic specialists is focused on the development of minimally invasive strategies to treat and/or reverse moderate disc degeneration. Many approaches focus on injectable therapeutics for the nucleus pulposus (NP) that can normalize disc mechanical function, attenuate chronic inflammation, and/or potentiate native tissue regeneration.[3,4] For in vivo evaluation of such therapeutics, a preclinical large animal that recapitulates key characteristics of moderate human disc degeneration is required. The large frame goat represents an attractive model given its disc geometry that is comparable to that of the human and that it provides a clinically relevant model for percutaneous approaches. Catabolic mediators such as chondroitinase ABC (ChABC) and interleukin-1 beta (IL-1β) have shown promise in vitro and in vivo in instigating moderate disc degeneration, including loss of disc height and glycosaminoglycan content, and altered biomechanical properties.[5-10] The objectives of this study were to evaluate a minimally-invasive, percutaneous technique for the introduction of catabolic agents into the goat NP, and to compare the efficacy of ChABC and IL-1β as initiators of moderate disc degeneration.

Methods

Animal studies were performed following IACUC approval. Large frame goats (n=11) were placed in right lateral recumbency under general anesthesia. Lateral fluoroscopic images were used to verify number of lumbar vertebrae and levels for injection using the ribs and the sacrum as anatomical landmarks. Following a 5mm skin incision, an 18 gauge spinal needle with a blunt trocar was advanced via a posterolateral approach under fluoroscopic guidance and docked on the outer annulus fibrosus. The trocar was removed, and a 22 gauge spinal needle was introduced into the center of the NP (Figure 1) under fluoroscopic guidance and distinct tactile feedback. Treatment groups were: ChABC, 1 U/ml in saline (L1-2 or L3-4, randomized); 2) saline sham (L2-3); 3) IL-1β, 100 ng/ml in saline (L1-2 or L3-4, randomized); and 4) intact (non-injected) control (L4-5). The injection volume was 100 μl. Animals were returned to normal housing and euthanized 12-weeks post-surgery. Lateral radiographs of the lumbar spine were obtained pre-operatively, and at 6 and 12-weeks post-operatively. Changes in disc height index (DHI) at the 6 and 12 week time points relative to pre-operative values were calculated using a custom Matlab program. Measurements were performed independently by 2 blinded assessors. Following euthanasia, 7 spines were imaged using magnetic resonance imaging (MRI). Series of T1rho and T2-weighted images were acquired on a 3T MR Scanner (Trio; Siemens) using turbo spin-echo sequences. The T2 images used TR=3000 ms and 6 evenly distributed echo-times between 13 and 78 ms, while the T1rho images used TR/TE=3000/12 ms with 5 evenly distributed spin-lock pulse durations from 12-60ms with a 500 Hz spin-lock pulse amplitude. T1rho and T2 scores were obtained using a regression of intensity data within the NP from the images. The remaining 4 spines were processed for paraffin histology. Mid-sagittal sections from

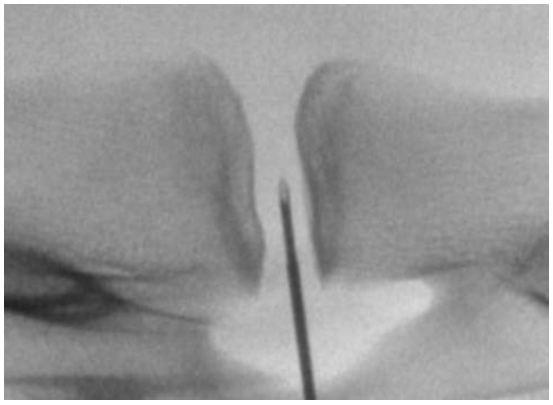

Figure 1. Placement of 22 gauge needle in the NP under fluoroscopic guidance.

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Andrew.Milby@uphs.upenn.edu

each disc were stained with alcian blue (GAG) and picrosirius red (collagen), and qualitatively assessed for morphological changes consistent with degeneration. Differences in DHI changes after 6 and 12 weeks, and differences in T1rho and T2 scores after 12 weeks between treatment groups were established using repeated measures ANOVAs with post-hoc, pairwise Student Neumann Keul's tests.

Results

For quantitative MRI assessments, T1rho scores were significantly different between groups ($p=0.009$), with post-hoc tests revealing that ChABC was significantly lower than all other treatment groups and the intact group (Figure 2A). T2 scores (Figure 2B) showed a trend toward decreases with ChABC treatment, but did not reach the level of significance compared to intact ($p = 0.06$). One spine was excluded from MRI analysis due to signal artifact. No significant changes in radiographic DHI were found between groups at either 6 or 12 weeks post-operatively. A high degree of inter-assessor variability was observed for DHI measurements, likely due to the inconsistent orientations of discs within the radiographic field of view, and the small effect size. With respect to histological evaluations, no signs of degeneration were apparent for any group (Figure 3).

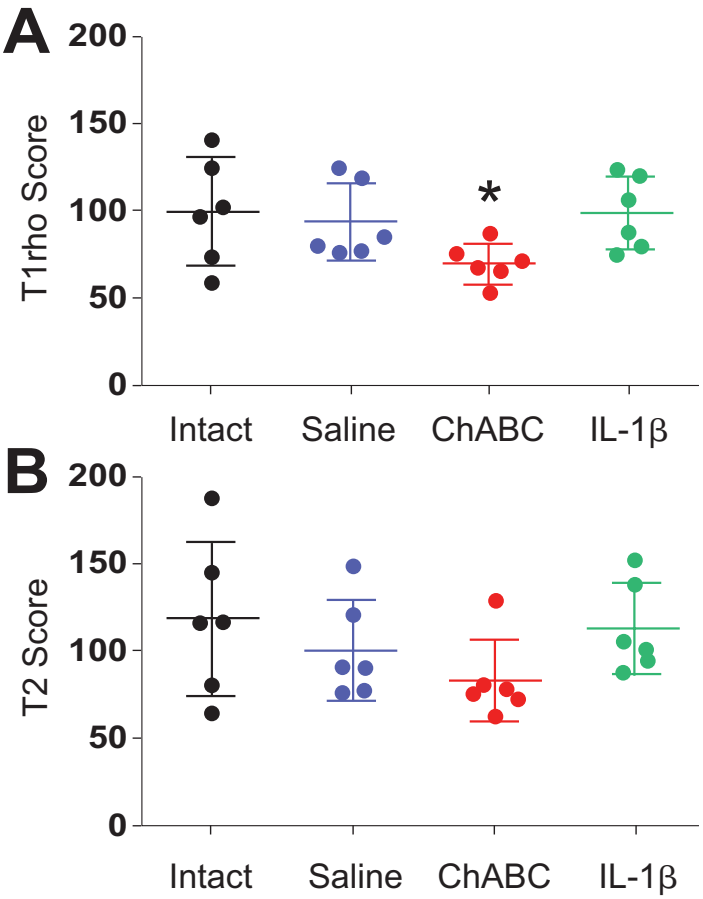

Figure 2. Quantitative MRI assessment of disc condition. A) T1rho scores. B) T2 scores. *$p<0.05$ vs all other groups.

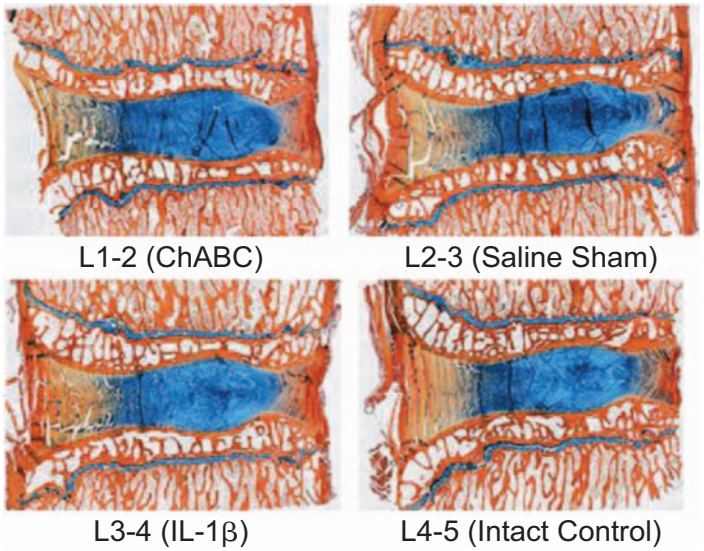

Figure 3. Histological assessment of disc condition. No morphological differences were apparent between treatment groups.

Discussion

In this study, we used a percutaneous surgical approach to initiate moderate degeneration in the goat disc. This minimally invasive, clinically translatable approach allows for the successful delivery of injectable agents to the disc space with an acceptable safety profile. Ongoing work will seek to further refine this model, and ensure accurate and repeatable delivery of agents to the goat NP. Previously, our team has successfully used both ChABC and IL-1β to induce glycosaminoglycan loss in vivo in the rat disc.[9,10] The current findings in the goat suggest that IL-1β is less effective at inducing disc degeneration than ChABC, at least at the dosage evaluated in this pilot study. Despite this limitation, our results show that quantitative MRI is a sensitive method for identifying early degenerative changes in this model compared to both histological assessment and measurements of disc height from radiographs. Higher dosages of ChABC may be required to induce more consistent, measurable degenerative changes. Following further evaluation of this model (including biomechanical and biochemical assays), future studies will refine the model and use this platform to evaluate novel, minimally invasive therapeutics for disc degeneration, including bioactive hydrogel implants that are currently under development by our group.

Significance

Low back pain resulting from intervertebral disc degeneration is a significant socio-economic burden. The large animal model of moderate disc degeneration developed herein provides an important preclinical platform in which to evaluate minimally-invasive therapeutics for disc regeneration.

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A Rat Model for Elbow Allotransplantation

[1]Scott M. Tintle, MD
[2]Juyu Tang, MD
[3]L. Scott Levin, MD, FACS

[1]Walter Reed National Military Medical Center, Oakton, VA, USA

[2]Xiangya Hospital Central-South University, Changsha 410008, PR China

[3]University of Pennsylvania, Philadelphia, PA, USA

Introduction

There is no durable solution for end stage elbow arthritis in the young active patient population. Potential surgical solutions to include elbow debridement, resurfacing arthroplasty, non-vascularized allograft elbow transplantation, and total elbow replacement have not proven to be the successful long term solution to this problem. In the current patient with end stage elbow arthritis or elbow destruction as a result of injury, infection or failed arthroplasty, the only viable solution is often surgical arthrodesis, or resection arthroplasty leaving a patient with a minimally useful extremity with minimal to no motion. An ideal replacement for these patients with elbow joint destruction would be a living joint allogeneic transplant that exactly matches the dimensions and structural properties of the missing joint. The purpose of this study was to create an animal model for elbow joint vascularized composite allotransplantation. (VCA)

Methods

We developed an animal model for VCA of the elbow joint in rats. Microvascular elbow VCA was performed in 9 rats across a major histocompatibility barrier. 3 rats were treated with full dose immunosuppression consisting of cyclosporine until sacrifice. 3 rats were provided with 10 days of immunosuppression and then the cyclosporine was stopped. Finally, 3 rats were utilized as a control and were given no immunosuppression. Joint mobility and weight-bearing capability were assessed throughout 90 days of life. Pedicle patency, bone blood flow, and histologic analysis were performed at the time of sacrifice.

Results

In the cyclosporine group, forelimb activity was gradually recovered over the postoperative 90 days. The operated extremity was utilized in daily activities such as ambulating and eating. There was little to no range of motion or utilization of the limb in the cyclosporine taper or the control groups. The vascular pedicles were patent at the time of sacrifice in the cyclosporine-treated group but not in the remaining groups. Micro-CT scan performed 3 months following the transplants revealed union at the bone junctions and the elbow joint appeared grossly normal upon sacrifice in the cyclosporine treatment group only. Incomplete healing was observed in the other two groups, and the elbow joints were grossly destroyed. Flow cytometry of blood samples obtained on days 14, 30, 60 and 90 showed no recipient cell chimerism in any of the groups. Histologic examination of the elbow joints is currently being performed.

Discussion

We have provided an animal model for elbow VCA. In our cyclosporine-treated rats we have shown that animals regain near normal function of their forelimbs after bone union and maintain grossly normal elbow cartilage. Without cyclosporine treatment, both our control groups and the short term cyclosporine group rejected their allotransplants.

Significance

No current model for elbow allotransplantation currently exists. This model will help further the study of the potential for this type of transplantation in the future. Significant progress with immunosuppressive regimens is necessary prior to making this a clinical reality, and it is therefore important that an animal model be established.

Acknowledgments

Dr. L. Scott Levin, Dr. Juyu Tang, Hainan Zhu, Xusong Luo.

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scott.levin@uphs.upenn.edu

Gain-of-Function Alk2 Mutation Enhances Chondrocyte Differentiation and Promotes Heterotopic Endochondral Ossification

[1,2,3]Andria L. Culbert
[2,3]Salin A. Chakkalakal
[2,3]Robert J. Caron
[1,2,3,4]Eileen M. Shore

[1]Cell and Molecular Biology Group, University of Pennsylvania, Philadelphia, PA, USA

[2]Center for Research in FOP and Related Disorders, University of Pennsylvania, Philadelphia, PA, USA

[3]Department of Orthopaedic Surgery, University of Pennsylvania, Philadelphia, PA, USA

[4]Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA

ALK2 (activin receptor-like kinase 2) is an evolutionarily conserved type I bone morphogenetic protein (BMP) receptor that responds to exogenous ligand to mediate downstream BMP signaling. Gain-of-function mutations in ALK2 cause the rare genetic disorder fibrodysplasia ossificans progressiva (FOP), characterized by progressive heterotopic (extra-skeletal) endochondral ossification. We hypothesized that the mildly activating FOP patient mutation in Alk2 (R206H) predisposes or accelerates chondrogenic differentiation of progenitor cells and induces heterotopic endochondral ossification within soft connective tissues. To test this hypothesis, mouse embryonic fibroblasts (MEFs) were harvested from wild-type and knock-in $Alk2^{R206H/+}$ embryos as a progenitor cell model. $Alk2^{R206H/+}$ MEFs showed increased canonical BMP signaling as detected by phosphorylation of Smads1/5/8 and increased expression of BMP responsive genes in both the absence and presence of BMP ligand. Under chondrogenic culture conditions, the addition of BMP ligand increased the sensitivity of $Alk2^{R206H/+}$ MEFs toward chondrogenesis. Consistent with these results, $Alk2^{R206H/+}$ MEFs showed earlier appearance of chondrocyte morphology and accelerated onset with increased abundance of early chondrogenic transcripts during BMP-induced differentiation. We determined that Alk2 mRNA is most abundant in undifferentiated MEFs and decreased upon differentiation, suggesting important roles during early differentiation. Loss of Alk2 prior to chondrogenic culture severely inhibited differentiation of MEFs. MEFs implants in hind-limb muscle of wild-type mice demonstrated that $Alk2^{R206H/+}$ MEFs promote heterotopic endochondral ossification *in vivo*. Our data show that heterozygous expression of Alk2 (R206H) in progenitor cells enhances chondrogenic differentiation *in vitro*, promotes heterotopic ossification *in vivo*, and supports early chondrogenic differentiation as an important therapeutic target for preventing heterotopic bone formation in FOP patients.

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andriast@mail.med.upenn.edu

Heterozygous Inactivation of Gnas Induces Heterotopic Ossification and Impairs Normal Skeletal Development

[1,4]Girish Ramaswamy
[1,4]Deyu Zhang
[1,2,4]Frederick S. Kaplan
[1,2,4]Robert J. Pignolo
[1,3,4]Eileen M. Shore

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

[2]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA

[3]Department of Genetics, University of Pennsylvania, Philadelphia, PA, USA

[4]Center for Research in FOP and Related Disorders, University of Pennsylvania, Philadelphia, PA, USA

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 *GNAS*, a gene that encodes multiple transcripts including the α-subunit of the stimulatory G-protein ($G_s\alpha$) of adenylyl cyclase. All these disorders exhibit subcutaneous heterotopic ossification (HO); however, POH is the most severe form and is characterized by HO progression into deeper connective tissues including muscle and fascia. The *GNAS* gene shows genomic imprinting and POH is associated with paternal inheritance of the mutation. Mice with paternal inheritance of heterozygous deletion of exon 1 (Gnas $Ex1^{+/-}$) have lower body weight and length, and develop subcutaneous ossifications with age. But whether reduced Gnas expression leads to alterations in the formation or quality of skeletal bone remains undetermined. To investigate the effects of Gnas mutation on skeletal development, we performed μCT and histological analyses to examine the effects of paternal allele inactivation of Gnas on developing bone and cartilage. At postnatal days 1 (P1) and 14 (P14), $Ex1^{+/-}$ mice weighed significantly less than wild-type (wt) littermates. Tibiae from $Ex1^{+/-}$ mice at these ages were significantly shorter in length (15%±4). Trabecular bone parameters, analyzed through μCT scans of the distal epiphyseal region in P14 mice, revealed dramatic reductions in bone volume (36%±11) and bone volume fraction (20%±12). Microarchitecture of trabeculae was altered with a significant decrease in trabecular thickness and a concomitant increase in the structure model index, suggesting that trabecular bone is more rod-like in these mutants than wt littermates. μCT analyses of the femoral mid-diaphysis region showed reduced cortical thickness (20%±10) and cortical bone volume (35%±8) in P14 mutants. Histology of hindlimb sections from P14 mice showed a marked decrease in the length of the hypertrophic zone of the growth plates of $Ex1^{+/-}$ mice. The calvaria of P1 and P14 heterozygous mutants were reduced in size in both antero-posterior and medial-lateral dimensions. Taken together with our previous findings, heterozygous paternal allele inactivation of Gnas not only alters postnatal progenitor cells to form heterotopic ossification, but also adversely affects normal skeletal development that impacts both endochondral and intramembranous bone formation.

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American Society for Bone and Mineral Research
rgirish@mail.med.upenn.edu

"Together We Build" Penn Orthopaedics and the Philadelphia 76ers

Brian J. Sennett, MD
Head Team Physician, Philadelphia 76ers

Together We Build! As the season began this year against the Miami Heat on October 30th, 2013, every attendee at the opening night game was given a t-shirt with this inscription on the front: "Together We Build." The evening ended with a tremendous first win over the NBA Champions, and the season was underway. As I reflect on that night, I realize that five years ago, the same process began at Penn Orthopaedics when Dr. L. Scott Levin joined the Penn family as Professor and Chairman. He, too, challenged us to build together, and the program has flourished with him at the helm. This similarity between the two programs has not escaped me as we near the season's completion.

It has been a wonderful time at Penn Orthopaedics, as we have become the Official Medical Providers of the Philadelphia 76ers. Serving as the Head Team Physician has allowed me to put together a fantastic medical team utilizing the tremendous assets of our department and Penn Medicine. It is truly a multidisciplinary medical care team. Dr. Rahul Kapur, who works at the Penn Sports Medicine Center and in the Department of Family Medicine, has served as my Chief Medical Physician, overseeing all things non-orthopaedic with conditions ranging from cardiac clearances to migraines to bizarre dermatologic conditions. In addition, Rahul and I are present for almost all home games and typically spend up to five hours at the arena each game day with evaluations pre and post-game. The other Penn Sports Medicine faculty, including Drs. James Carey, John Kelly, and Miltiadis Zgonis, has also been an integral part of our team, providing clearances, evaluations, and game coverage during any absences. Dr. Zgonis has also been intimately involved with the medical care of the Delaware 87ers, the Sixers' Developmental League franchise. Penn Ophthalmology, under the direction of Dr. Paul Tapino, is also present at all of our home games, providing urgent care for any eye emergencies. Many other Penn Orthopaedic faculty members have also been involved with providing expertise care, ranging from a complex ankle evaluation to Dr. Levin's surgical care of Brandon Davies's hand.

While Penn Orthopaedics has tremendous talent, we couldn't care for a team like the Philadelphia 76ers without all of Penn Medicine. The talent and resources that make Penn Medicine one of the premier medical institutions in the country have allowed us to provide impeccable and timely care. In caring for the team, every player requires comprehensive medical screening prior to putting on the Sixers uniform. This battery of medical evaluations even includes stress echocardiography on every athlete. MRI evaluations are also frequently done during clearances, and Penn Cardiology and the Department of Radiology have been nothing short of phenomenal in our comprehensive care! During the season, injuries have occurred and, most of the time, need to be evaluated quickly and thoroughly to provide the athlete and team with accurate diagnosis and treatment plans. Travel requirements for the players are more extensive than the rest of professional sports and only add complexities to their medical care.

One of the programs the Sixers have in place is "Heroes Among Us," in which a special group is honored by the team at each home game. This award for our program would go to the Penn Facilitated Services, who provide the coordination of care between all of the departments. They have been spectacular in allowing us to provide seamless care across Penn Medicine. In caring for the Philadelphia 76ers, many departments have been involved, and it has truly been a multidisciplinary approach to medical care. It definitely has been an extremely busy year, probably the busiest of my career. This would never have been possible without support, and personally I have been blessed to have a wife and nurse practitioner as wonderful as Bobbiann.

It has been also been extremely rewarding to work with an organization as professional as the Philadelphia 76ers. The training staff, led by Head Athletic Trainer Kevin Johnson, who is one of the most experienced trainers in the league, is impressive in its expertise, care, organization, and focus on the health of the athlete. Working with this training staff and a front office who always cares for the health and well-being of their athletes has been a wonderful experience. Sam Hinkie, the President and General Manager of the Philadelphia 76ers, is very similar to Dr. Levin, as they are both extremely bright, focused, organized, and caring. These attributes, present throughout the Sixers organization and Penn Orthopaedics, have made it a fantastic experience with "Together We Build" with the Sixers and for the past five years with Dr. Levin at Penn.

Editorial

Clinical Research Update

Annamarie D. Horan, PhD

The Human Subjects Research (HSR) program in the Department of Orthopaedic Surgery is a subset of the overall musculoskeletal research enterprise in the department. HSR differs in important ways from basic and cadaveric research. Costs and revenues in HSR can vary considerably from study budgets due to many contributing factors that include the high cost of regulatory maintenance and the clinical trial reimbursement process. Historic patient profiles do not guarantee an eligible patient population and stringent study criteria further limits enrollment. It is common for research staff at the University of Pennsylvania Health System to pre-screen hundreds to even thousands of patients before encountering a patient who not only qualifies for a particular study but who is also interested in participation. We thank our dedicated Clinical Research Coordinators and Project Managers for their dedication to improving patient care through research. We are also especially grateful to those of our patients who volunteer their participation in our numerous studies.

In the past four years, the Department of Orthopaedic Surgery has made a considerable investment in the HSR program, and the early returns suggest that our faculty will continue to grow and diversify the departmental portfolio of clinical research (Figure 1). The success of the department's HSR growing program is strengthened by the diversity of the divisions engaged in extramurally sponsored studies. A selection of these studies is shown in Table 1. Of note, there are over 120 active clinical protocols in the department, many of which involve collaborators within the department, within the institution, and at one or more institutions across the country and around the world.

Two of our clinical faculty have been selected to serve as overall study Principal Investigators for upcoming randomized clinical trials. Dr. L. Scott Levin has been selected as the national co-PI with collaborator Dr. Jason Isaacs in an upcoming study to evaluate the superiority of a peripheral nerve graft product. Dr. David Bozentka will serve as the Penn PI for this study. Dr. Frederick Kaplan has been invited by a new pharmaceutical company to be the global PI of the first ever drug trial in the treatment of Fibrodysplasia Ossificans Progressiva (FOP). Dr. Robert J. Pignolo will serve as the Penn PI on this trial. The honor of these leadership roles in clinical research can only be attributed to the renown of these two outstanding faculty. We look forward to being able to report the success of these two pending trials as well as similar recognition for our other faculty in years to come!

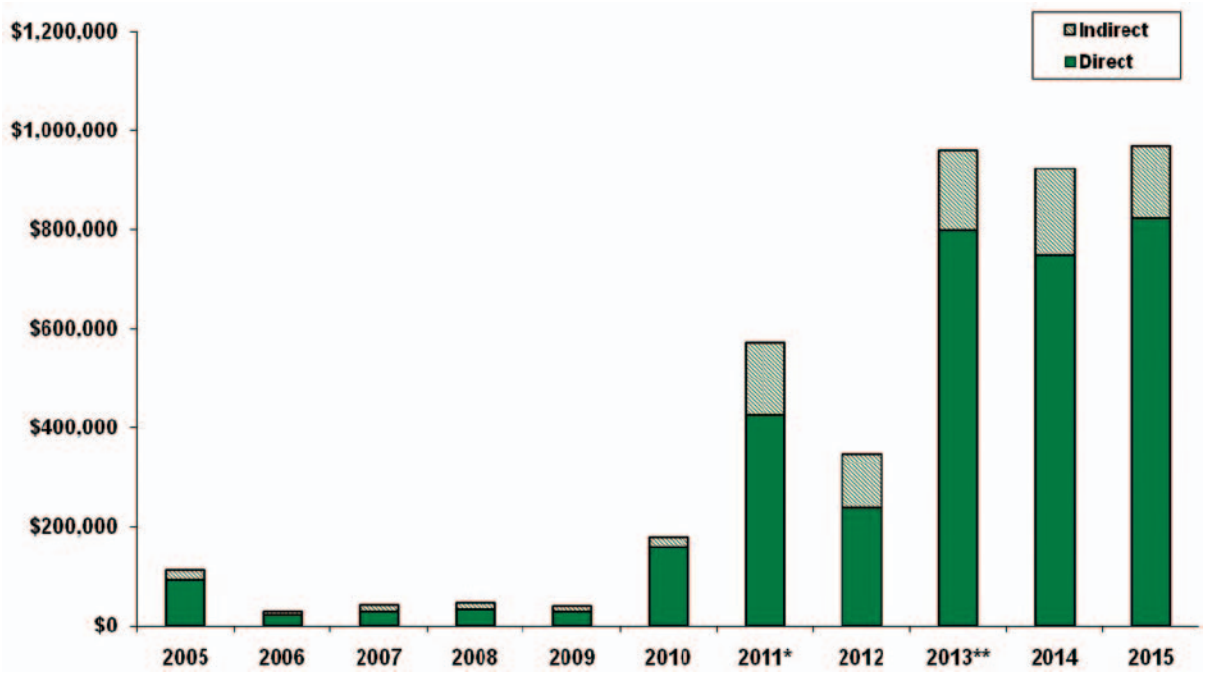


Figure 1. Clinical research revenues in the Department of Orthopaedic Surgery. (FY08-FY15). *FY11 reflects an accumulated back-payment from an industry sponsor as well as a double posting of funds from an NIH grant which ends in FY15.**FY13 information includes two DOD grants in trauma, one of which ended in FY14. Indirects for almost all activity in clinical research is lower than for basic research awards per institutional policy. In the case of federally sponsored clinical research, reduced indirect revenues are realized due to the proportion of funds required to pay other sites and contractors. Funds depicted for FY14 and FY15 are projections and may vary.

Table 1. Representative extramurally sponsored studies

Division & PI	Sponsor	Study Title
Adult Reconstruction		
Gwo-Chin Lee, MD	CD Diagnostics	Acquisition of Synovial Fluid Samples: Creating a Repository for Biomarker Research
	CEM-102 Pharmaceuticals, Inc.	An Open-Label, Multi-Center, Randomized Study to Evaluate the Safety and Efficacy of Oral Fusidic Acid (CEM-102) in Combination with Oral Rifampin for Prosthetic Joint Infection, in Comparison with Standard of Care Intravenous Antibiotic Treatment Regimens, during Two-Stage Prosthesis Exchange.
Eric Hume, MD	DePuy Orthopaedics, Inc.	PMA Post-Approval Study for Ceramax™ Ceramic Hip System
	DePuy Orthopaedics, Inc.	36mm Ceramax™ Ceramic Hip System PMA POST-APPROVAL STUDY: Short to Mid-Term Follow-up of New Study Subjects
Hand		
David Bozentka, MD	University of Michigan	A Clinical Trial for the Surgical Treatment of Distal Radius Fracture in the Elderly: Wrist and Radius Injury Surgical Trial (WRIST)
Shoulder		
G. Russell Huffman, MD and John D. Kelly IV, MD (Co-PIs)	Auxilium Pharmaceuticals, Inc.	A Randomized, Double-Blind, Placebo-Controlled Study Of The Safety And Efficacy Of Aa4500 For The Treatment Of Adhesive Capsulitis Of The Shoulder
Sports Medicine		
Brian J. Sennett, MD	Histogenics Corporation	A Randomized Comparison of NeoCart® to Microfracture for the Repair of Articular Cartilage Injuries in the Knee
Trauma		
Samir Mehta, MD	Hansjoerg Wyss Fund for Orthopaedic Genomics and Immunology*	Biomarker Identification in Fracture healing
Foot & Ankle		
Keith Wapner, MD	Small Bone Innovations	2-Year Post-Approval Study To Investigate The Star Ankle Under Actual Conditions Of Use

*The Hansjoerg Wyss Fund for Orthopaedic Genomicx and Immunology is a generous gift that is shared between Dr. L. Scott Levin, for immunologic research, and Dr. Samir Mehta for genomics research.

Penn Orthopaedics in Nicaragua

Ryan M. Taylor, MD, Mara L. Schenker, MD, Jaimo Ahn, MD, PhD, and Samir Mehta, MD

Through a generous donation from the Biedermann Family, we had the unique opportunity to participate in a medical mission trip to Managua, Nicaragua, organized through Health Volunteers Overseas (HVO). HVO is a private, nonprofit organization founded in 1986 that focuses on delivery and improvement of healthcare internationally with programs in more than 25 countries. The programs include specialties such as primary care, oncology, infectious disease, and general and surgical subspecialties.

In Managua, we were graciously hosted by Dr. Dino Aguilar and Dr. Mario Cuadra, two local orthopaedic surgeons who have both spent time abroad advancing their own orthopaedic knowledge in order to better serve their local population. Dr. Aguilar is a local legend of sorts, who after many years as an instructor at the government hospital, now has his own private practice and is part owner of one of the local orthopaedic implant distributors. Dr. Caudra recently completed his residency at the same teaching hospital and is being developed as a future leader of orthopaedic surgery in Nicaragua. After completing his residency in Nicaragua, he traveled extensively in the United States, doing short fellowships, most recently at the Cleveland Clinic.

We worked mainly out of the government hospital, Hospital Escuela Antonio Lenin Fonseca (HEALF), the same institution where Dr. Caudra had recently completed his residency training. From the moment we entered Fonseca, it was clear that we were there to work. We got a brief tour from Dr. Cuadra, but shortly thereafter we were whisked away to the surgical suite to review radiographs and implants for the coming cases. The operating complex was simple but sufficient, with multiple operating rooms and a common scrub area. The front desk worked not unlike the one at our own institution, and every case performed in the hospital was documented in a massive ledger for later reference. Most of the cases were done under regional anesthesia and the attending anesthesiologists were extraordinarily adroit at placing spinal catheters.

Once we started discussing cases, it was clear that in anticipation of our arrival, they had saved some especially difficult fractures for us to tackle. Radiographs of long discussed cases appeared and were passed around, and there was intense interest as to how we would handle each case. Instinctively, we inquired about what implants were available. Not surprisingly, the selection of implants was minimal and did not include periarticular or locking plates, this being in sharp distinction to what we are used to in the US. Most often the available implants were those that were no longer in circulation for use in American storerooms. Some of the implants readily available tended to be of sizes and lengths that were not often used. Frequently, plates and screws were cut to fit the needs of the particular procedure, and the intramedullary nails used were the best approximation of length and diameter. Principles of fracture fixation, such as the tip-apex distance, are well known by the residents and staff, but often could not be implemented due to the available lag screw lengths. Through it all, the local and visiting surgeons

utilized their creativity to limit the untoward effects of the available resources.

There are several facets of their care system which we found unique and somewhat different than the US. When a patient in the US presents with a fracture, the necessary implants for the case are obtained via a phone call to the control desk of the operating room or to the implant manufacturer. In Nicaragua, the surgeons will write a prescription for the desired implant, and the patient goes to an outpatient implant distributorship to buy their implant. If the patient cannot afford commercial implants (e.g., Smith and Nephew, Synthes, Stryker, Zimmer, etc.), there are options for more generic or inexpensive replicas. Once the implant is purchased, the consultant for that company not only attends the case, but also scrubs in and assists with the surgery.

The similarities between the local surgeons and those of us visiting are striking in the sense that they share the same struggles with fracture patterns and patient disease that we do in the US. The surgeons in Nicaragua are very skilled, just as well-read, and even more creative than many of us in the US. Not only do they tackle the same complex fracture patterns we do, they do it often weeks to months after the initial injury and mostly without the aid of specialized surgical tools and implants.

Our experiences in Nicaragua have been unmatched by anything during residency or in practice. The graciousness of our hosts and the desire to perfect their orthopaedic craft for the benefit of their patient population is unparalleled. At the same time, their willingness to teach us about their culture and their system was also extremely satisfying, a good lesson for us to take away as we host others. We would make this trip again in a heartbeat and recommend it to others. If only we could stay longer and see and experience more….

Penn Orthopaedics in Trinidad

Nicole S. Belkin, MD, and Vincent M. Arlet, MD

Dr. Vincent Arlet, Chief of Orthopaedic Spine Surgery at Penn Orthopaedics, participates in a Scoliosis Research Society-endorsed global outreach program. Through this program, Dr. Arlet partners with Dr. David Toby in Port-of-Spain, Trinidad. Dr. Toby provides orthopaedic care at the Princess Elizabeth Centre of Physically Handicapped Children. Dr. Toby performs an average of 50 spinal deformity procedures annually at the center. Dr. Arlet travels to Trinidad 3–4 times per year to perform complex surgical cases necessitating two spine surgeons. In addition, Dr. Arlet brings with him volunteer equipment and staff to perform intraoperative neuromonitoring, donated implants and, frequently, a resident assistant. For Dr. Arlet, this is commendable outreach work to say the least, but for the residents, it is a potentially career altering experience. It is difficult to express in words the gravity of experiencing different cultures in the role of healthcare provider. For a US trainee, it is enlightening to experience firsthand what can be accomplished surgically with relatively sparse resources and the impact of that care on the patient population. Additionally, the opportunity to observe pathology not frequently encountered stateside, such as scoliosis deformity secondary to polio or neuromuscular scoliosis as a sequelae of Guillain-Barré Syndrome, is invaluable. Aside from the educational enrichment provided, the venue itself provided a rich cultural experience. As the

southernmost island of the Caribbean with a truly melting pot heritage, combining British, French, Dutch, and Spanish influence, Trinidad provides an pleasant dry season, diverse culinary traditions, ethnically diverse peoples, and world-class rum. I feel very blessed to have had the opportunity to participate in this program and would not hesitate to do so again in the future.

From the Penn Orthopaedics Human Tissue Lab

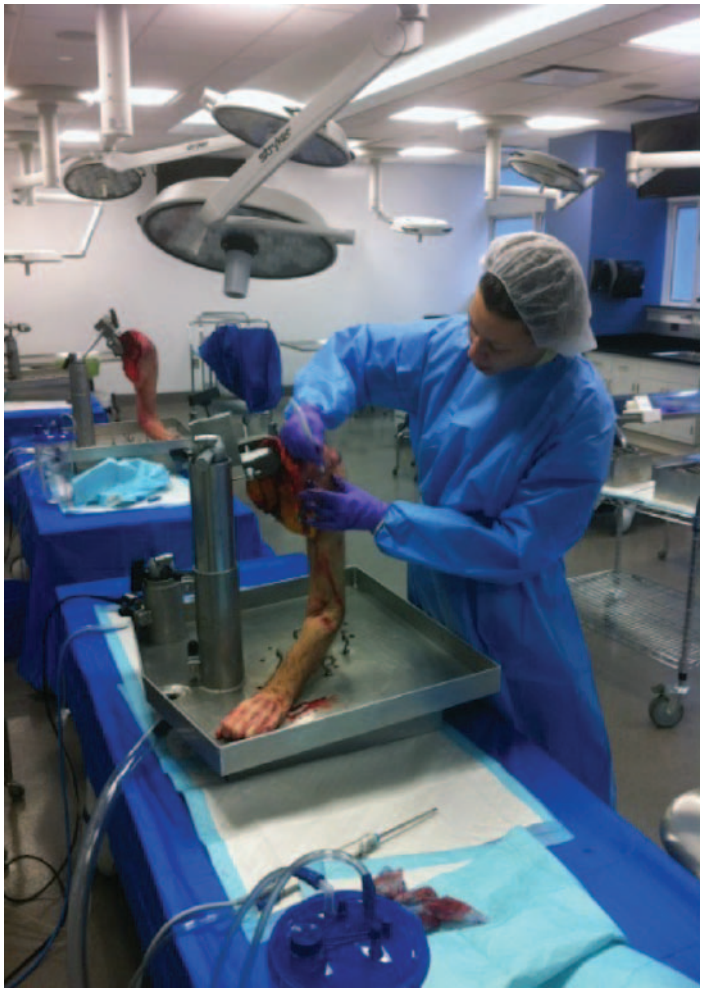
Joshua A. Gordon, MD

The Penn Orthopaedics Human Tissue Lab (HTL) was founded under Dr. L. Scott Levin on May 1, 2011. Now in its third year of use, it continues to exemplify Penn's commitment to educating the next generation of leaders in orthopaedic surgery. It has increasingly been an integral part of our weekly curriculum and has provided a meeting place for specialists across the region to congregate and teach. The exchanges that have taken place in the HTL over the past year have been lively, fun, and very earnestly directed at educating younger orthopaedic surgeons either in early phases of their careers or still in residency and fellowship.

This year, a regular wet arthroscopy lab session was added to monthly upper extremity dissections and visiting professor workshops as part of the Penn Orthopaedics hands-on resident education curriculum. In addition to these regular sessions, Penn has been the grateful host to numerous courses and symposia: the Cartilage Repair Symposium, AAOS Live-Streaming Hip Replacement Sessions, the International Congress for Joint Reconstruction (ICJR) Philadelphia Revision Arthroplasty Course, the Foundation for Orthopaedic Trauma Upper Extremity Course, the American Society for Reconstructive and Transplant (ASRT) Surgery second annual Face and Hand Transplantation Course, the first annual Microsurgical Skills Cadaver Course for Hand Fellows and Residents, and a session with Dr. Reinhold Ganz from Bern, Switzerland, held this past April. These listed courses only begin to highlight how this addition to our facilities has transformed our education as orthopaedic residents. In this section of *UPOJ*, we highlight two such events that were well attended by residents, fellows, and faculty.

The Penn Orthopaedic community is particularly grateful to the faculty who have dedicated their time and traveled sometimes very long distances to contribute to our education. The residents hope that in the future, we have the opportunity to participate in a similar way while visiting our national and international colleagues.

Of course, this brief editorial would not be complete without thanking Lorianne Kish-Burdsall and those who help her manage the HTL. They work tirelessly so that it is readily available for resident education, research, and courses.



A regularly scheduled wet arthroscopy lab session.

Penn Microsurgical Skills Cadaver Course for Hand Fellows and Residents

T. Shane Johnson, MD, Joshua A. Gordon, MD, and L. Scott Levin, MD, FACS

This past November marked the first annual Penn Microsurgical Skills Cadaver Course for Hand Fellows and Residents.The two-day course was comprised of a collaborative effort by an international group of recognized experts in hand and microsurgery who convened in Philadelphia to teach the next generation of hand and microsurgeons.

Module I	Intrinsic flaps (first dorsal metacarpal artery, heterodigital, homodigital, Moberg, V-Y, cross-finger), radial forearm flap, posterior interosseous flap
Module II	Lateral arm flap, scapular flap, latissimus dorsi flap, serratus anterior flap, medial femoral condyle flap
Module III	Fibula flap, toe transfer, brachial plexus approaches (supraclavicular, infraclavicular), nerve transfers (spinal accessory to suprascapular, Oberlin's, triceps to axillary, distal AIN to ulnar motor)
Module IV	Anterolateral thigh flap, gracilis flap, digit replantation

Dr. L. Scott Levin directed the course with invited faculty including:

- Dr. Allen Bishop, Mayo Clinic
- Dr. David Bozentka, University of Pennsylvania
- Dr. Heinz Bürger, Facharzt Für Unfallchirurgie, Salzburg, Austria
- Dr. Benjamin Chang, University of Pennsylvania
- Dr. Geoffrey Hallock, Lehigh Valley Hospital, Allentown, PA
- Dr. James Higgins, Curtis National Hand Center
- Dr. Neil Jones, University of California Irvine
- Dr. Stephen Kovach, University of Pennsylvania
- Dr. Scott Kozin, Shriners Hospital for Children, Philadelphia, PA
- Dr. Ines Lin, University of Pennsylvania
- Dr. David Steinberg, University of Pennsylvania
- Dr. Milan Stevanovich, University of Southern California
- Dr. Joseph Upton, Beth Israel Deaconess Medical Center
- Dr. Eric Zager, University of Pennsylvania

The course was attended by an international group of hand surgery fellows, orthopedic surgery residents, and practicing hand surgeons and had a faculty-to-student ratio of one-to-four during the dissection modules.This high faculty-to-participant ratio was seen as essential. As the American Society for Surgery of the Hand has recognized an ongoing deficiency in microsurgical training, both in residency and fellowship, such courses offer a critical means of covering a broad range of procedures and filling gaps in sometimes varied clinical exposure. Cadaver dissections were performed in the University of Pennsylvania Human Tissue Laboratory with in-depth exploration of cutaneous, muscular, musculocutaneous, and osteocutaneous flap options. Modules covering digit replantation, toe-to-hand transfer, brachial plexus exposure, and common nerve transfers were also included (Table 1).

Post-course survey results notably found that the majority of respondents were very satisfied with the overall course as well as with individual modules. Plans for this year's course are already underway, with a focus on increasing participant numbers.

International Congress for Joint Reconstruction Inaugural Philadelphia Revision Arthroplasty Course

James E. Murphy, MD, and Joshua A. Gordon, MD

This past April, the International Congress for Joint Reconstruction welcomed a distinguished list of faculty from around the country to participate in the inaugural Philadelphia Revision Arthroplasty Course. The course was held on April 26-27, 2013, at the Human Tissue Lab (HTL) at the University of Pennsylvania and was chaired by Dr. Charles Nelson, Chief of the Adult Reconstructive Division at the University of Pennsylvania. In addition, Drs. Craig Israelite, Gwo-Chin Lee, and Neil Sheth served as Course Directors.

Guest faculty included:

- Dr. Fred D. Cushner, Insall Scott Kelly Institute for Orthopaedics and Sports Medicine
- Dr. William A. Jiranek, Virginia Commonwealth University Medical Center
- Dr. Mark A. Hartzband, Hartzband Center for Hip and Knee Replacement
- Dr. Matthew S. Austin, Rothman Institute
- Dr. Michael P. Bolognesi, Duke University
- Dr. Nitin Goyal, Anderson Orthopaedic Clinic
- Dr. Steven B. Haas, Hospital for Special Surgery
- Dr. Arlen D. Hanssen, Mayo Clinic
- Dr. Eric L. Hume, University of Pennsylvania
- Dr. Norman A. Johanson, Drexel University College of Medicine
- Dr. Young-Min Kwon, Massachusetts General Hospital
- Dr. Adolph V. Lombardi Jr., The Ohio State University
- Dr. Thomas H. McCoy, OrthoCarolina Hip and Knee Center
- Dr. Michael Meneghini, Indiana University School of Medicine
- Dr. David G. Nazarian, University of Pennsylvania
- Dr. Wayne G. Paprosky, Rush University Medical Center
- Dr. Aaron G. Rosenberg, Rush University Medical Center
- Dr. Giles R. Scuderi, Insall Scott Kelly Institute for Orthopaedics and Sports Medicine
- Dr. Bryan D. Springer, OrthoCarolina Hip and Knee Center

The course had sessions aimed at the full spectrum of reconstructive cases. Each day started with a didactic session based on expert opinion and focusing on tips and tricks for most aspects of revision arthroplasty of the hip and knee. Additionally, the expert faculty shared some of their most recent research and progress in the field of adult reconstruction. Each afternoon began with a video demonstration followed by participant cadaver dissection, with the first day focused on revision arthroplasty of the hip and the second focused on revision arthroplasty of the knee. Each of the visiting faculty members provided insight and surgical "pearls" of wisdom picked up over years of experience. The course provided participants with hands-on practical experience. The success of the course was evident based on participant feedback and the overwhelmingly positive responses from regional and national surgeons.

As an added benefit, the weather during the course was spectacular, showcasing a vibrant Philadelphia with ample opportunities for participants to eat, tour, or shop after the hands-on portion of the course wrapped up each day. The University of Pennsylvania was alive with the concurrently held Penn Relays, which provided an excellent backdrop for the teaching that occurred in the HTL. Lastly, this course highlighted Penn Orthopaedics as a world leader in Adult Reconstruction.

Administrative Chief Residents' Perspective

Mara Schenker, MD, Adam Griska, MD, and Chancellor Gray, MD

It seems like yesterday that Dr. Lackman welcomed us to Penn. "Residency….it will go by fast," is what I recall him saying, as he distributed our white coats and cell phones.

I didn't believe him.

It seems like yesterday that I looked up to Karen Boselli, Jonas Matzon, and Eric Richetti, our administrative chief residents as interns, thinking how much they knew about orthopaedic surgery and what tremendous doctors they were.

I knew I had a lot to learn.

Five years later, I was the rounding chief resident at HUP on the first day of the new interns. One of our brand-new interns in his brand-new creased white coat dropped the entire bucket of dressings on the floor, and did not realize that the beeping pager belonged to him. I laughed and called him a "rookie." (NB: he has since done a fantastic job). It was today that I took a junior through a subtrochanteric femur fracture. It went well. And it won't be that long until we're headed off to our fellowships. It won't be that long before we'll be in practice. Residency did fly by. Dr. Lackman didn't lie. Somehow, sometime, somewhere, we made that transition from "rookie" to chief resident.

In the last several years, we have seen an influx of new faculty, a new chairman, new residency directors. We have made mistakes, learned from our mistakes, and have become orthopaedic surgeons. Some of the most influential people along our path have been our administrative chief residents, including: Jonas Matzon, Karen Boselli, Eric Richetti, Nirav Patel, Stephan Pill, Derek Donegan, Andy Kuntz, Surena Namdari, John Scolaro, Eileen Crawford, and Jason Hsu. We are forever indebted to Drs. Levin, Israelite, Mehta, Ahn, as well as our faculty and resident mentors who have taught us orthopaedic surgery.

When we were asked to serve in the role of Administrative Chief Resident for 2013-14, we humbly accepted it as a way to give back to a system that had given us so much. Like our predecessors, we set goals for what we could accomplish in a short year for the good of the residency. This included an iPad reading curriculum, first by obtaining an iPad mini for each resident with the support of the Department. After that, we formalized a reading curriculum, which includes 10-15 review or classic articles for each rotation. As a junior resident, we had no idea where to begin our reading. With the new iPad reading curriculum, we hope that our junior residents have a launching point for self-directed reading and learning. We hope that they carry this forward to create additional online educational resources. The second was a curriculum on "Leadership and Leaving the Nest." One of the resounding gaps in our formal education was the ACGME competency on "Systems Based Practice." This three-month curriculum held in the evenings during our Academic Night includes lecturers from our own Department, from Wharton business school, and from faculty from across the country on topics ranging from leadership to practice finance to quality improvement to work/life balance and contract negotiations. In addition, with the guidance and mentorship of our faculty, we organized the core curriculum and visiting professor Grand Rounds curriculum and invited a variety of speakers from around the world, including:

- *Ralston Lecture:* Dr. Kevin Black, Professor and C. McCollister Evarts Chairman, Penn State Hershey
- *OREF Lecture:* Dr. William Obremskey, Professor of Orthopaedics, Vanderbilt University
- *Leo Leung Lecture:* Dr. David Ruch, Chief, Orthopaedic Hand Service, Duke University
- *Stein Lecture:* Dr. Kevin Bozic, William R. Murray Professor and Vice Chair, University of California, San Francisco
- *Tronzo Lecture:* Professor Reinhold Ganz, Bern, Switzerland
- *Nicholson Lecture:* Dr. James Sanders, Professor of Orthopaedics, University of Rochester
- *Inaugural Turen Lecture:* Dr. Andrew Burgess, Professor and Vice Chairman, UT Houston Medical Center
- *AO Spine Lecture:* Dr. Howard An, Professor of Orthopaedic Surgery, Rush Medical Center

Thank you to everyone at Penn for a great residency. We hope that we were able to give back a small percentage this year to all that you have given us.

Editorial

Penn Orthopaedics Service Summary

2013 at a Glance

Lori Gustave, Fabian Marechal, and Ryan Gonzales

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 2013

A total of 36 clinical faculty, 42 medical residents, and 12 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 2013:

- Total Patient Visits: 78,940
- Total Inpatient Cases: 4,758
- Total Outpatient Cases: 4,462
- Total Cases: 9,220

2013 Total Cases

Specialty	Total Cases
Joint Replacement	2,907
Trauma and Fracture	1,390
Hand Surgery	1,362
Sports Medicine	1,182
Foot and Ankle	1,004
Shoulder and Elbow	865
Spine	248
Neuro-Orthopaedics^	200
Orthopaedic Oncology*	62
Total	9,220

** Includes volume from April to December 2013*

^Includes volume from the Children's Hospital of Philadelphia

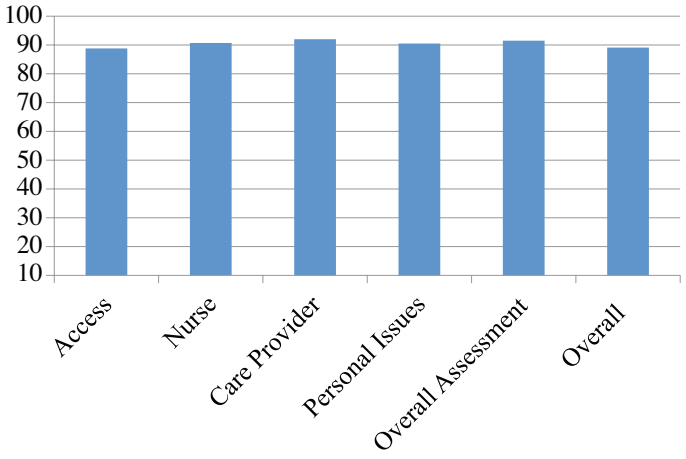
Physician Relationships

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, particularly in specialties such as trauma and orthopaedic oncology. The majority of physician-to-physician consultations and referrals are from the tri-state area, consisting of Pennsylvania, New Jersey, and Delaware. In addition, physicians from 21 other states across the US consulted with Penn Orthopaedics on behalf of their patient.

Patient Satisfaction

Over the past several years, an increased focus has been placed on meeting the needs of the musculoskeletal patient. Penn Orthopaedics has improved patient satisfaction by embracing innovation, implementing new check-in kiosks, a new series of scheduling questionnaires, 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 89.1.

2013 Patient Satisfaction



Penn Orthopaedics is a top program in the Greater Philadelphia region and is ranked among the nation's best by *US News & World Report.*

A Tribute to Anthony (Tony) Searles (11/3/37–2/28/14)

Frederick S. Kaplan, MD

Known endearingly as "Dr. Tony" to generations of admirers, Anthony (Tony) Searles died in Philadelphia on February 28, 2014, at the age of 76 following a long and valiant struggle.

For nearly four decades, attendings, fellows, residents, students, and patients from the University of Pennsylvania, the region, and the world, entered his iconic domain at the Hospital of the University of Pennsylvania (HUP) to seek his advice, counsel, and wisdom, and to garner help in plying his legendary and artistic brand of therapeutic magic.

Tony Searles was an icon, a living legend, not only in the tight circles of Philadelphia Orthopaedics but more widely throughout the region and the nation. His cast room on 2 Silverstein at HUP was not the grandiose corner office of Department Chairman or the sanctified operating suite of the surgical staff, but his signature and legendary headquarters was where he presided in solitary command for nearly four decades, and where the most difficult orthopaedics battles were often won or lost.

Tony's cast room was much more than an orthopaedic service station where fractures were reduced or gypsum encasements were applied. It was a command center and artist's studio where decisions on orthopaedic care were made in high-level collaboration and consultation between traditionally trained orthopaedic surgeons and a master craftsman and clinician.

Carl T. Brighton, MD, PhD, former Chairman of Orthopaedic Surgery at Penn (1977-1993) recounted, "During my early days as a junior faculty member, fresh out of the Navy, I remember meeting Tony. He was already working in orthopaedics. I was instantly impressed with his intellect and artistry. It was immediately obvious to me that he was special. He thought deeply about each patient. He was highly intellectual and immensely practical. He asked great questions about therapy, and I could see by the way he handled plaster that he was far better than most of the faculty in this regard. I asked him to put on all my casts. Soon, he was doing the same for the entire orthopaedics faculty. Tony was very special."

In an article entitled, "Casting Call," in *HUPDATE* several decades ago, Rebecca Harmon discussed Searles's early days. "As a young man, he wanted to be an artist, so he studied sculpture at the Philadelphia College of Art but got drafted for the Korean Conflict." Searles recalled, "They asked me what I did, and I told them I was a sculptor, so they trained me in facial reconstruction. It was a sobering job making molds for implantation on soldiers who had parts of their faces blown apart by mines or bullets." Harmon continued, "But, it was a job at which the young draftee was extremely successful. He was so successful that he was conscripted as a surgical assistant and was sent to Northwestern University for formal medical training as a surgical assistant in prosthetic surgery." Later, Searles worked with several European physicians in both France and Switzerland, and during those days he remembers making his own plaster rolls. Searles recalled, "Large strips of gauze were sprinkled with plaster and dipped in buckets of water, and the water just had to be just the right temperature—not too hot and not too cold—or the plaster would dry too quickly."

Searles recalled his philosophy, "I have my own theory of medicine. Seventy-five percent of a diagnosis comes from listening to a patient; fifteen percent comes from Xrays; and the remaining ten percent from lab results. If we just treat medical problems, then we are doing assembly-line medicine. But, if we treat the whole individual, by getting to know a little bit more about them other than their medical problems, we are practicing good medicine."

Searles lived and breathed this philosophy during decades of practice and teaching.

"I would probably give a mother with two preschoolers a fiberglass cast instead of a plaster cast, which takes three days to dry, so she would have immediate mobility if the injury allowed."

"And you can't just look at a patient and say, 'Well, this guy had a fractured bone.' You have to look at him and say, 'This guy had a fractured bone, and two months ago, he had a myocardial infarction, so what can you do to keep the cast lightweight so there is no extra stress on his heart?'" Searles said.

Tony at the beginning of his art career

HUP physicians quickly came to depend on Searles's immense talent and creativity.

Searles laughed when he recalled his greatest creation. "A southern socialite came to HUP because of a broken bone in her upper arm," he says. "She says she needed a cast which would not interfere with her clothes or her ability to give and attend cocktail parties. So, I made her what I call my 'Venus de Milo' cast, which allowed her to wear her off-the-shoulder dresses, and pearls, and stuff."

Nothing was too difficult for Searles, nor did he ever lack for a challenge. He always had a great smile, a cheerful attitude, and a colorful bow tie, and made the patient comfortable and at ease with engaging stories and anecdotes that could have filled volumes. Tony could talk sports, politics, history, chemistry, horsemanship, motorcycles, meteorology, material sciences, astrophysics, wine tasting, engineering, art, movies, theater, and restaurants, and that was just for starters! Whether it was a university president, a matriculating freshman, or a member of the housekeeping staff who was in his cast room, Tony would focus them on something other than their orthopaedic problem and, in doing so, begin the process of healing and rehabilitation.

A retired nurse whose daughter was treated by Searles recalled, "He was a man who practiced what he preached. My daughter, who had undergone a knee fusion, could not tolerate anesthesia because of a rare infection. So, when it was time to remove six stainless steel pins from the bones of her legs, Tony was called in. Even though I am a nurse, I could not believe what I saw. Tony used Lamaze breathing techniques and his personal knowledge and skills to gently coax my daughter through the discomforting procedure. While he held her leg, Tony taught her to breathe and talked her through it. After one pin was out, he gave her a little rest, and then took another out. It took two hours to remove all six pins. Tony was fantastic. I was overwhelmed with the compassion with which he helped my daughter."

The Black Baron

In addition to the accolades for his orthopaedic work, Searles was a folk hero and rock star to generations of Penn medical students. In 1997, the senior class of the University of Pennsylvania School of Medicine honored Searles at their graduation ceremony with the highest honor that the school could bestow on an allied health professional. Searles received the University of Pennsylvania School of Medicine Award for Excellence in Teaching by an Allied Health Professional, an award that was created specifically for him. The award was bestowed upon Searles by William N. Kelley, MD, PhD, Dean of the School of Medicine and by Gail Morrison, MD, Senior Vice Dean for Education.

In the testimonial letters that supported his nomination and award, many former students noted that Tony was singularly responsible for their trajectory into orthopaedics. Many others who did not pursue a career in orthopaedics said that Tony taught them the most practical lesson that they learned in medical school, to listen carefully to patients' stories and to be a caring and compassionate doctor.

Ellen Passloff, MD (Penn Medicine '90), a former student of Searles's and pediatrician now practicing in Seattle, WA, commented, "Because of Tony's amazing example, I have learned to truly connect with all of my patients, no matter how young they may be. I spend the majority of their appointment time REALLY listening to every detail of their symptoms and concerns. In addition to being a wonderful teacher, Tony was a good friend, an incredible mentor, and an emergency rescuer with his orthotic devices! He cured me of all of the injuries I sustained while training for both the 1988 and 1989 New York City Marathons. He made a special orthotic for my Morton's neuroma and a great wrist splint to heal the injury I sustained when I fell off my bike on the way back from the Wissahickon Drive, where I had just completed a twenty mile training run. Tony was truly gifted in the art of plaster and fiberglass creations, and he regaled me with amazing stories while performing his magic! His wonderful smile and spirit are permanently engraved in my memory. He was really one of the finest teachers I have ever had. I will miss him dearly."

Tony clearly enjoyed teaching medical students. For generations, they entered his cast room for the required "Principles and Practice of Splinting and Casting," but they

left with far more than knowledge of casts and splints. Tony recalled, "When I first started teaching the medical students, I thought the course was boring so I livened it up by including historical information, letting them cast one another, and observing patients." Those efforts brought handsome dividends in accolades, testimonials, and awards for Searles from generations of medical students and ensured that his legacy would be forever enshrined in the Pantheon of Penn Medicine.

Born in Philadelphia on November 3, 1937, Anthony Searles spent his childhood intrigued by art during a time of war. He loved sculpting and painting. He attended the Philadelphia College of Art before serving in the navy in Korea. During the Vietnam War, he served in the army and later completed his medical corps service at Fort Dix. His early post-military employment was at Atlantic City Hospital and later Graduate Hospital, where he worked with orthopaedic surgeons, Dr. Jesse Nicholson and Dr. James Nixon.

Searles came to the University of Pennsylvania in the mid-1960s, where he worked with Dr. Elliot Stellar in Anatomy before joining the Department of Orthopaedic Surgery, where he prevailed for nearly 40 years. Searles retired from orthopaedics in May 2013, at 75 years of age, only nine months before his untimely death.

Tony was a family man. He is survived by his wife Donna, a brother, two sisters, children, grandchildren, and great-grandchildren. He was "Pop-pop" to his loved ones. He was not a religious man but was deeply spiritual, and respected all religions and all beliefs.

Tony had a great enthusiasm for horsemanship and for history. He enjoyed being an urban horseman, serving in this important capacity to bring history to youngsters. On weekends, he could be seen riding a horse, dressed in full Civil War regalia, as a member of the "Buffalo Soldiers," a reenactment unit that paid homage to the four all-black army units formed by Congress at the end of the Civil War.

Tony standing in front of a portrait of him painted by another artist.

Tony enjoyed collecting antique guns, knives, vintage Port, and bow ties. He loved fly-fishing and kayaking, fine restaurants, and motorcycles.

"Tony was as legendary in his neighborhood as he was at work. He was a big part of the community," said Donna Casagrande, Assistant Director of the Office of Admissions at Penn Medicine, and Tony's beloved wife and partner for 33 years. "He enjoyed coming home after a long day, walking the dog, and smoking a cigar – every night. Tony loved music, all kinds of music: classical, Motown, dance music, the Blues, jazz, and gospel (in particular the Dixie Hummingbirds). He was my Tony."

Tony was part African-American, part American-Indian, and just plain American, yet there was nothing plain about him. His life encompassed so much of American culture and American traditions. He was outspoken on politics, a distinguished veteran, and a true patriot.

On hearing news of his passing, accolades and testimonials poured in from the region and the world. "Tony inspired a generation of medical students. He was a great person, unbelievably energetic, talented, charismatic, and enthusiastic, and we will miss him greatly," one wrote. Another wrote, "He was a great guy. I never saw anything but a smile on his face. I know he put a lot of smiles on a lot of other people's faces as well." Yet another wrote, "He helped many patients and young physicians. I have missed him every day he has not been at HUP. We will continue to miss him." And another wrote, "Tony knew more about orthopaedics than most people, and he always had a treatment plan. Clinic hasn't been the same since he left." Still another noted, "Tony was a brilliant clinician and a favorite with the students. He won major teaching awards and was the only person in the universe who could roll plaster without tucks. His loss is a sad day for all of orthopaedics."

Many noted that it would be a great honor to name the cast room in the new orthopaedic institute after Tony and that there should be a portrait there for future generations of medical students, residents, fellows, attendings, and patients to ab-

sorb the legacy of this great man. Dr. Scott Levin, Chairman of the Department of Orthopaedic Surgery, wrote, "Consider it done."

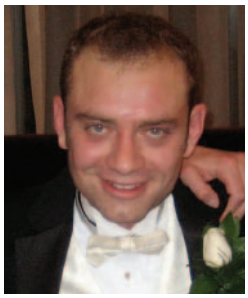
A retired professor wrote, "Tony was a unique person with much knowledge, skill, experience, a strong work ethic, and a warm and helpful personality. He certainly will be missed." Another orthopaedic attending wrote, "I was privileged and honored to work with this prince of a man for the past 38 years. He was a wonderful mentor and friend. He will be sadly missed by all of us, by our grateful patients, and by an entire generation of Penn medical students who all knew him, loved him, and deeply respected him as we all did." A professor of orthopaedic surgery, and one of Tony's former students wrote, "I will never forget him. His approach to life and his dedication to the concept of lifelong learning and to his many students and patients were exemplary. We all learned from him. I am honored to have known him." Another orthopaedic professor and former student of Searles wrote, "Tony was loved by all. His skill and knowledge were unsurpassed. The good old days of long leg casting with windows and wedging, ischial weight bearing, hip spicas, the best Unna boot in the business may be a lost art but live on in the hundreds of trainees he helped educate." A professor of orthopaedic surgery and department chairman at a distinguished university in the Midwest wrote, "Tony is now and was in his time, a legend. We have lost a great man, friend, and teacher."

Tony used every thread in his rich cultural and social loom along with his devoted work ethic, discerning eye, and keen intellect to weave an intricate professional tapestry that was uniquely his own. Tony's widow, Donna, noted, "Tony was the most interesting man in the world. He was like the Dos Equis man, that bearded, debonair gentleman in his 70s, who believed that life should be lived interestingly. Tony was a true Renaissance man. He didn't have a favorite color. Color was his favorite color. He didn't have a favorite movie. Movies were his favorite movie. He didn't have a favorite bow tie. Bow ties were his favorite bow tie. Tony lived a remarkable life, larger than all of us."

One of my patients who suffered from a rare genetic disease that locked her body in a state of permanent immobility loved to stop in and visit Tony on her appointments at the hospital. She often told me that Tony would always find time to get her a soft pillow or a bendable straw no matter how busy he was, something to make her difficult life easier and more comfortable. "But most of all," she said, "He made me smile and laugh. Dr. Tony was a great man."

Tony's vision of heaven. There, the fish are always biting.

Chief Residents



Hassan Alosh, MD

Hometown: Fairfax, Virginia
Undergraduate: University of Maryland
Medical School: Johns Hopkins University
Fellowship: Rush University Arthroplasty Fellowship
Future directions: Academic arthroplasty
Highlights: Dedication to improving the residency by Drs. Levin, Mehta, Israelite, and Ahn. Tremendous teaching and commitment to education by our joints and trauma faculty.

Christina F. Endress, MD

Hometown: Bloomfield Hills, Michigan
Undergraduate: University of Michigan
Medical School: University of Michigan Medical School
Fellowship: Indiana Hand to Shoulder Fellowship
Future directions: Returning to Michigan for private practice in hand and upper extremity surgery.
Highlights: My co-residents; hand surgery with Dr. Bozentka, Dr. Levin and Dr. Steinberg; Health Volunteers Overseas trip to Nicaragua with my parents and Dr. Donegan.

Chancellor F. Gray, MD

Hometown: Wexford, Pennsylvania
Undergraduate: Princeton University
Medical School: Jefferson Medical College of Thomas Jefferson University
Fellowship: University of California at San Francisco Adult Reconstruction Fellowship
Future directions: Join a practice with a focus on total joint reconstruction where I can be involved in resident education
Highlights: Getting to know my fellow chiefs and the faculty through the last few years and becoming a real part of the Penn Orthopaedics family as well as learning from and teaching all of my co-residents.

Adam T. Griska, MD

Hometown: Penn Valley, Pennsylvania
Undergraduate: Brown University
Medical School: Tufts University School of Medicine
Fellowship: Tufts Medical Center Combined Hand Surgery Fellowship
Future directions: Hand and upper extremity surgery
Highlights: Hand Surgery, Trauma, Sports, Shoulder and Elbow, and Pediatric rotations. Additionally I enjoyed my overseas outreach experience in Nicaragua, my community orthopaedics rotation at Bayhealth, and my experience serving as an Administrative Chief Resident. Ultimately, my greatest highlight was meeting my fiancée on Dulles 6.

Sunil S. Jani, MD, MS

Hometown: Nutley, New Jersey
Undergraduate: University of Pennsylvania
Graduate School: University of California at San Francisco
Medical School: Rutgers University Robert Wood Johnson Medical School
Fellowship: Taos Orthopaedic Institute Sports Medicine Fellowship
Future directions: Sports medicine practice
Highlights: I am very appreciative for my knowledge, experience, and growth under the attendings at Penn. Thank you to the mentors who will be with me throughout my career (including the entire sports medicine faculty). A special thank you to my caring family for their limitless love and support.

Mara L. Schenker, MD

Hometown: Pittsburgh, Pennsylvania
Undergraduate: University of Pittsburgh
Medical School: University of Chicago Pritzker School of Medicine
Fellowship: Harborview Medical Center Trauma Fellowship
Future directions: TBD - definitely research and clinical trauma practice, either in academics or semi-private academics.
Highlights: They are too numerous to name, but if I had to list them: excellent teaching and mentorship from the attending faculty; spending time on the trauma service; our leadership (Drs. Levin, Israelite, Mehta and Ahn) and their commitment to making Penn ever better; the lab year under the guidance of Dr. Mauck; my fellow residents; and last but not least Barb Weinraub - they simply don't make them like her anywhere else.

Rehan S. Shamim, MD

Hometown: Somerset, New Jersey
Undergraduate: Princeton University
Medical School: Rutgers University Robert Wood Johnson Medical School
Fellowship: University of California at Los Angeles Sports Medicine Fellowship
Future Direction: Orthopaedic practice with a focus on sports medicine
Highlights: My five years at Penn have been a transformative experience. I am so fortunate to have trained under such excellent mentors, especially the sports medicine and trauma faculty. I will also never forget being in the trenches with all of my fellow residents, and our late night runs to the CHOP cafeteria and Wawa (or anywhere else that was open!) in between trauma consults and OR cases. Finally, thanks to my mom and dad for always being a support through the demands of residency, and to my wife, Ferheen, whose smile has always been a shining light that I looked forward to coming home to after every day of work.

U·P·O·J

Current Residents

Clinical Year 4

Nicole S. Belkin, MD*

Undergraduate:
University of Florida

Medical School:
University of Florida

Fellowship:
Sports Medicine, HSS

J. Gabe Horneff III, MD

Undergraduate:
Rutgers University

Medical School:
University of Pennsylvania

Fellowship:
Shoulder and Elbow, Rothman Institute

Kevin J. McHale, MD

Undergraduate:
LaSalle University

Medical School:
Thomas Jefferson University

Fellowship:
Sports Medicine, MGH

Christos D. Photopoulos, MD

Undergraduate:
McGill University

Medical School:
Dartmouth

Fellowship:
Sports Medicine, Kerlan-Jobe Orthopaedic Clinic

Matthew P. Sullivan, MD

Undergraduate:
Tufts University

Medical School:
Boston University

Fellowship:
Trauma, Harborview Medical Center

Ryan M. Taylor, MD

Undergraduate:
Dartmouth

Medical School:
UT – Southwestern

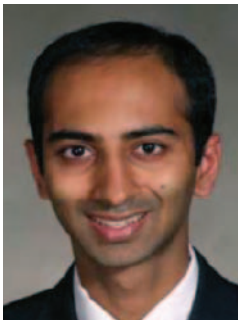
Fellowship:
Trauma, UT Houston

Stephen J. Torres, MD

Undergraduate:
University of Florida

Medical School:
Albert Einstein

Fellowship:
Deferred (Military)



Pramod B. Voleti, MD*

Undergraduate:
Princeton

Medical School:
SUNY Downstate

Fellowship:
Sports Medicine, HSS

** Six-Year Research Track*

Clinical Year 3

P. Maxwell Courtney, MD

Undergraduate:
Washington and Lee

Medical School:
Georgetown

Stephen Y. Liu, MD

Undergraduate:
Tufts University

Medical School:
Tufts University

Michael H. McGraw, MD

Undergraduate:
Howard University

Medical School:
Howard University

Christopher M. Melnic, MD

Undergraduate:
Boston College

Medical School:
Tufts University

Andrew H. Milby, MD*

Undergraduate:
Washington University

Medical School:
University of Pennsylvania

Nicholas Pulos, MD

Undergraduate:
University of Pennsylvania

Medical School:
University of Pennsylvania

Jonathan B. Slaughter, MD

Undergraduate:
University of Pennsylvania

Medical School:
Wright State

Sarah M. Yannascoli, MD*

Undergraduate:
Cornell

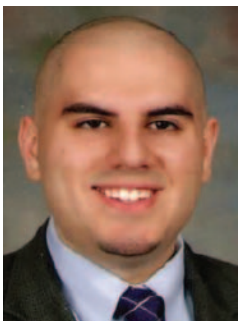
Medical School:
Albert Einstein

Clinical Year 2

Jason B. Anari, MD

Undergraduate:
College of New Jersey

Medical School:
UMDNJ



Tyler R. Morris, MD*

Undergraduate:
University of Pennsylvania

Medical School:
Drexel

Alexander L. Neuwirth, MD*

Undergraduate:
Rutgers University

Medical School:
UMDNJ

Philip A. Saville, MD

Undergraduate:
University of Leicester

Medical School:
University of Leicester

** Six-Year Research Track*

Russell N. Stitzlein, MD

Undergraduate:
Miami University

Medical School:
Cleveland Clinic–Lerner College

Michael T. Talerico, MD

Undergraduate:
Notre Dame

Medical School:
Saint Louis University

Nathan A. Wigner, MD, PhD

Undergraduate:
North Carolina State

Medical School:
Boston University

Chase Woodward, MD, MPH

Undergraduate:
Northwestern University

Medical School:
Northwestern University

Clinical Year 1

Keith P. Connolly, MD

Undergraduate:
Michigan State

Medical School:
Central Florida

James M. Friedman, MD*

Undergraduate:
Duke University

Medical School:
Duke University

Cody D. Hillin, MD*

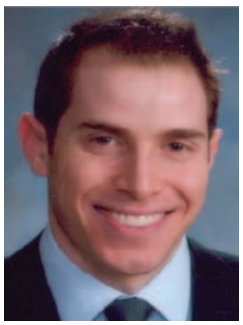
Undergraduate:
University of Rochester

Medical School:
Baylor

Daniel P. Lim, MD

Undergraduate:
USC

Medical School:
USC



Joshua C. Rozell, MD

Undergraduate:
Emory University

Medical School:
Drexel

Joshua T. Steere, MD

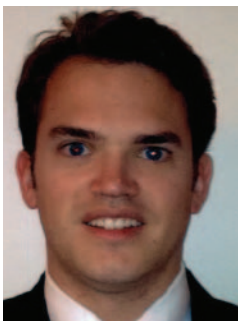
Undergraduate:
Creighton University

Medical School:
Loyola University

Chia H. Wu, MD, MBA

Undergraduate:
University of Pennsylvania

Medical School:
University of Pennsylvania



Zachary R. Zimmer, MD

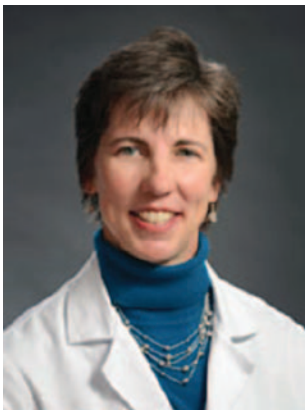
Undergraduate:
Colgate University

Medical School:
Stony Brook University

** Six-Year Research Track*

New Faculty

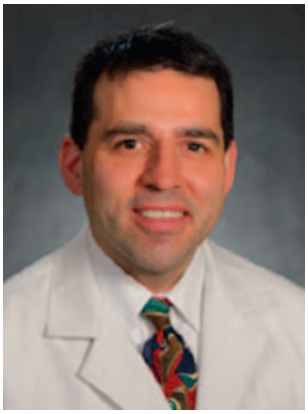
The University of Pennsylvania Department of Orthopaedic Surgery has recently experienced tremendous growth. In a few short years, the number of clinical faculty has doubled and has been matched by an expansion of facilities, educational opportunities, and high quality research output. The numerous editorials in this journal highlight recent events in the Department and describe many of the different facets of this period of growth. This year, we have added five outstanding faculty members in a range of subspecialties, each of whom has expanded the Department's expertise while also furthering our research and educational missions. We are delighted to welcome this outstanding group of clinical faculty and applaud our leadership for its exceptional recruiting ability.



Kristy L. Weber, MD

Professor of Orthopaedic Surgery, Vice Chair of Faculty Affairs, Chief of the Division of Orthopaedic Oncology, Director of the Sarcoma Program at the Abramson Cancer Center

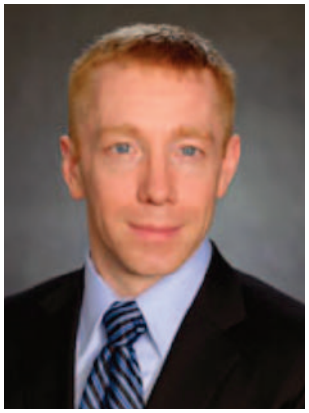
Dr. Weber has long been a leader in orthopaedic oncology and in orthopaedic research. After serving as Chief of the Division of Orthopaedic Oncology at Johns Hopkins for ten years, Dr. Weber moved to the University of Pennsylvania to assume the role of Professor and Vice Chair of Faculty Affairs as well as Chief of the Division of Orthopaedic Oncology and the Director of the Sarcoma Program at the Abramson Cancer Center. Dr. Weber will direct clinical and research programs aimed at developing new treatments for sarcoma. She brings tremendous clinical and scientific acumen to each of these roles. Dr. Weber also has an interest in methods of improving efficiency and productivity in our workforce at Penn Orthopaedics. Early efforts to achieve this goal have been focused on optimizing workforce diversity. As we expand, it is critical that we maintain diverse perspectives so that we, as a group, are always challenged to do better. Dr. Weber is firmly committed to this multifaceted mission. We look forward to the substantial contributions Dr. Weber will make as an outstanding clinician and a leader in our department.



Daniel C. Farber, MD

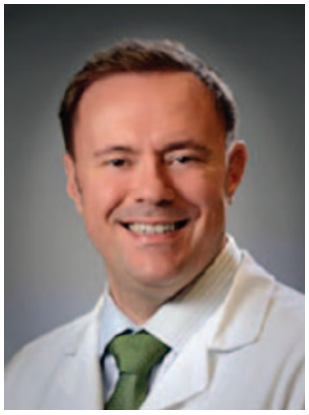
Assistant Professor of Orthopaedic Surgery

Dr. Farber joins Penn Orthopaedics after a decade of practice, with the last seven years spent at the University of Maryland. In addition to a broad set of clinical skills as a foot and ankle surgeon, Dr. Farber also brings particular expertise in resident and fellow education and an interest in research in foot and ankle pathology. Dr. Farber has trained and mentored countless residents and medical students and has served as a mentor for the American Orthopaedic Foot and Ankle Society's Resident Scholarship Program. Since joining the faculty in recent months, Dr. Farber has already reached out to the McKay Orthopaedic Research Laboratory and others interested in research collaboration. We are delighted to welcome Dr. Farber and his wealth of experience.



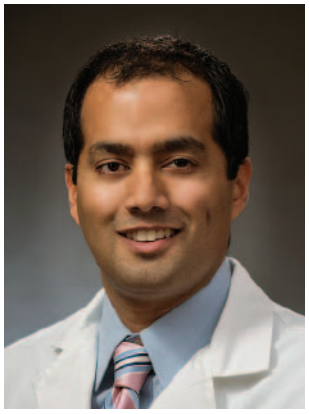
Harvey E. Smith, MD
Assistant Professor of Orthopaedic Surgery

Dr. Smith joins Dr. Vincent Arlet in the Division of Spine Surgery. Prior to joining our faculty, he served as an Assistant Professor at Weill Cornell Medical School while also serving as the Co-Director of the Spine Advanced Technology Laboratory at Methodist Hospital Research Institute in Houston, TX. He continued his development as an Assistant Professor of Orthopaedic Surgery at Tufts University and brings years of clinical experience and a background in clinical and basic spine research. He joins our department as the second fellowship-trained spine surgeon on staff. In addition to his clinical and research expertise, Dr. Smith has actively participated in resident education. He and Dr. Arlet host regular journal clubs at their homes where review of the spine literature is accompanied by dinner and discussion. We warmly welcome Dr. Smith to Penn Orthopaedics.



Miltiadis H. Zgonis, MD
Assistant Professor of Orthopaedic Surgery

Dr. Zgonis rejoins Penn Orthopaedics after completing a fellowship in Sports Medicine at Duke University. Dr. Zgonis brings energy, a focus on resident education, and substantial research experience to the Department. In his short time as a faculty member, Dr. Zgonis has already established weekly wet arthroscopy sessions in the Human Tissue Laboratory as well as a dry arthroscopy practice lab. His efforts have allowed residents to regularly sharpen their skills prior to getting into the OR. Additionally, he has been an active participant in educational conferences and is an active collaborator with the McKay Orthopaedic Research Laboratory. We are delighted to welcome him back and look forward to his ongoing contributions as a faculty member.

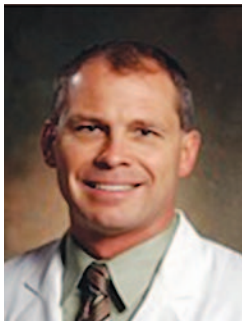


Atul F. Kamath, MD
Assistant Professor of Orthopaedic Surgery
Director, Center for Hip Preservation

Dr. Kamath, the newest addition to our growing faculty, rejoins Penn Orthopaedics after completing a fellowship in hip and knee reconstruction at the Mayo Clinic, where he received the Mark B. Coventry Adult Reconstructive Surgery Award. He then pursued advanced fellowship training in hip preservation, restoration, and reconstruction in Europe through generous awards from the Maurice Müller Foundation, Charnley Foundation, and the Hip Society. Through these experiences and with a wealth of research and clinical skills, Dr. Kamath brings tremendous new talent to our adult reconstruction, young adult, and sports medicine services. The Department will further benefit from his enthusiasm for clinical and policy research, which Dr. Kamath hopes to use to help train future generations of leaders in orthopaedic surgery. Penn Orthopaedics is extremely pleased to welcome back Dr. Kamath.

Dedicated Lectureships

OREF Lectureship
William T. Obremskey, MD, MPH, MMHC
Chief of Orthopaedic Trauma, Vanderbilt University
February 20th, 2014
Covered by Jason B. Anari, MD



William T. Obremskey, MD, MPH, MMHC

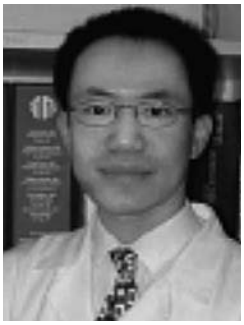
The Orthopaedic Research and Education Foundation (OREF) welcomed Dr. William T. Obremskey to Penn Orthopaedics for a scintillating Grand Rounds on February 20th, 2014. Dr. Obremskey has made substantial contributions to the orthopaedic literature with over 100 peer-reviewed publications, numerous book chapters, and service through educational sessions and review committees. Exemplifying his commitment to the education of future generations in orthopaedics, Dr. Obremskey recently completed another degree, Masters of Management in Health Care (MMHC). Prior to arriving at Vanderbilt, Dr. Obremskey spent time serving in the military in Arizona and as a faculty member at the University of North Carolina. He currently lives in Nashville with his wife and three children.

The topics Dr. Obremskey covered included operative indications for scapular fractures, his personal experience with necrotizing fasciitis, and acute treatment of knee dislocations. Currently, the Orthopaedic Trauma Department at Vanderbilt is involved in a prospective multicenter study aimed at determining which patients with scapular fractures require operative intervention as the current literature on the subject is minimal.

The night prior to his talk, Dr. Obremskey took the residency program through a cadaveric demonstration of the Modified Judet approach to the scapula in the Human Tissue Laboratory (HTL). During Grand Rounds the next day, Agnew Grice auditorium fell silent as Dr. Obremskey retold his account of how he acquired necrotizing fasciitis from a patient he operated on a few summers ago. It was hard not to notice how life-altering this experience was to our distinguished guest as he spoke about how this affected him, his family, and the Vanderbilt Health System. Dr. Obremskey concluded with a talk on how he manages patients who present with acute knee dislocations and the long-term complications in that population.

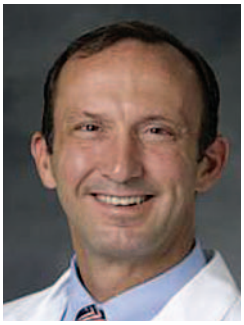
It was a great privilege for Penn Orthopaedics to hear and learn from Dr. Obremskey. We hope that he will soon return to further our education with his expertise and knowledge.

10th Annual Leo Leung Endowed Lectureship
David S. Ruch, MD
Professor, Chief of Hand Surgery, and Vice Chairman of Orthopaedic Surgery, Duke University
February 27th, 2014
Covered by Nathan Wigner, MD, PhD



Leo Leung, MD

Each year the Leo Leung Endowed Lectureship memorializes Dr. Leo Leung, a resident in the Department of Orthopaedic Surgery who passed away suddenly in April of 2002. Dr. Leung was a model resident; he deeply cared for his patients and acted as trusted mentor and educator to the residents and medical students who had the privilege to learn from him. He served as the editor of *UPOJ* in 2001-2002 and was voted by his co-residents to serve as Academic Chief Resident in 2002-2003. He had hoped to pursue a career in hand surgery and was actively recruited by the top hand surgery fellowships in the country. All the funds supporting this endowed lectureship were directly donated by faculty and friends of Dr. Leung. In his honor each year, we invite a guest speaker who embraces the ideals that defined Dr. Leo Leung.



David S. Ruch, MD

This year, we were delighted to welcome Dr. David S. Ruch, Professor and Vice Chairman of Duke University Orthopaedic Surgery, as he gave the 10th annual Leo Leung Endowed Lecture on February 27th, 2014. Dr. Ruch earned his medical degree and completed his orthopaedic residency training at Wake Forest University, followed by a Hand/Upper Extremity Surgery fellowship at Duke University. His professional interests include microscopic and minimally invasive techniques for treating degenerative and traumatic conditions of the upper extremity; avascular necrosis of the hand, elbow, and hip; as well as vascularized free fibular bone grafting.

Dr. Ruch has long been devoted to improving the field of orthopaedics through research. His focus is on traumatic and reconstructive challenges of the upper extremity. An author of over 130 peer-reviewed publications, his research interests include nerve injuries, fractures of the wrist and elbow, tendon

injuries, and arthritis of the upper extremity. In addition, he serves as an editor for numerous peer-reviewed journals including *Journal of the American Society for Surgery of the Hand*, *Journal of Hand Surgery*, and *Journal of Orthopaedic Trauma*.

Dr. Ruch's firm commitment to improving orthopaedics through resident education and mentorship makes him an excellent selection for this particular lecture series. He has a keen sense of the importance of teaching residents through both research and clinical activities and has given back by molding the next generation of orthopaedic surgeons. Here at Penn, he took the time to share his tips and tricks for elbow arthroscopy in the HTL on the evening of February 26th, followed by lectures the next day on "Avoiding complications in the management of distal radius fractures" and "Traumatic elbow instability." The lab and lectures were notable for the lively discussion between Dr. Ruch and the residents and carried on our annual tradition of honoring Dr. Leo Leung with an exchange of the ideas and ideals that he embodied.

Irvin Stein Endowed Lectureship

Irvin Stein Endowed Lectureship
Kevin J. Bozic, MD, MBA
William R. Murray, MD, Endowed Chair, Vice Chair of Department of Orthopaedic Surgery, University of California at San Francisco
March 27th, 2014
Covered by Tyler R. Morris, MD

Irvin Stein, MD

Penn Orthopaedics welcomed Dr. Kevin J. Bozic as the invited speaker for the annual Irvin Stein Endowed Lectureship on March 27th, 2014. This occasion honors Dr. Irvin Stein, a former Professor of Orthopaedic Surgery at the University of Pennsylvania and an early leader in orthopaedic surgery. He made major contributions to our understanding of metabolic diseases of bone, evaluation of bone density on imaging, and countless other areas of musculoskeletal health. Furthermore, he was among the founding members of the Orthopaedic Research and Education Foundation, demonstrating how his vision continues to shape our field. Each year in Dr. Stein's honor, we invite a speaker who demonstrates a steadfast commitment to research, education, and advancement in orthopaedic knowledge to honor Dr. Stein's commitment to these ideals throughout his career. Dr. Bozic was a wonderful addition to the long list of distinguished guests who have honored the memory of Dr. Stein.

Kevin J. Bozic, MD, MBA

Dr. Bozic is a graduate of the University of California at San Francisco Medical School and did his orthopaedic surgery residency at the Harvard Combined Residency Training Program. He completed a fellowship in musculoskeletal traumatology at Massachusetts General Hospital, where he also earned his MBA, followed by a fellowship in adult reconstructive surgery at Rush-Presbyterian-St. Luke's Medical Center. Dr. Bozic is a nationally recognized leader in complex adult reconstructive surgery as well as healthcare reform and quality improvement. He lives in San Francisco with his wife and three daughters. During his visit, Dr. Bozic was able to share his unique perspective on the changing dynamics in healthcare, particularly the role of efficiency and quality measurement in our changing professional landscape, as well as his tips on balancing personal and professional obligations.

Dr. Bozic began his visit by hosting a journal club the night before his Grand Rounds lectures with the majority of the Department in attendance. Along with input from our Chief of Orthopaedic Trauma, Dr. Samir Mehta, and Chairman, Dr. L. Scott Levin, Dr. Bozic focused on issues germane to healthcare reform and strategies for improving the quality of delivered care. Using an interactive format, he touched on numerous subjects including physician reimbursement, tort reform, and innovations in healthcare. He was able to generate a dynamic dialogue, which was both instructive and thought-provoking. The evening certainly left our residents better equipped to think about the future of our field and how to better participate in guiding its development.

The following morning, Dr. Bozic presented a lecture on "Work-life balance," which was followed by his formal Grand Rounds lecture entitled, "Shifting from volume to value: preparing for healthcare reform." Dr. Bozic was able to accurately illustrate many of the problems and possible solutions concerning the current state of healthcare in the United States. He emphasized the importance of providing efficient, value-driven care in such a way as to maximize both clinical outcomes and efficiency.

It was a true honor and privilege for Penn Orthopaedics to listen and learn from Dr. Bozic. It is our sincere hope that he will return soon to further our education with his knowledge and experience.

Hospital of the University of Pennsylvania

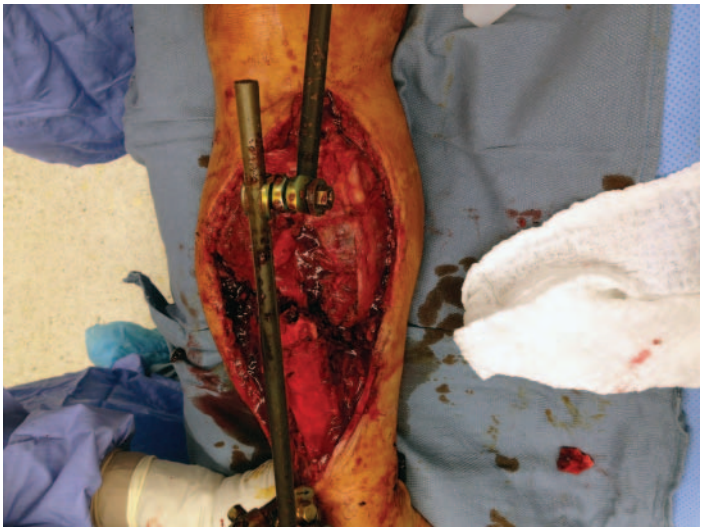
John L. Esterhai, MD, Jaimo Ahn, MD, PhD, Derek Donegan, MD,
Keith Baldwin, MD, MPH, MSPT, Kristy Weber, MD,
L. Scott Levin, MD, FACS, and Samir Mehta, MD

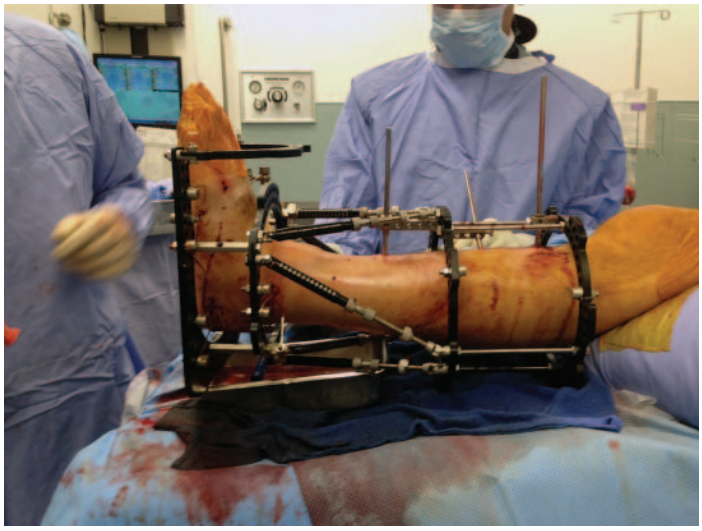
February 5, 2015 - the premier Level I Trauma Center at Penn will have a new home on that date when HUP will close its doors as a Level I Designated Trauma Center, and the University of Pennsylvania Health System will relocate all of its trauma and injury services to the Penn Presbyterian Medical Center campus and the new Acute Care Pavilion.

As I write this, I realize that this will be the last "HUPdate" I will be writing. I am sure the resident editors of *UPOJ* are thrilled since I am chronically behind and submit these at the last minute. I will be handing over those reigns to Drs. Weber and Baldwin, who will remain at HUP and continue to build the Orthopaedic Oncology and Neuro-Orthopaedics Services, respectively. Dr. Weber has already made a tremendous difference by bringing a team-based approach to the care of these patients. And she has made a tremendous impact on the resident education component of orthopaedic oncology.

I think back for a moment at the history of the Orthopaedic Trauma Service at HUP, with names and faces like Bruce Heppenstall, Bill DeLong, Chris Born, and John Esterhai. I think of ALL of the residents who have passed through these halls doing orthopaedic trauma, learning to take care of some of the worst injuries in the region, and recognizing HUP as a leader when it comes to care of the injured. I think of all the conferences and case presentations in Ralston Library. I think of my own education when I was in awe of what the human body could endure.

I also recognize the building of a culture over the past several decades in taking care of those who are injured and less fortunate. I recognize the effort put forth by the residents, the mid-level providers, the office staff, the nurses, and all the teams that make trauma "go." One of the most unique aspects of trauma care is that it truly is a team effort.

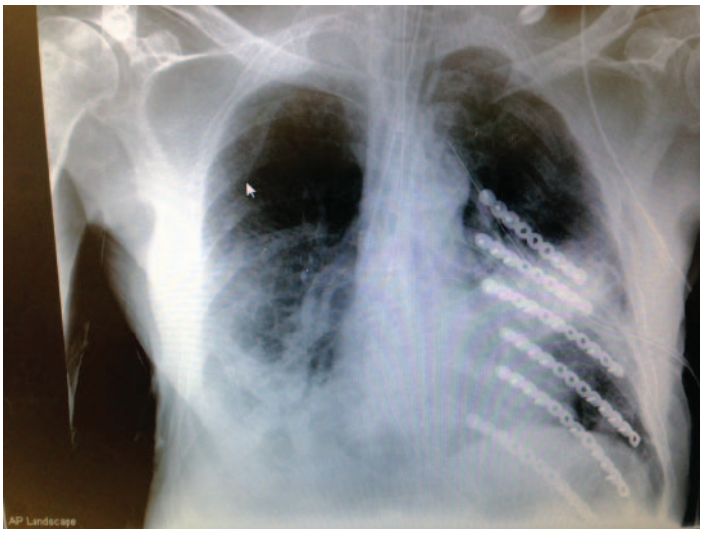




As we plan to leave HUP, I look back at the state of the Orthopaedic Trauma and Fracture Service. I can truly say that any success we have had has been on the shoulders of giants, including our leadership. Clinically, orthopaedic trauma volume has increased 26% over the last five years, but with the addition of Derek Donegan, we have room to grow. In addition, we have two skilled mid-level providers on the outpatient side (Ms. Katie Marine and Mr. Scott Day) and, of course, Adele Hamilton, NP, on the inpatient side, who has been with us for seven years and continues to excel in her role. We are looking to grow with an additional mid-level provider. The Orthopaedic Trauma Service has also expanded its clinical skill set through the work of Dr. Ahn on deformity correction and through our combined efforts with general trauma on rib fracture fixation in our traumatized patients. I would also argue that we also boast the best extremity soft tissue service lines in the country with Drs. Levin and Stephen Kovach. Our ability to manage open fractures is second-to-none.

In addition, the Orthopaedic Trauma and Fracture Service has continued to grow its clinical research efforts through the work of Kelly McGinnis and Patrick Hesketh as our clinical research coordinators for orthopaedic trauma in conjunction with Dr. Annamarie Horan, director of our clinical research efforts. Through their combined efforts, the Orthopaedic Trauma Service continues to be a departmental leader in prospective funded studies.

The Orthopaedic Trauma and Fracture Service has been working diligently on an international component, which came to fruition through the support of the Biedermann



family. Through their generous gift, we were able to send multiple residents and faculty to Managua, Nicaragua via Health Volunteers Overseas. The experience was nothing short of remarkable.

Over the last decade, orthopaedic trauma has "come of age." At its most basic level, the care of the traumatically injured patient is at the core of being an orthopaedist. The ability to deliver care to this unique and often underserved patient population is also at the heart of being a physician. However, being a successful Level I Trauma Center is centered on the concept of the "team." At a macroscopic level, the team consists of hospital administrators, physicians, nursing staff, and tangible structures (like ICUs and Resuscitation Bays) coming together to create an environment to care for those who sustain traumatic injuries and put into place mechanisms which will facilitate this process.

Upon this foundation, Level I Trauma Center triage and care requires intense interaction not only outside our department but also within. Our very busy rotating night and weekend call schedule best demonstrates our collegiality and depth of caring for one another within our department. With an increased eye toward outcomes and quality improvement, we have started to "close" the call system and deliver care based on algorithms for various injury patterns. Several of the non-trauma faculty share call, 24/7/365, at no small personal sacrifice, to meet the burden of emergency orthopaedic care for our region.

Each of us who works with patients with these difficult injuries realizes that it is not our personal skill that cures. Year after year, participating in the care and watching the healing is a humbling experience. We are reminded of how truly lucky we are and how important the "team" is in making this a reality.

PENN Orthopaedic Trauma

Penn Presbyterian Medical Center

David J. Bozentka, MD

Chief of Orthopaedic Surgery, Penn Presbyterian Medical Center

It has been an exciting year for the Department of Orthopedic Surgery at Penn Presbyterian Medical Center (PPMC), as the service continues to expand while providing excellence in musculoskeletal care, education, and research.

The Department of Orthopedic Surgery plays an integral role at PPMC, which has been recognized for its exceptional service with multiple accolades. This past year, PPMC was the recipient of the Beacon Award for excellence and was identified by Truven Health Analytics as one of the top 100 hospitals in the nation. The annual 100 Top Hospitals list identifies the top hospitals in the United States based on their overall organizational performance in 10 areas, including patient safety, patient ratings of hospital performance, and complication and mortality rates. PPMC was acknowledged in the category of Major Teaching Hospitals and is one of only five in Pennsylvania in the 2014 report.

The Department of Orthopedic Surgery at PPMC also continues to be recognized for exemplary care. The hip and knee service has been awarded the Joint Commission's Gold Seal of Approval and a Blue Distinction by Independence Blue Cross. These nationwide programs identify departments that outperform their peers in quality care, safety, and efficiency. These awards are a testament to the preeminence of our hip and knee service at PPMC with an emphasis on quality of care. This quality is exemplified by our top 10 rank of hospitals with lowest mortality by the University Health System Consortium (UHC). The consortium is made up of 104 academic health systems nationwide. This accomplishment is due in large part to the support and close relationship with the Medical Co-Management team led by Dr. Laura Kosseim.

Construction continues on the PPMC campus with the building of two new facilities, including Penn Medicine University City and the Advanced Care Pavilion. The facility on 3737 Market Street, Penn Medicine University City, will house the Penn Musculoskeletal Center to include the Departments of Orthopedic Surgery, Rheumatology, Physical Medicine and Rehabilitation, Pain Medicine, Musculoskeletal Radiology, and Physical Therapy supported by Good Shepherd Penn Partners. The facility will include 110 exam rooms, an outpatient radiology center, and six outpatient operating rooms in the ambulatory surgery facility (ASF). Dr. Brian Sennett has led a multi-specialty executive committee which has developed plans for the transition to the ASF. The group has included representation from the Departments of Anesthesiology, General Surgery, and Nursing. This state-of-the-art facility will provide efficient, comprehensive outpatient surgical care for the sports medicine, shoulder, and hand surgery services. The Department of Orthopedic Surgery outpatient care, administrative, and academic services plan to move into the building in August 2014.

Ms. Karen Bernardi has accepted the position of Associate Clinical Director for the ASF, where she will be responsible for the day-to-day operations and serve as lead administrator for the building. Ms. Bernardi comes to PPMC with a wealth of perioperative management and ambulatory experience. Most recently, she was the Clinical Director of Perioperative Services at Atlantic Care Regional Medical Center, where she was responsible for two facilities that included 18 operating rooms, the Post-Anesthesia Care Unit, Short Stay Unit, and Endoscopy Units at each campus. Prior to this, she spent several years at Summit Surgical in Voorhees, NJ, in both staff and management positions. In addition, Ms. Bernardi has received several management and leadership awards.

Penn University City will house the Penn Human Performance Laboratory. The center will allow the diagnosis, treatment, and rehabilitation of musculoskeletal disorders. State-of-the-art biomechanical, physiological, and kinematic testing will provide the capability for motion analysis, electromyography, metabolic measurement, and neuromuscular testing. The motion analysis will include an optical system with four digital cameras allowing real-time assessment of movement and performance. A force platform system for motion analysis will be used concomitantly with strain gauge technology, providing the most accurate assessments currently available. The metabolic measurement system will allow for cardiopulmonary stress testing using maximal O_2 consumption measurements. In addition to the extensive research opportunities these modalities provide, the Laboratory will allow assessment of a wide range of musculoskeletal disorders and provide patients with immediate feedback to help develop the optimal treatment plan.

The Advanced Care Pavilion, on the corner of 38th Street and Powelton Avenue, is being constructed concurrently. The facility will be a Level I Regional Resource Trauma Center. The projected move date for the trauma component of orthopaedic surgery, general surgery, and the neurosurgical services from the Hospital of the University of Pennsylvania is slated for February 2015. The new 178,000 square foot building at PPMC will house facilities for critical care, emergency, and surgical trauma, including the John Pryor Trauma Bay. This state-of-the-art trauma resuscitation area for patient evaluation and stabilization will have upgraded emergency and radiology services for improved efficiency. In addition, a helipad will be available for the PennStar flight program for transportation of critically injured patients.

Considering the multiple accolades and continued growth, the future is bright for the Department of Orthopaedic Surgery at PPMC. We are fortunate to be part of a group with a proud tradition of leaders in musculoskeletal medicine and who strives for excellence.

Pennsylvania Hospital

Neil P. Sheth, MD

Pennsylvania Hospital (PAH) has a long-standing history in Philadelphia as it is the nation's first hospital. Located in the heart of South Philadelphia, its brand name equity has drawn thousands of patients annually to receive their care at the corner of 8th and Spruce Streets. Specifically, orthopaedic and musculoskeletal care have been considered top notch over the past several decades. However, PAH over the past 12-18 months has experienced a series of major changes. With the departure of the 3B private orthopaedic practice, a void in orthopaedic care was anticipated. The PAH administration had a great deal of concern regarding the financial viability of the hospital based on the historic high volume orthopaedic services provided to patients.

In response to this potential absence of orthopaedic care and quality service, the Department of Orthopaedic Surgery at the University of Pennsylvania has staffed nine attending surgeons from different sub-specialties to populate the orthopaedic clinic on the first floor of the Cathcart Building. Among the sub-specialties are adult hip and knee reconstruction, foot and ankle, hand/plastic surgery, neuro-orthopaedics, shoulder and elbow, spine/deformity, sports medicine, and trauma.

In a short period of time, the orthopaedic volume has reached 87% of the historic volume performed at PAH, and orthopaedic surgery is present in the operating room every day of the week. The administration has replied to this dramatic increase in volume over a short interval of time and has hired Sue Horne as a dedicated orthopaedic coordinator. She has taken on the task of coordinating the daily efforts of our service and identifying effective practice efficiencies to help increase patient throughput in the operating room and optimizing our ability to provide quality patient care.

In the arena of resident education, PAH is staffed now by a PGY-2 and a PGY-5 rotation over six-week blocks. Residents are typically in the operating room four days per week, with Thursday dedicated to patient clinic for the trauma service. We have maintained the orthopaedic internship rotation; the intern receives additional support during the day from a series of orthopaedic-dedicated nurse practitioners. These nurse practitioners also moonlight at nighttime to take care of the orthopaedic service. The addition of the combined arthroplasty/trauma conference on Friday morning has added to the already existing foot and ankle and spine conferences, enhancing the overall commitment to resident education.

Future plans call for the addition of faculty to both the adult reconstruction and foot and ankle sections. The continued support of the administration is critical as the orthopaedic volume is expected to continue to grow, allowing PAH to maintain its reputation in the region as a first-class hospital.

The Children's Hospital of Philadelphia

John P. Dormans, MD, and Ashley Trocle, BS

The Division of Orthopaedic Surgery at the Children's Hospital of Philadelphia (CHOP) has had another successful year marked with significant growth. We have continued to develop our clinical and research programs, as evident by notable academic and clinical achievements. We are pleased to announce that CHOP was ranked first in pediatric care by both *Parents* magazine and *US News and World Report* in 2013. The Division of Orthopaedics Surgery at CHOP was ranked second in pediatric orthopaedic surgery in the United States.

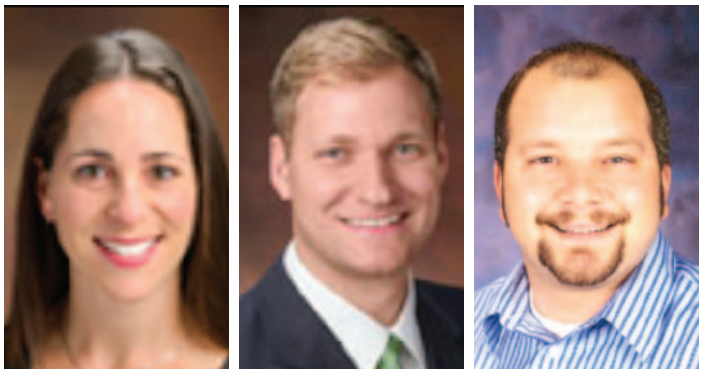
Clinical Program

Our orthopaedic faculty continues to expand and is currently comprised of twenty-eight total providers, including eighteen specialty-trained pediatric orthopaedic surgeons (thirteen operative and five nonoperative), five pediatricians with sports medicine training, and five transition-to-adult care faculty.

CHOP Orthopaedics is thrilled to announce the addition of two pediatricians with sports medicine training to the division. Dr Naomi Brown (Figure 1A) obtained her medical degree from Tufts University School of Medicine in Boston, MA. She completed her residency at CHOP in 2009 and a fellowship in sports medicine at Boston Children's Hospital. Dr. Brown has served as a co-investigator on a number of clinical studies, including a publication in *Pediatrics* which analyzes the duration of concussion symptoms. Dr. Christian Turner (Figure 1B) joined the Division of Orthopedic Surgery in July 2013 after completing a fellowship in primary care sports medicine here at CHOP. Dr. Turner received his medical training at the State University of New York in Syracuse, NY. He completed his residency at Connecticut Children's Medical Center in Hartford, CT. Dr Turner has served as team physician or assistant team physician for the University of Pennsylvania, West Chester University, two Philadelphia-area high schools, and at training camp for the Philadelphia Eagles. Both Drs. Brown and Turner are members of the American Academy of Pediatrics, the American College of Sports Medicine, and the American Medical Society for Sport Medicine. The division will be welcoming Dr. Brian T. Vernau (Figure 1C) in Fall 2014 after his completion of a sports medicine fellowship at CHOP. Dr. Vernau is also a pediatrician with sports medicine training.

Our department also staffs sixteen nurse practitioners, two registered nurses, five physician assistants, five cast technicians, and two athletic trainers who are able to evaluate, diagnose, and treat the full range of musculoskeletal disorders, as well as an additional staff of 41 office personnel.

This past year also marked the beginning of construction on the Buerger Center for Advanced Pediatric Care. The



A B C

Figure 1. (A-C): From left to right, Drs. Naomi Brown, Christian Turner, and Brian Vernau.

Buerger Center, opening in 2015, will stand "as the nation's most state-of-the-art facility for outpatient medicine" (Figure 2). We are also looking forward to the opening of the newest CHOP Orthopedics facilities in Princeton, NJ, King of Prussia, PA, and Chadds Ford, PA. CHOP has also continued to develop a partnership with Virtua Memorial Hospital. In 2012, Virtua opened a Specialty Care Center where CHOP orthopedic physicians have a large presence. CHOP surgeons began providing fracture care in the emergency department at Virtua in 2013. The partnership with Virtua Memorial has centralized inpatient and outpatient emergency care.

Figure 2. Buerger Center for Advanced Pediatric Care will open its doors in 2015 and will be a state-of the art outpatient care facility which will house an orthopedic ambulatory care center.

Teaching

CHOP Orthopaedics currently funds four one-year clinical fellowships, and three one-two year research fellowships. The 2013-2014 clinical fellows are Patrick O'Toole, MD (Figure 3A); Rushyuan J. Lee, MD (Figure 3B); Ronald J. Mistovich, MD (Figure 3C); and Anish Potty, MD (Figure 3D). This year's research fellows are Nariman Abol Oyoun, MD, from Egypt (Figure 4A); Emmanuil Grigoriou, MD, from Greece (Figure 4B), and Muayad Kadhim, MD, from Syria (Figure 4C). Following completion of their clinical fellowships, Dr. O'Toole will be returning to Ireland to accept an academic position in orthopaedic surgery. Dr. Lee will be accepting an academic position at Johns Hopkins Hospital in Baltimore, MD, where he will focus on trauma and sport medicine. Dr. Mistovich is currently looking for an academic position in pediatric orthopaedic surgery in the Midwest with his wife who is a pediatrician. Dr. Potty will be continuing his medical training in Tampa, FL, as a clinical fellow in sports medicine. After completing his research fellowship, Dr. Grigoriou hopes to complete an orthopedic surgery residency program in the United States; Dr. Kadhim plans to complete a clinical or research fellowship in the United States; Dr. Abol Oyoun will be returning to Assiut University in Eqypt, where she was an attending orthopedic surgeon.

The Division of Orthopaedic Surgery continues to reach out to the international community of specialists by participating in the Visiting International Scholars Program (VISP), a program designed to provide international orthopaedic surgeons with the opportunity to observe clinical care of pediatric patients in a high volume, academic setting. Over the past year, CHOP Orthopaedic Surgery has had numerous Visiting International Scholars, including Thiago Nogueira Pereira from Brazil, Wei Hsun Wang from Taiwan, Bagaria Vaibhav and Atul Malhotra from India, Jasqui Salomon from Mexico, and Li Lianyong and Jacky Hua from China. Some of our Visiting International Scholars have gone on to be accepted as Research or Clinical Fellows here at CHOP or at other institutions in the United States.

Basic Science Research

The past year has been an exciting and productive one for our Basic Research Program, led by Maurizio Pacifici, PhD (Figure 5), with many activities and research initiatives related to a number of skeletal pathologies. Our faculty members and their associates continue to work diligently on the aims of our several current NIH R01 grants and one DOD grant to understand the pathogenic mechanisms of pediatric and adult conditions, including Heterotopic Ossification (HO), Hereditary Multiple Exostoses (HME), and other musculoskeletal pathologies. Work led by one of our faculty members, Dr. Masahiro Iwamoto, and supported by the Muscular Dystrophy Association aims to exploit a new pharmacological pathway to enhance muscle tissue repair after trauma or congenital conditions, such as muscular dystrophies. 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 has recently received a new grant from the Arthritis Foundation 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

A B C D

Figure 3. (A-D): From left to right, the CHOP Orthopaedic 2012-2013 Clinical Fellows: Drs. Patrick O'Toole, Ronald J. Mistovich, Rushyuan J. Lee, and Anish Potty.

A B C

Figure 4. (A-D): From left to right, the CHOP Orthopaedic Research Fellows: Dr. Emmanouil Grigoriou from Greece, Dr. Muayad Kadhim from Syria, and Dr. Nariman Abol Oyoun from Egypt

Figure 5. Group picture of the CHOP Orthopaedic Translational Research team led by Maurizio Pacifici, PhD. Back row from left to right: Eiki Koyama, Cheri Saunders, Rachel Mascareno, Colleen Larmour, Masahiro Iwamoto, Kenta Uchibe, Rebekah Decker, Federica Sgariglia. Front row: Agnese DiRocco, Julianne Huegel, Jiyeon Son, Rebecca Berger, Motomi Enomoto-Iwamoto, Maurizio Pacifici, Leslie Cantley, and Chloe Williams.

new light on the biology of those cells and suggest ways to maintain their function during aging or restore it in chronic conditions including osteoarthritis. In a related development, our faculty member Dr. Eiki Koyama has joined forces with Dr. Hyun-Duck Nah, a faculty member in the CHOP Division of Plastic and Reconstructive Surgery, to understand the development and growth of the temporomandibular joint and identify possible therapeutic means to treat TMJ osteoarthritis, a condition particularly common in women. The data and insights stemming from all the above research lines have generated publications in top peer-reviewed journals.

An exciting biomedical development is that our basic research work on HO has allowed further progress toward a possible clinical trial to treat children affected by Fibrodysplasia 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/FOP in experimental animal models of the disease. In the past year or so, the Canadian-based pharmaceutical company Clementia has been working closely with us and with our colleagues at the Penn FOP Foundation, Drs. Fred Kaplan, Bob Pignolo, and Eileen Shore, to organize and implement a Phase 2 trial for FOP in the very near future using such pharmacological treatment.

Our clinical division remains a major national and international center of diagnosis, care, and surgical treatment for children affected by HME. As indicated above, our Basic Research Program continues to be actively engaged in understanding the pathogenesis of HME, using animal models and cells in vitro. Thus, to extend these basic research efforts toward translational medicine outcomes, we have recently recruited a senior investigator, Dr. Paul Billings, to create new cell-based bioassays to screen chemical libraries and identify drugs able to correct a specific polysaccharide deficiency that causes HME. If identified, 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.

Genetic Research

CHOP Orthopaedics is also working in collaboration with the Center for Applied Genomics (CAG), led by 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) of the knee, and multiple hereditary extoses (MHE). In 2011, CAG and Orthopaedics won the Scoliosis Research Society (SRS) Russell Hibbs Award for Best Basic Science Paper in 2011 for their study entitled, "A Genome Wide Association Study Identifies IL17RC as an Adolescent Idiopathic Scoliosis Locus." Our most recent efforts involve an analysis of whole exome sequencing on familial blood samples which will further elucidate the influence of genetics on the development of AIS. Our current finding presents the potential opportunity for diagnostic applications and for novel therapeutic intervention for AIS by providing novel entry points in known scoliosis biological pathways.

Biomechanical Research

Our division welcomes Saba Pasha, PhD (Figure 6), to the research team. Dr. Pasha is a post-doctoral researcher with an interest in 3D analysis of skeletal deformities using the EOS imaging system, gait analysis, and clinical evaluation of medical devices in the pediatric population. CHOP expanded its diagnostic toolkit in 2013 with the addition of the EOS imaging system, which uses low doses of radiation to provide high quality 3D images. This enables accurate diagnosis and more informed treatment decisions.

Figure 6. Saba Pasha, PhD, is completing postdoctoral research at CHOP.

Clinical Research

The CHOP Orthopaedic Surgery Division is currently conducting 101 IRB approved clinical research projects. This includes a number of randomized clinical trials and multicenter studies. Investigators within the division have been awarded funding from both internal and external sources to conduct these studies. In the past two years, the division has published over 110 articles in major orthopaedic journals, including (but not limited to) *JBJS, SPINE, JPO* and *CORR*.

Our pediatric orthopaedic faculty continues to present research studies at orthopaedic conferences around the world, including the American Academy of Orthopaedic Surgeons (AAOS), the Pediatric Orthopaedic Society of North America (POSNA), the European Pediatric Orthopaedic Society (EPOS), the Scoliosis Research Society (SRS), the American Orthopaedic Society for Sports Medicine (AOSSM), the International Meeting on Advanced Spine Techniques (IMAST), the Societe Internationale de Chirurgie Orthopedique et de Traumatologie (International Society of Orthopaedic Surgery and Traumatology, SICOT) and many more.

In 2009, our department initiated an annual Benjamin Fox Scholarship Award for current medical students who are interested in conducting a year of clinical research within orthopaedics. In June, our department awarded Christine Goodbody, (Figure 7A) an upcoming fourth year medical student at the Perelman School of Medicine at the University of Pennsylvania and Afamefuna Nduaguba, (Figure 7B) a fourth year medical student at Harvard University with this scholarship. While at CHOP, Christine has concentrated her research on complications of supracondylar humerus and lesser trochanter avulsion fractures, effect and outcomes of BMI on scoliosis presentation, and treatment of tibial shaft fractures. Afamefuna has focused his research on developmental hip dysplasia (DDH) management, septic arthritis of the knee, effects of BMI on ACL ruptures and chondral injuries, and the accessibility of surgical services in developing counties.

A

B

Figure 7. 2013-2014 Benjamin Fox Research Fellows Christine Goodbody (A) and Afamefuna Nduaguba (B). Christine and Afamefuna are upcoming fourth year medical students who have taken a year to do clinical research in pediatric orthopaedic surgery at CHOP.

Recognitions and Achievements

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

Robert Campbell, MD, has continued to expand and develop the Center for Thoracic Insufficiency at CHOP. Dr. Campbell was nominated by the American Academy of Orthopaedic Surgeons for representation on the Center for Devices and Radiological Health (CDRH) Medical Advisory Committees' Orthopaedic and Rehabilitation Devices Panel. Dr. Campbell has been recognized in the past by the Food and Drug Administration (FDA) for his work on the VEPTR.

Denis S. Drummond, MD, CHOP Orthopaedics Chief Emeritus, has continued to serve as the Co-Director of the CHOP Orthopaedic Fellowship Program. Dr. Drummond was the Director of Clinical Research until 2012 and remains an active member of the research program in CHOP Orthopedics.

Keith Baldwin, MD, MSPT, MPH, is the current director of clinical research in the Division of Orthopedic Surgery at CHOP. Dr. Baldwin is also the Health Policy Chair of the Orthopedic Rehabilitation Association and an Associate Editor for Rehabilitation for the *Journal of Bone and Joint Surgery (JBJS)*.

Jack Flynn, MD, is currently the President of the Pediatric Orthopaedic Society of North America (POSNA) and will host the 30th Annual Meeting of POSNA in Hollywood, CA, in April. Dr. Flynn and Dr. Stu Weinstein just released the 7th edition of *Lovell and Winter's Pediatric Orthopaedics*, considered to be the authoritative text in the field. Dr. Flynn led CHOP's effort in the landmark NIH BrAIST trial, which conclusively proved the efficacy of bracing as a treatment for scoliosis. He co-chaired the International Pediatric Orthopaedic Symposium (IPOS) and began his service as Chair of the American Academy of Orthopaedic Surgeons 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, including the new planned sports medicine center in King of Prussia and Chadds Ford. In 2013, Dr. Ganley collaborated on the creation of the new Penn/CHOP Orthopedic Sports Medicine Fellowship with Dr. Brian Sennett as well as departmental chairmen, Drs. Scott Levin and John Dormans. He was the Director of the AAOS/POSNA sponsored course entitled, "Cutting Edge Techniques in Pediatric Orthopedic Surgery" at the AAOS orthopedic learning center. He was selected as moderator or instructor at instructional course lectures for the following annual meetings: the AAOS, AAP, AOSSM, POSNA, and IPOS. He was an advisory board member for the International Pediatric Orthopedic Symposium and ran the sports medicine section of the Surgical Simulation Lab. He 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. Dr. Ganley has been selected as a visiting professor and invited lecturer this year at Harvard Boston Children's Hospital, Case Western Reserve University, Union Memorial Hospital, and the Mexican Society of Pediatric Orthopedics in Villahermosa.

B. David Horn, MD, was the Pediatric Chair of the Pediatric Orthopaedic Scored and Recorded Self-Assessment Examination, which was published by the American Academy of Orthopaedic Surgeons (AAOS) in 2013.

John Todd Lawrence, MD, PhD, received the OmeGa Core Competency Grant in 2012. This funding has supported the creation of a fracture reduction model (patent pending) as a means to educate and improve resident performance in fracture reduction and casting techniques. Dr. Lawrence, along with Dr. David Horn and Dr. Richard Davidson, was a visiting professor in Austria at the Open Medical Institute. He presented four lectures on the topic of sports medicine.

Christina Master, MD, in conjunction with the Mind Matter: Improving Pediatric Concussion Management Program at CHOP, has written and lectured extensively on the topic of concussions in children and adolescents. In November 2013, Dr. Master participated in a Congressional Panel at the House of Representatives regarding concussion in athletics. She is also a co-investigator on a number of grants which fund research relating to concussion treatment.

Wudbhav Sankar, MD, is the Director of the Young Adult Hip Preservation Program at CHOP and has played a key role in the development of a comprehensive hip database. Dr. Sankar was the Program Chair of the POSNA at the 2014 Annual Meeting. He is also the section editor of the spine section of *Operative Techniques in Orthopedics Surgery,* 2nd Edition. Along with his professional achievements this year, Dr. Sankar and his wife welcomed their second child, Kamran, on March 12, 2013.

David Spiegel, MD, was awarded the 2013 Humanitarian Award from the Pediatric Orthopaedic Society of North America (POSNA) for his "outstanding service to the underserved children of the world with musculoskeletal disorders." He was also accepted into the American Academy of Orthopedic Surgery (AAOS) Achievement Award Program. Dr. Spiegel continues his work with the World Health Organization, traveling to Port of Spain, Trinidad and Tobago,

and Geneva, Switzerland, in the past year. He is currently on the board of Orthopaedics Overseas, the Ponseti International Association, and Miracle Feet.

Lawrence Wells, MD 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 Program Chair for the Philadelphia Orthopaedic Society in 2013-2014 and is a member of the executive committee for the section on orthopaedics for the American Academy of Pediatrics. He was also appointed to the Physicians Leadership Academy of the University of Pennsylvania.

John P. Dormans, MD, FACS, Chief of Orthopaedic Surgery at CHOP, was elected into the Presidential Line of the Scoliosis Research Society (SRS) and will host the SRS 50th Anniversary meeting as President in Minneapolis, MN, in 2015. Dr. Dormans recently completed his term as Chairman of Société Internationale de Chirurgie Orthopédique et de Traumatologie (SICOT) USA. He is currently the Secretary General of the SICOT Foundation. Dr. Dormans is the President Elect of the World Orthopaedic Concern (WOC) and will serve as President for the 2014-2017 term. He also completed his term as President of POSNA in 2010.

Philadelphia Veterans Affairs Medical Center

John L. Esterhai, MD

Chief of Orthopaedic Surgery, Philadelphia Veterans Affairs Medical Center

Today, one in ten Americans is an armed forces veteran. 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 Veterans Affairs 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 healthcare 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 Affairs 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 healthcare 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 125 medical schools.

The University of Pennsylvania orthopedic rotation at the Philadelphia VAMC allows our PGY-2 and PGY-5 residents to care for veterans in an intensive, general orthopedic practice setting under the direct supervision of Drs. Bernstein, Ecker, Esterhai, Gentchos, Hume, Kelly, Kuntz, Sheth, Steinberg, Warner, and Zgonis. Dr. Harvey Smith, our spine surgeon, teaches and works with a PGY-3 resident. Dr. Levin volunteers his time without compensation.The few 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, Kuntz, Sheth, and Steinberg have each applied for or been awarded research funding through the Veterans Administration competitive grant system. Our department has six Merit Grants. Dr. Smith has applied for a Career Development Award. Our PVAMC clinical faculty members collaborate actively with intra and extramural 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, and Lou Soslowsky.

Since the last publication of the *UPOJ* in 2013, Dr. Mauck, our Director of Orthopedic Research, has been elected to the American Institute of Biological and Medical Engineering College of Fellows, an honor bestowed upon only two percent of the biological and medical engineers in the country. He has opened more than 4300 square feet of new orthopaedic research space and energized collaboration with Rheumatology and Physical Medicine and Rehabilitation scientists. 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; added a new full-time Director of the SICU; improved perioperative pain management and postoperative floor care. In the year ahead 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. After 15 years in private practice and a decade at the PVAMC, Chip continues to provide immediate, timely interaction with referring physicians and outside consultants, coordination of pre-bed evaluations, surgery scheduling, interaction with the primary care providers, liaison with VA referral health centers, and acute and chronic pain management. John has had the daunting task of assisting in the operating room and coordinating all of Dr. Smith's orthopaedic spine care for our veterans.

Outpatient care has improved dramatically as the electronic medical record has become even more useful. All records, including consent forms and imaging studies, are electronic. Progress notes, laboratory results and imaging studies are available at the workstations on the inpatient units, offices, and outpatient care areas and individual examination rooms from local and satellite VA care facilities. It is the best electronic medical record (EMR) system in the country.

We have patient office hours on Mondays, Wednesdays, and Fridays allowing us to provide more than 5200 patient visits each year. New patients are scheduled within thirty days of their primary physician's request for consultation. The emergency room is very busy. We perform 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, Kris Dumon, and the nurses, administrative support personnel, and physician staff of the PVAMC. This year the Vice President for Surgery and Anesthesia, John Wylie, retired after forty years of service. He will be sorely missed.

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 preoperative patient screening and preparation, rigorous instrument processing, new operating room instrument tables (replacing case carts), heightened awareness of potentials for intraoperative contamination, perioperative antibiotic dosing, and patient retention for onsite 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; WWII, 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 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.

Bayhealth Medical Center

Christos D. Photopoulos, MD, and Stephen G. Manifold, MD

The Department of Orthopaedic Surgery at Bayhealth Medical Center and our partnership with Penn Orthopaedics enjoyed another successful year, marked by faculty expansion, productivity, and continued enhancement of our resident curriculum.

This year, we are pleased to welcome Dr. Trinity Pilkington to our faculty as medical director of orthopaedic traumatology. Dr. Pilkington graduated from the University of South Carolina School of Medicine and completed his orthopaedic surgical residency at Allegheny General Hospital in Pittsburgh, PA. He subsequently completed a combined fellowship in trauma and arthoplasty in Boston, MA at Massachusetts General Hospital and Brigham and Women's Hospital. Dr. Pilkington's clinical interests include complex orthopaedic fracture care as well as joint arthoplasty, specializing in the muscle sparing anterior approach to the hip.

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Overall, this has been a great year for the Department of Orthopaedic Surgery at Bayhealth. As we look to the year ahead, we look forward with much excitement to continued productivity, resident interaction, and integration with the Penn Orthopaedic community.

McKay Orthopaedic Research Laboratory

Louis J. Soslowsky, PhD

Director, McKay Orthopaedic Research Laboratory

The McKay Orthopaedic Research Laboratory of the Department of Orthopaedic Surgery in the Perelman School of Medicine continues to explore important problems in musculoskeletal research. The research facility, including labs and offices, occupies just over 15,000 square feet of space on the 3rd, 4th, and 5th floors of Stemmler Hall. There are over 95 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 of over $6.5 million and continues to rank within the top 5 orthopaedic programs in the country in terms of funding from the National Institutes of Health (NIH). This past year has seen a very impressive and continued rise in new grant activity among the faculty.

We have had several new grants awarded this year. These include:

- Robert Mauck, PhD, received a new 2014 Cellular and Molecular Bioengineering (CMBE) Conference grant.
- Ling Qin, PhD, is PI of a NIH R01 titled, "Role of EGFR signaling in bone formation and the anabolic actions of PTH." Dr. Qin is also the PI of an ASBMR grant titled, "The novel role of EGFR in PTH anabolic actions in bone."
- Eileen Shore, PhD, is PI of a Morphotek Inc. grant titled, "ACVR1 Antibodies and HO - an Initial In Vivo Evaluation."
- Eileen Shore, PhD, and Robert Mauck, PhD, are dual PIs of a NIH supplement titled, "The Cellular and Molecular Basis of FOP Lesions."
- Lachlan Smith, PhD, is PI of a National MPS Society grant titled, "Pathogenesis of Bone Disease in Mucopolysaccharidosis Disorders."
- Joseph Bernstein, MD, Robert Mauck, PhD, and Louis Soslowsky, PhD, are PIs of a VA grant titled, "The Role of Local NSAID Administration and Inflammation on Tendon Healing."
- Louis Soslowsky, PhD, is PI of a NIH R01 titled, "Challenging Treatment Paradigms for Achilles Tendon Ruptures in an Animal Model," and a renewed NIH T32 titled, "Training in Musculoskeletal Research," along with a supplement titled, "Mechanisms of Joint Damage Following Tendon Injury." Dr, Soslowsky is also PI of a subcontract with CHOP titled, "Stimulation of Tendon Repair by Retinoid Nuclear Receptor Agonists" and a SRA with DJO Surgical titled, "Rotator cuff tendon to bone healing using P^2 porous coating."

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 include:

- Joshua Gordon, MD, is PI of an OREF grant titled, "The Effect of Early Mobilization After Surgical Repair of an Achilles Tendon Rupture in a Rat Model."
- G. Russell Huffman, MD, received a Surgical Shoulder and Elbow Fellowship from DePuy.
- Craig Israelite, MD, received a Residency Enhancement Grant from OREF.
- Gwo-Chin Lee, MD, is PI on a SRA from CD Diagnostics titled, "Acquisition of Synovial Fluid Samples: Creating a Repository for Biomarker Research" and a clinical study from CEM-102 Pharmaceuticals titled, "An Open-Label, Multi-Center, Randomized Study to Evaluate the Safety and Efficacy of Oral Fusidic Acid (CEM-102) in Combination with Oral Rifampin for Prosthetic Joint Infection, in Comparison with Standard of Care Intravenous Antibiotic Treatment Regimens, during Two-Stage Prosthesis Exchange."
- L. Scott Levin, MD, is PI of a DOD subcontract with CHOP titled, "Novel Immunomodulatory Therapies for Vascularized Composite Allotransplantation."
- Samir Mehta, MD, is PI of clinical trials from Synthes titled, "Patellofemoral Changes following Tibial Nailing: Does Approach Matter," from the AO Foundation titled, "DLS 5.0: A Multi-Center Randomized Controlled Pilot Study of Dynamic Locking Screws 5.0 vs. Standard Locking Screws in Fractures of Distal Femur Treated with Locked Plate Fixation," and from McMaster University titled, "Fixation Using Alternative Implants for the Treatment of Hip Fractures (FAITH): A Multi-Centre Randomized Trial Comparing Sliding Hip Screws and Cancellous Screws on Revision Surgery Rates and Quality of Life in the Treatment of Femoral Neck Fractures."
- Brian Sennett, MD, received a fellowship grant from DePuy Mitek.
- We have also received several grants from Synthes for residents to attend various courses as well as educational grants from Zimmer and Stryker.

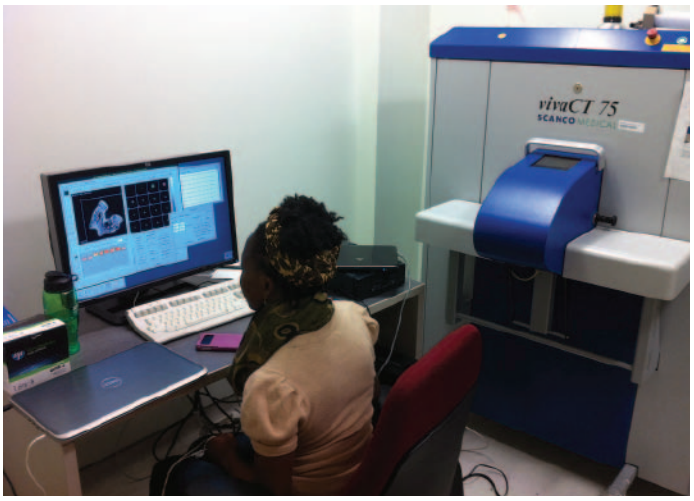
This year, we have recruited Dr. Lachlan Smith, linking Neurosurgery and Orthopaedic Surgery, and Dr. Foteini "Faye" Mourkioti will join our faculty on 7/1/14, adding expertise in muscle stem cell biology. Growing musculoskeletal research, not only within the Department of Orthopaedic Surgery but across the Penn campus has been a primary objective for our program, and these efforts have been particularly successful thus far. We look forward to another exciting year.

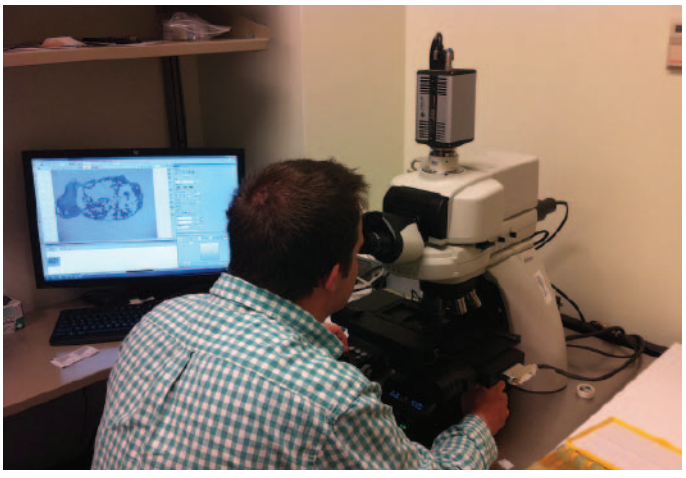
The PVAMC Translational Musculoskeletal Research Center is "Open for Business"

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

Aches and pains are 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 often more prevalent among veterans. While improvements in armor and "in theater" medical care have introduced incredible life-saving technologies, an increasing number of our wounded warriors return home with damaged limbs and joints. In response, the Department of Veterans' Affairs has focused research efforts to improve our understanding of MSK tissues and to develop novel technologies to optimize tissue healing and regeneration. Indeed, the last five years have witnessed 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 at the PVAMC, together with basic scientists and bioengineers from the University of Pennsylvania, are currently carrying out research projects to better understand the natural healing of MSK tissues, including tendons, ligaments, disc, bone, meniscus, and cartilage, after injury. Additional studies are underway to develop new technologies that may one day aid in the repair or replacement of these tissues and ultimately improve function and quality of life.

To further support MSK research activity at our PVAMC, the Medical Director Joseph M. Dalpiaz, Chief of Staff Dr. Ralph M. Schapira, and Associate Chief of Staff for Research and Development Dr. Kyong-Mi Chang recently have set in motion an exciting new research endeavor and inaugurated the Translational Musculoskeletal Research Center (TMRC) at the PVAMC. This new center brings together for the first time investigators from Orthopaedic Surgery, Rheumatology, Physical Medicine and Rehabilitation, Neurosurgery, and Bioengineering, all under one roof. Drs. Robert Mauck and George Dodge co-direct this new enterprise with input, advice, and support from a joint PVAMC/Penn TMRC Advisory Committee. 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 is greater than $1.3 million in direct costs per year. In addition, the VA has committed more than $2 million in equipment to outfit this new space in support of TMRC activities, including state-of-the-art equipment such as in vivo micro-CT, fluoroscopy, atomic force microscopy, and super-resolution confocal imaging. Building from this auspicious starting point, the goal of the TMRC is to develop into 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.





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Building Our Tomorrow

Alyson Cole, MPM

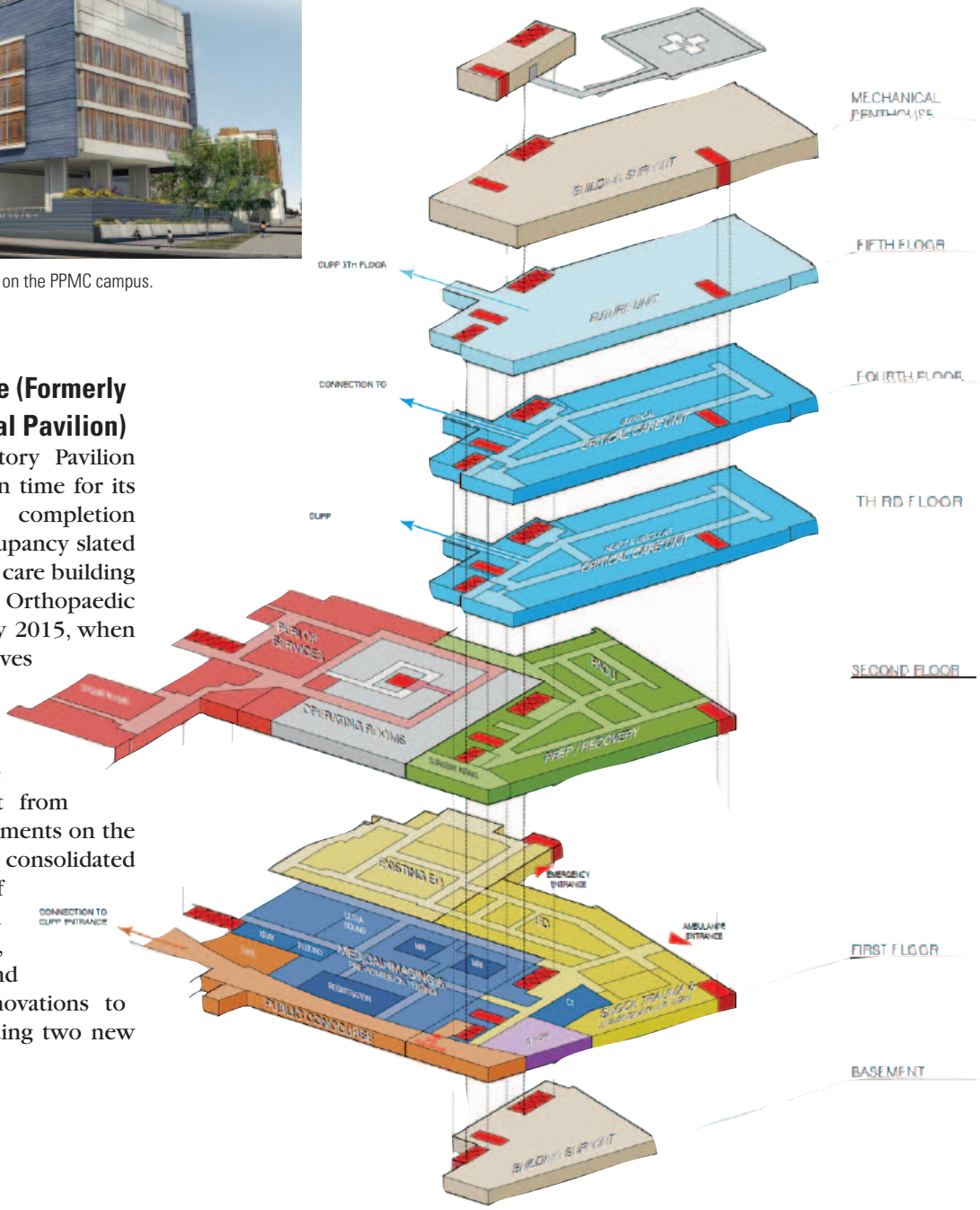
Assistant Executive Director of Penn Presbyterian Medical Center

The Penn Presbyterian Medical Center (PPMC) Cornerstone project is well underway as the construction on both corners along 38th Street proceeds onward and upward.

Rendering of the Pavilion for Advanced Care on the PPMC campus.

Pavilion for Advanced Care (Formerly the Advanced Care Hospital Pavilion)

Construction of the six-story Pavilion for Advanced Care (PAC) is on time for its scheduled November 2014 completion with move-in and patient occupancy slated for early 2015. The new acute care building will be the operative hub for Orthopaedic Trauma beginning in February 2015, when the Level 1 Trauma Center moves from HUP. The Orthopaedic Trauma Service along with the adult reconstructive, shoulder, hand, and spine teams at PPMC will benefit from numerous acute care enhancements on the campus, including a new and consolidated radiology suite, expansion of the PENNStar flight program with an additional helipad, entirely new preoperative and postoperative units, and renovations to the perioperative suite including two new operating rooms.



Schematic drawing of the Pavilion for Advanced Care. First floor: trauma bays, imaging, Emergency Department expansion (alongside previously existing structure), café, and registration. Second floor: pre and postoperative areas, perioperative services, operating rooms. Third floor: Heart and Vascular Intensive Care Unit. Fourth floor: Surgical Intensive Care Unit. Fifth floor: Room for continued expansion. Sixth floor: mechanical support and helipad for expanded PENNStar flight support.

Penn Medicine University City (Formerly the Penn Center for Specialty Care)

The 13-story state-of-the-art facility housing "Penn Medicine University City," located on the corner of 38th and Market Streets, is nearly complete. The new building contains eight floors of brand new space for ambulatory care and is due to open in August 2014. The University City tower will be the new home of the academic offices of the Department of Orthopaedic Surgery. The Penn Musculoskeletal Center on the 7th and 8th floors will occupy over 38,000 square feet of the tower and is complimented by services and programs tailored to the care of the musculoskeletal patient that occupy much of the remainder of the building. These include a full-service musculoskeletal imaging unit with Xray, 3T MRI, CT, ultrasound, and dexa scan; outpatient laboratory; pre-admission testing unit; pharmacy; the six operating room PPMC Surgery Center; the Penn Center for Human Performance, and a floor of outpatient therapy provided by Penn Therapy and Fitness.

Penn Medicine University City under construction.

Rendering of Penn Medicine University City on the corner of 38th and Market Streets.

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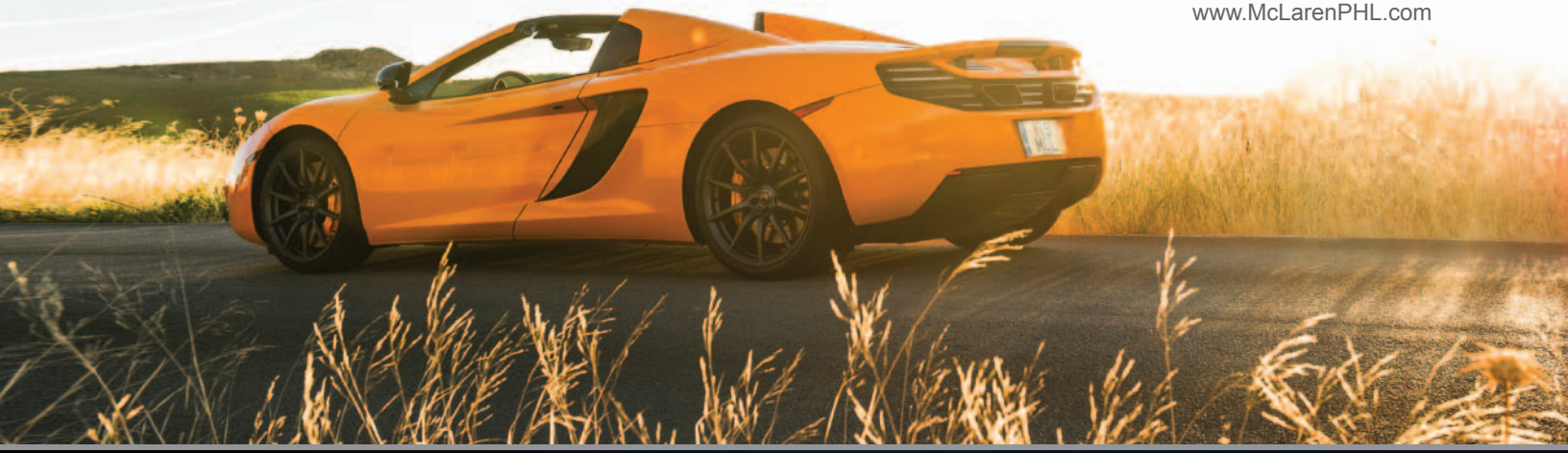

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