Temple University Journal of Orthopaedic Surgery & Sports Medicine

Volume 3
Spring 2008

A John Lachman Society Publication

The Temple University Department of Orthopaedic Surgery and Sports Medicine would like to extend their appreciation to

SYNTHES®

for their generous support of the John Lachman Orthopaedic Research fund

Synthes is the leader in orthopaedic internal fixation devices.

As the sole licensee of the AO ASIF, we develop, manufacture, and market the AO ASIF system of orthopaedic implants and instruments. Our goal is to provide the most advanced implants, biomaterials, instruments, and technologies that meet or exceed the highest expectations in safety and quality. Our products are designed to ensure reliable operating procedures, rapid recovery, and a pain-free life after surgery.

Synthes has committed significant resources to assist medical schools and the AO ASIF organization in conducting the most comprehensive post graduate training programs available for the orthopaedic surgeon. With emphasis on practical work in a laboratory setting, these courses enable the surgeon to learn how to use AO ASIF implants and instruments for a wide range of fracture types and surgical techniques.

SYNTHES® Original Instruments and Implants of the Association for the Study of Internal Fixation – AO ASIF

Table of Contents

Medical Student Research Projects: *Supervised by the Office of Clinical Trials*

Case Report

Review

Abstracts

Reprints

Lectureships

Philadelphia Orthopaedic Society Resident Bowl

Departmental News

Instructions to Authors

How to Reach Us

Editorial Office: Temple University Hospital, Department of Orthopaedic Surgery
and Sports Medicine, 6th Floor Outpatient Building
Philadelphia, PA 19140
Telephone: (215) 707-3411 • Fax: (215) 707-7976

Statement from the Chairman

It is my pleasure to present Volume III of the Temple University School of Medicine Department of Orthopaedic Surgery and Sports Medicine *Journal.* In addition to the collaborative efforts of our basic science and clinical research activity, this year's *Journal* includes a section dedicated to medical student projects. It has been exciting to see the enthusiasm among our medical students to participate and contribute to Orthopaedic research here at Temple.

Things on campus continue to move forward with both the Temple University School of Medicine and the Temple University Health System. The construction of the new medical school is on time and will be operational for the 2009–2010 academic year. On the hospital side, the Department of Orthopaedic Surgery and Sports Medicine is to play a major role in the reuse of the building that formerly housed the Children's Medical Center. It is anticipated that clinical operations will move into renovated space in the Boyer Pavilion along with Neurosciences and Rheumatology to create a Musculoskeletal and Neurosciences Center. We will also be moving into the operating suites in the Boyer Pavilion and inpatients will be placed on floors in the building dedicated to Orthopaedics. We anticipate that this will greatly enhance our ability to deliver excellent levels of care to our patients.

The Department of Orthopaedic Surgery and Sports Medicine here at Temple University continues to take great pride in its tradition of excellence in clinical service, education and research. I would like to acknowledge the Temple/Shriners Orthopaedic Alumni Association and The John Lachman Research Foundation for their continued support of resident education. I would also like to express my gratitude to Drs. Joseph Torg, MD, Saqib Rehman, MD, Asif Ilyas, MD and Simon Chao, MD, for their tireless efforts in making this *Journal* a continued success.

On a sad note, as most of you know, John W. Lachman, MD, passed away this past fall. His memory is eloquently eulogized by Philip D. Alburger, MD, in a section of this *Journal.* We will all miss his presence greatly and will realize, perhaps now more than ever, the impact he has had on all of us associated with Temple Orthopaedics. I am honored and proud to be enabled as one of his successors to attempt to carry on the standards that he set for Orthopaedic education and training.

Joseph J. Thoder, MD

Letter from the Dean

A Spectacular New Home for Temple University School of Medicine

The future is now — and Temple University School of Medicine is ready.

We have a full year behind us with our innovative and integrated curriculum. We have attracted 262 additional faculty members from leading institutions around the country and the world over the past four years. We are operating nine world-class, multi-disciplinary research centers, and our overall research enterprise is growing by leaps and bounds. Our reputation as a premier urban medical school is growing. We are attracting sharper and more socially conscious students every year.

We have broken ground for a spectacular new home for the school. Its impact will be nothing short of transformative. At a projected cost of $150 million, the 11-story structure rising on the northwest corner of Broad and Tioga Streets, just north of the existing complex, is the largest capital project in the history of Temple University — and the first new medical school building to be constructed in nearly 40 years. Slated to open in 2009, the new building will become the primary site of teaching and research within the school. It will stand as a striking symbol of Temple's commitment to teaching the medicine of tomorrow — *today.* Most important, it is designed to meet our needs well into the future, supporting the continued evolution of medical education.

With more than 301,052 net square feet of space, the new building will alleviate the severe space constraints under which the school has operated for many years, providing a truly state-of-the art setting for teaching, learning, and research. Its flexible, open design will house 100,010 square feet of academic space, 157,920 square feet of research space, and 43,122 square feet of public and support space, increasing the school's capacity for further creativity and innovative teaching and research. This facility is going to have a profoundly positive impact by recruiting stellar faculty and students, making Temple more attractive than ever.

Among the scores of features and facilities to support academic and community life in the new structure are high-tech dry labs that can simulate wet lab experiences. A wired and wireless infrastructure will support the latest educational technologies. The classrooms, able to facilitate large lectures, may be quickly reconfigured for small-group sessions. The new library within the building will serve not only students and faculty in medicine but also Temple's programs in pharmacy, dentistry, nursing, and related health professions, further facilitating the interdisciplinary nature of contemporary health sciences. An attractive café, a spacious and comfortable lobby, and ample study and meeting space will support the community life of the school. A glass-enclosed collaborative learning and research tower will house a series of stacked, multi-purpose rooms that can be used for teaching, meetings, office space, instructional support, study space or dining. The third-floor bridge, connecting the new building with the old, will breathe new life into Kresge Hall, allowing the older building to be used in concert with the new.

Seven floors of the new building are dedicated to research: 157,920 square feet of open, airy space, adaptable to projects both large and small, of short duration or long, and with input from a single discipline or a collaboration among many. Open, flexible laboratories will mark a significant shift in the research culture toward collaboration and interdisciplinary study, supporting current trends toward interdisciplinary and translational (bench to bedside) research.

The building's glass exterior and soaring atrium will be a spectacular landmark for the approximately 10,000 people who traverse Broad Street every day. It is more than just a wonderful structure; it's a real *home* for our thriving community. Where do blueprints end and professions begin? When is a building just a building or something more — an institution, a place of rich tradition and promise, a school, a home? It

is time for Temple University School of Medicine to have facilities that are commensurate with the quality of our faculty, students, research enterprise and curricula.

I am enormously excited about this new home for our school, and am enormously proud of our students and faculty. What they have accomplished in cramped, outdated quarters for so many years is remarkable. Imagine what will happen when we really have the space to spread our wings.

John Daly, MD

Letter from the President of Temple University

The start of a new year brings opportunities for the students, faculty and staff at Temple University. On campus and in the community, Temple is thriving.

With the final structural beam set in place on November 9, the new School of Medicine building is one step closer to transforming medical education at Temple. The building, the largest capital project in Temple's history, is on track to be completed in May 2009. When finished, its 480,000 square feet will double the amount of space used by medical faculty and students. The addition of 110,000 square feet of research labs will allow the university to recruit new faculty members and expand class size. Including a recent $1 million challenge grant from the Kresge Foundation, Temple's fundraising efforts for the project have reached approximately $25 million. Our initial goal — $30 million — is now clearly in sight.

In other Health Science Center news, Temple University Hospital (TUH) was named an American Society for Metabolic and Bariatric Surgery, Bariatric Surgery Center of Excellence. To earn a Center of Excellence designation, TUH underwent a series of site inspections where all aspects of the program's surgical processes were examined closely. The ASMBS Center of Excellence designation recognizes surgical programs with a track record of favorable outcomes in bariatric surgery.

Gary Foster, director of the Center for the Obesity Research and Education (CORE) and professor of medicine and public health at the College of Health Professions and School of Medicine, was appointed president of the Obesity Society for 2008. Dr. Foster, renowned obesity researcher who investigates the behavioral and biological effects of dieting and weight loss, has brought several ongoing National Institutes of Health studies to Temple that total more than $4 million per year.

On a sadder note, this season we mourn the passing of a devoted and inspiring leader. President Emeritus Marvin Wachman passed away on December 23. As the sixth president of Temple University from 1972–1983, President Wachman was best known for improving facilities, community relations and finances. During his tenure, he eliminated Temple Hospital's $50 million debt, oversaw the co-existence of a faculty union with a viable faculty senate and launched a centennial fundraising challenge. During retirement, President Wachman served as professor emeritus in the history department and honorary chancellor of the university. He and his wife, Adeline, recently pledged $1 million to support the Marvin Wachman Director of the Center for Force and Diplomacy Fund. I know the entire Temple community joins me in mourning this tremendous loss and extending condolences to the Wachman family. Temple will celebrate President Wachman's life and many contributions at an event being planned May 13.

I hope you enjoy reading about the remarkable progress of Temple University. With your continued support, there is no limit to what this university can achieve in the coming year.

Ann Weaver Hart, PhD

Letter from the Editor-in-Chief

We are proud to present the third volume of the *Temple University Journal of Orthopaedic Surgery and Sports Medicine.* In keeping up with the tradition of our past editions, this year's *Journal* represents a culmination of research endeavors within Temple University pertaining to the field of Orthopaedic Surgery and Sports Medicine. It is representative of the tireless efforts and burgeoning research endeavors of our Department.

In this edition, we have continued to work on including articles that encompass a broad spectrum of topics related to orthopaedics. We have compiled research from within our department with contributions from the Departments of Anatomy and Cell Biology, Physical Therapy, and Kinesiology at Temple University. Also, new to this year's volume is a section in our *Journal* dedicated to research sponsored by our Office of Clinical Trials, which sponsored research fellowships to medical students for academic research over the academic year.

There have been many significant milestones and events within our department in the past year which are chronicled in this year's *Journal.* With the passing of John Lachman, MD, the second Chairman of our Department, we mourned the loss of a great mentor, educator, and friend to innumerable people. It is his life that has inspired thousands of orthopaedic surgeons around the country, and we hope to carry on the tradition of excellence as the Department continues to strive towards new goals and heights in upcoming years. This volume of the *Journal* is dedicated in memory of this great man.

Finally, the entire editorial staff would like to thank the authors and reviewers for their contributions to this year's publication. Each individual who has participated in this year's *Journal* has devoted valuable time and energy to this project that has resulted in the work which you now hold. We are grateful to the advertisers and to the John Lachman Society for the financial support of our project, and recognize that without their support, this endeavor would not be possible.

On behalf of the editorial staff of the *Temple University Journal of Orthopaedic Surgery and Sports Medicine,* we hope you find this issue a pleasure to read.

Sincerely,

Simon Chao, MD

Latch in his Teaching Mode

The John Lachman Society supporting the John Lachman Orthopaedic Research Fund

LATCH IN HIS TEACHING MODE: Charlie Parsons' excellent drawing depicting "Latch in his teaching mode" has been adopted as the Society's logo. We are happy to inform that those who have accepted membership in the Society with a monetary commitment have received prints of Charlie's drawing autographed by Latch and suitable for framing.

Message from the John Lachman Society

The John Lachman Society was founded in 2004 to honor Dr. Lachman and propagate his principles of integrity, teaching, and excellent patient care. The Society will also provide discretionary funds for the Chairman to promote and support the academic mission of the Department including student and resident research. The mechanism to accomplish these goals will be through the Society's support of the John Lachman Orthopedic Research Fund (JLORF), incorporated in Pennsylvania as a non-profit corporation. The Internal Revenue Service has determined that The John Lachman Orthopedic Research Fund is exempt from federal income tax under 501 (C) (3) of the Internal Revenue Code and that contributions to the fund are tax deductible.

The mission of The John Lachman Society is twofold: 1) to promote the Lachman principles of integrity, resident training, and quality patient care by various proactive means and programs; and 2) to provide discretionary funds for the chairman to foster and support both the academic and research mission of the Department. Of the total contributions received in any calendar year, 75% will be invested in an endowment to be determined by Finance Committee with the approval of the Board of Trustees and 25%, plus interest on the endowment, will be used to support the aforementioned mission. Proposals for appropriation of funds may be initiated by Executive Committee, working committees of the Society, or the Chairman and will require the approval of both the Chairman and 51% of the Board of Trustees or two-thirds of the Board of Trustees.

Membership in The John Lachman Society will include the following groups and initiation contribution levels:

1) Physician group — $5,000.00 over five years;
2) Scientists and allied health professionals — $1,250.00 over five years;
3) Friends of John Lachman — $5,000.00 over five years.

Once an individual has met his or her initiation contribution, he or she will be a member in perpetuity. It is anticipated that contributions to the fund will also be forthcoming from satisfied patients and members of industry. Checks should be made payable to The John Lachman Orthopedic Research Fund and forwarded to P.O. Box 7283, St. Davids, PA 19087.

Those interested in membership in The John Lachman Society should contact the Chairman of the Membership Committee, Philip Alburger, MD, c/o The John Lachman Society, P.O. Box 7283, St. Davids, PA 19087.

JOHN LACHMAN SOCIETY MEMBERSHIP

Philip Alburger, MD
Mohammed-Tarek Al-Fahl, MD
Henry Backe, Jr., MD
Stephen Bair, ATC
Richard Boal, MD
Barry Boden, MD
Christopher Born, MD
Jim Bumgardner, MD
Patrick Carey, MD
John Casey, Jr., MD
Michael Cavanaugh, MD
Eugene Chiavacci, MD
David Clements, MD
Charles Cole, Jr., MD
William Cox, MD
William DeLong, MD
Ellen DeGroof, MD
Douglas Ditmars, MD
Kevin Flynn, MS
Kristine Fortuna, MD
John Gottlieb, MD
Stephen Heacox, MD
James Hurley, MD
David Junkin, MD
David Junkin, Jr., MD
Michael Kalson, MD
John Kelly, IV, MD
E. James Kohl, MD
John Kolmer, Jr.
Kevin Kolmer
Matthew Landfried, MD
Michael Larkin, MD
John Lehman, MD
Frederic Liss, MD
Robert Lykens, MD
Owen McIvor, MD
James McLamb, MD
Pekka Mooar, MD
Ray Moyer, MD
Stephen Orlevitch, MD
Charles Parsons, MD
Kenneth Peacock, MD
John Pell, MD
Edward Resnick, MD
Robert Richards, Jr., MD
James Rogers, ATC
Michael Romash, MD
Jeff Ryan, PT, ATC
Anthony Salem, MD
Richard Sandrow, MD
Samuel Santangelo, MD
H. William Schaff, MD
Joseph Scornavacchi, MD
Gene Shaffer, MD
K. Donald Shelbourne, MD
Michael Sitler, PhD
Gary Smith, MD
Charles Springer, MD
John Stelmach, MD
Zigmund Strzelecki, MD
Robert Sutherland, MD
Joseph Thoder, MD
Joseph Torg, MD
Bruce Vanett, MD
John Van Orden, MD
John B. Webber, MD
Albert Weiss, MD
Paul Weidner, MD
F. Todd Wetzel, MD
Gerald Williams, MD
Steven Wolf, MD
John Wolf, MD
Thomas Yucha, MD

RESIDENT RESEARCH SUPPORT: The following resident research projects have been or are currently being supported by The John Lachman Orthopedic Research Fund:

1) Anbari, A: "The Relationship Between Posterior Shoulder Capsular Tightness and SLAP Lesions."
2) Hsu, V.: "Elastic Instability, Columnar Buckling, and Orthopedic Injury."
3) Yucha, D.T., Junkin, D.M., Ilyas, A., D'Addesi, L.L., Purchase, R.J.: "Evaluation of the Relationship of the Dorsal Sensory Branch of the Ulnar Nerve to the 6U and 6R Arthroscopic Portals — An Anatomic Study."

4) Junkin, D.M.: "The Arthroscopic Anatomy and the Closure of the Rotator Interval."
5) Junkin, D.M., D'Adessi, L.L.: "Distal Radio-ulnar Joint Subluxation Resulting from Proximal Migration of the Radius — Defining the Pathologic Lesion and Treatment."
6) Purchase, R.J., Hsu, V.: "12–15 Year Follow-up of High Density Polyethylene Prosthetic Anterior Cruciate Ligament Reconstruction."
7) Reish, M.: "Intermediate Term Results of Arthroscopic Cuff Repair: Correlation of Outcome and Degree of Humeral Head Coverage."
8) Reish, M.: "Outcome of Arthroscopic Repair of Massive Rotator Cuff Tears."
9) Hsu, V.: "Functional Outcomes Following Radial Head Replacement."
10) Ilyas, A.M.: "Intramedullary Fixation of Distal Radius Fracture: A New Technique for an Old Problem."
11) Matullo, K.S., Sewards, J.M.: " Proximal Carpectomy: A Novel Surgical Technique."
12) Chao, S., Yucha, D., Thomas, S.: "The Effects of Scapular Fatigue on Shoulder Motion."
13) Chao, S., Thomas, S., Yucha, D: "The 'Bear Hug' Test in Detecting Upper Subscapularis Insufficiency — An EMG Study."
14) Matullo, K., Codjoe, P.: "Refurbished Drill Bits: Effectiveness in the Operating Room."
15) Matullo, K., Ilyas, A., Thoder, T.: "First Carpometacarpal Arthroplasty: A Review of Treatment Options and Introduction of a Limited Incision Technique."
16) Matullo, K., Samdani, A., Betz, R.: "Low Back Pain and Unrecognized Cobb Syndrome in a Child Resulting in Paraplegia."
17) Matullo, K., Sewards, M., Coll, A., Thoder, J.: "Proximal Row Carpectomy: Clinical Evaluation of a Novel Surgical Technique."
18) Matullo, K.: "A First Rib Ligament as a Potential T1 Nerve Compression Point."
19) Purchase, R., Stearne, D., Torg, J.: "Fourteen Year Prospective Results of a High Density Polyethylene Prosthetic Anterior Cruciate Ligament Reconstruction."
20) D'Addesi, L., "Biceps to Triceps Transfer for Elbow Extension in Persons with Tetraplegia."
21) MacIntyre, N., Rehman, S.: "Intra-Articular Civilian Gunshot Wounds to the Knee: Initial Management and Early Treatment."

WEBPAGE: The John Lachman Society web page can be entered at www.johnlachmansociety.org.

JOHN LACHMAN LECTURE: The inaugural John Lachman Lecture was held in conjunction with the Pennsylvania Orthopaedic Society annual meeting on Friday, November 11, 2004 at the Bellevue Hotel in Philadelphia. David Apple, MD, medical director of the Shepherd Spine Center in Atlanta, Georgia presented "Practical Ethics in Orthopedic Practice." Dr. Apple is a member of the Academy's Committee on Ethics and has published on the subject matter.

John Bergfeld, MD, Medical Director of the Cleveland Clinic Sports Medicine Program presented the second annual John Lachman Lecture entitled "Should the Team Doctor Pay to Play?" at the annual meeting of the Pennsylvania Orthopaedic Society in Pittsburgh on November 18, 2005. The lecture format was pro-con and John was suitably provoked by Joe Torg. We believe that this is a timely topic with profound ethical implications. The Pennsylvania Orthopaedic Society has made this lectureship a permanent part of their annual meeting itinerary.

The Third Annual John Lachman Lecture was presented by Michael A. Smerconish, well known radio talk show host, *Philadelphia Inquirer* columnist, and author of "Flying Blind" and "Muzzled." In addition, he is a frequent guest on several of the nationally televised news commentary shows. In view of the fact that most orthopedic surgeons are primarily pre-occupied with such matters as the anterior cruciate ligament, total joint arthroplasty, and tort reform, it seemed appropriate to indulge in matters of public policy and in the arena, Smerconish excels. The title of his talk was "Fifteen Points of Current Interest."

The venue for the talk was the Friday luncheon at the fall meeting of the Pennsylvania Orthopaedic Society, before a capacity audience in the ballroom at the top of the Bellevue. Smercornish opinioned on fifteen topics: Smerconish's talk was well delivered, well received, and reflected most favorably on the John Lachman Society!

Murray J. Goodman, MD, a member of the AAOS Committee of Professionalism, presented the Fourth Annual John Lachman Lecture. Dr. Goodman related how, in 2004, the Board of Directors of the Academy charged a group of orthopedic surgeons to develop procedures to review, hear, and adjudicate grievances between Fellows resulting from orthopedic expert witness testimony. The group broadened this charge and produced Standards of Professionalism which established mandatory, minimum levels of acceptable conduct for AAOS Fellows and Members that include: services provided to patients; professional relationships; expert witness testimony; research and academic responsibilities; advertising by orthopedic surgeons; and conflicts of interest with industry. Dr. Goodman's lecture was well received and clearly in keeping with the Lachman principles of integrity, education, and excellent patient care.

RESIDENTS DISSERTATIONS: The third annual John Lachman Society Research Day was held on April 14, 2007. Five resident research papers were presented. Kris Matullo was awarded $500 for best paper entitled "A First Rib Ligament as a Potential T-1 Nerve Compression Point." Lenny D'Addessi was awarded second place and $300 his paper "Biceps to Triceps Transfer for Elbow Extension in Patients with Tetraplegia." Robert Purchase was awarded third place and $200 for his paper "Fourteen Year Prospective Results of a High Density Polyethylene Prosthetic Anterior Cruicate Ligament Reconstruction."

TEMPLE UNIVERSITY JOURNAL OF ORTHOPAEDIC SURGERY AND SPORTS MEDICINE: A major accomplishment of the society was sponsorship of the second annual Temple University Journal of Orthopaedic Surgery and Sports Medicine. Forty-five hundred copies of the journal were distributed to members of The John Lachman Society, Temple University medical faculty and key University Administrators, members of the Pennsylvania Orthopaedic Society, Temple University School of Medicine alumni who trained elsewhere in orthopedic surgery, Chairman and Directors of orthopedic programs with residency training programs, selected members of the general orthopedic community including all members of the American Orthopedic Association, selected members of the National Athletic Trainers Association, and selected referring physicians. The Journal was well received and we believe clearly established the creditability of our academic program.

RESIDENTS LIBRARY SUPPORT: In keeping with the request of the Director of the residency program, The John Lachman Orthopedic Research Fund is committed to a $2,500 year expenditure for texts and other educational materials.

SYNTHES AWARD: Synthes has again for 2008 awarded The John Lachman Orthopedic Research Fund $20,000 to support the research and academic activities of the Department of Orthopedic Surgery.

FINANCIAL SUMMARY: Since its inception in 2005, the JLS has exceeded expectations in generating contributions to the JLORF sufficient to cover the Fund's operating expenses and has increased its' endowment, now over $175,000. Outstanding pledges in excess of an additional $200,000 bring the endowment to thirty-five percent of our goal of $1,000,000, which, conservatively invested, should yield enough money to carry our current level of annual expenses in perpetuity. This provides resources to the Department of Orthopedic Surgery at Temple University School of Medicine for research funding, resident education-related travel expenses, and publication of this Journal for the foreseeable future.

Joe Torg, MD
Secretary

In Memoriam

John W. Lachman, MD

John W. Lachman, MD
1919–2007

Delivered as a eulogy for Dr. Lachman on October 18, 2007 at Villanova University, St. Davids, PA.

Today, we mourn the passing of John W. Lachman, MD, distinguished Professor of Orthopaedic Surgery at Temple University School of Medicine and Chairman of the Department of Orthopaedic Surgery for more than 30 years. During that time, he was responsible for the education of over 200 orthopaedic surgeons and contributed to the education of thousands of medical students who are now physicians. He has already been memorialized professionally in many ways. His dedicated portrait hangs in a place of honor in the medical school. The Chair in Orthopaedics has been endowed in his name. He will be honored with the construction of an auditorium bearing his name in Temple's new $150,000,000 medical school scheduled for completion in 2009. He is also memorialized by the John Lachman Society, inspired by his principles of excellence in patient care, dedication to teaching, and the highest standards of medical ethics. His name is also universally recognized in orthopaedics around the world because of his innovation of the most reliable physical diagnostic maneuver for determining the presence of a torn anterior cruciate ligament. Yes, every time we see a team physician or trainer rush to the aid of a fallen athlete with a knee injury, we can consider it a tribute to Dr. Lachman since we can be sure that they are employing the maneuver which bares his name, the "Lachman Sign."

The facts and comportment of his life reveal some of the characteristics that made him so exceptional. He was always a diligent student blessed with a brilliant intellect. This became evident early on when he skipped third grade and finished grammar school early. As the top student in his high school's graduating class, he won a scholarship to Temple University. It was the Depression and times were tough, so he always appreciated the opportunity that Temple had given him to continue his education. Following college, he matriculated at Temple University School of Medicine, which he completed in three years and where he was again first in his class. There he met fellow student and life long friend, John Kolmer. A medical school professor of theirs whose name I don't know, but only the fact that they referred to him as "shifting dullness," continually irritated John by referring to him as Latchman rather than Lachman. Dr. Kolmer undoubtedly sensing a weak spot, immediately dubbed him "Latch" and it stuck. Here began a life long friendship. The Kolmers got a Godfather for the ages and Latch got another wonderful family to be a part of. For even though he never married, I considered Latch to be among the finest family man I've ever met. He was devoted to the Lachman families and all their children, and was also a surrogate member of the families, of many friends, former residents, students and patients. He may have been too busy to go to all of their cocktail parties, but if any of them had family members that were in trouble, or had any sort of problems, Latch would always be there to comfort and help. By the measure of the saying a "friend in need is a friend indeed," Latch was the best friend you could ever have.

His family and friends, however, were not the only beneficiaries of his extraordinary thoughtfulness and generosity. Latch seemed to make time for everybody, and had an inclination to help anyone in distress. If there was a patient left in the clinic at the end of the day without a ride home, Latch would drive him there himself. I know he once gave $2,000 to one of our trainers who wanted to go to physical therapy school, but could not afford it. Latch said, "I want him to be able to get his education." He gave money to a young caddy that was having difficulty getting to school and work because his car broke down. He gave financial assistance to his former maid when her family was in difficulty. He reduced his own salary so some of his staff could get raises. He is the only man I know who actually paid sticker price for a car because he liked the salesman. He gave of his time and resources routinely in many ways to those without the financial, social or political capital, to ever be able to repay him. He never wanted recognition. Among his peers, students, family and friends, he is universally respected as one of the finest gentleman that they

have ever encountered. But among all the benefactors of his virtues, the most fortunate may have been those of us who were nurtured by him as orthopaedic surgeons. To know him as he was, as a physician, the profession to which he devoted his life, was a stroke of extraordinary good fortune. He was the consummate clinician and a meticulous surgeon who seemed to make a personal connection with almost every patient. I was once treating a very urbane influential patient of Dr. Lachman's in his absence who was extolling Latch's praises, so I asked him what he thought made Latch so special? I expected him to mention Latch's extraordinary clinical acumen, but he replied "his humanity." When Latch injected a patient's knee, the beneficial effects lasted at least three months. When I, in his absence, would do the same to the same patient in exactly the manner that he taught us, they would return in three weeks to have it done properly by Dr. Lachman.

Talk about having presence. His patients loved him, and medically, it was as if he were a walking placebo effect. In addition to patient care, he had a passion for teaching, sharing his wisdom and knowledge with his students and residents. He was a true mentor and treated every resident as one of his sons. He tended to be extremely tolerant and forgiving of all sorts of our individual failings and idiosyncrasies. However, in matters of patient care and learning to be a skilled and gentle surgeon, he was an unrelenting task master in his demand for excellence and attention to detail. There was no escape from accountability. "It didn't just break." The aphorism went, "the road to failure is paved with blocks of sorries." If you made a mistake and said you were sorry, he would reply, "that makes no difference to the patient." You have to be more thoroughly prepared. If a resident failed to go to the emergency room to see a patient in a timely fashion, and the "man" as he was known found out about it, he might say something like, "Ed, I realize you were tired, but please if you ever find yourself in a situation where you can't make it to care for one of our patients, you must call me and not deny me the opportunity of coming in and caring for them properly myself." The problem with this type of scenario was that you knew that he meant it. This was not some sloganeer. This was not a detached administrator expositing a principal of patient care from a manual. This was a totally involved dedicated leader who never asked you to do anything he wouldn't do himself. He taught not by pontificating or admonishing, but by example. He simply expected us to meet the same standards to which he held himself, and he never had a self-serving motive or personal ambition. The single premise was to be totally responsible for all aspects of patient care. Consequently, he spoke with the commanding moral imperative of the only true authority, the authority to serve.

What motivates a man such as this? He certainly wasn't motivated by money. He cared nothing for fame or popularity. I think it might have something to do with the response I heard him give to an 85-year-old woman at the Waterford. She knew that he was a daily communicant and was never without his rosary. She said, "John, you are truly a holy man." He responded, "I'm not holy but I am trying to be." He was an ideal role model having led an impeccable life both professionally and personally. All of us who have studied under him, stand in awe of him and his level of excellence. We share a fraternal bond, for only having been taught by him could you possibly realize how much he cared for each and everyone one of us. We are in a sense "Latched" together. His departure leaves a huge void, for we know that we will not see another one like him come along in our life times. So it's time to see if the mentoring worked and we are left the daunting prospect of trying to emulate him so that his principals can endure. When I think of Latch, I'm filled with a great sense of gratitude to him for all he did for us, and to the good Lord for allowing us to have him for so many wonderful years. May he rest in peace.

Philip Alburger, MD

Artist Rendition of the New Temple University School of Medicine (Under construction — to be completed in 2009.)

John Lachman, MD '43
Medical School Building Capital Fund

Honor Roll

The follow individuals are major donors to the John Lachman Auditorium:

Easwaran Balasubramanian, MD
Berkshire Orthopaedic Associates, Inc.
Jack Michael Bert, MD
Daniel Bethem, MD
Barry P. Boden, MD
Mark Prince Brigham, MD
James L. Bumgardner, MD
Mrs. Roberta A. Butler
John Donald Casey, Jr., MD
Steven E. Casey, MD
William J. Cassidy, MD
Eugene John Chiavacci, MD
Leon D. Chipman, MD
David H. Clements, III, MD
Charles L. Cole, Jr., MD
William A. Cox, MD
Ellen L. DeGroof, MD
William G. DeLong, Jr., MD
Douglas Detrick Ditmars, MD
Robert A. Edelman, MD
Rachel I. Gafni, MD
Timothy Anthony Garvey, MD
John E. Gottlieb, MD
Dr. R. V. Gracilla
Michael J. Gratch, MD
Mark William Griffith, MD
Stephen A. Heacox, MD
Gary Wayne Hess, MD
David Maclean Junkin, MD
Michael Joel Kalson, MD
Leroy W. Krumperman, Jr., MD
Laurel Evaluations, PA
Guy Alan Lee, MD
John David Lehman, MD
Stephen Carroll Longenecker, MD
Robert Stewart Lykens, MD
John Thompson Magill, III, MD
The Medical Center Aurora
Matthew M. Mischinski, MD
Robert F. Ostrum, MD
Charles C. Parsons, MD
Kenneth C. Peacock, MD
Glenn B. Perry, MD
Edward J. Resnick, MD
Robert N. Richards, Sr., MD
Philip G. Roberts, Jr., MD
Robert A. Ruggiero, M.D
Anthony Walter Salem, MD
Samuel C. Santangelo, MD
Joseph M. Scornavacchi, Jr., MD
Michael L. Sidor, MD
Scott L. Silver, MD
Martin Barry Silverstein, MD
Charles P. Springer, MD
Mohamad Tarek Al-Fahl, MD
Harry Terrell Tate, MD
Temple/Shriners Orthopedic Alumni Foundation
Edward R. Thieler, III, MD
Joseph John Thoder, Jr., MD
Joseph Steven Torg, MD
Paul Louis Weidner, MD
Albert Aaron Weiss, MD
Louis H. Winkler, III, MD
John Henry Wolf, Jr., MD
Steven Brian Wolf, MD

Commentary

Critical Analysis of the Institute of Medicine Report on "Medical Errors"

JOSEPH TORG, MD

The purpose of this communication is to present a critical analysis of the report issued by the Institute of Medicine (IOM), a body chartered by the National Academy of Sciences, entitled "To Err Is Human: Building a Safer Health System." The release of this report stating that "at least 44,000 Americans die each year as a result of medical errors" and that "the number may be as high as 98,000" has resulted in front page media treatment, congressional and industry interest, and has served as a propaganda battle cry for some. It is my view that this report is grossly misleading, inaccurate in substance, inflammatory in nature, and portends a political agenda by demeaning the medical profession.

In the preface, William C. Richardson, PhD, Chairman of the Committee on Quality of Healthcare in America, makes several statements that deserve consideration. First, he states, "When agreement has been reached to pursue a course of medical treatment, patients should have the assurance that it will proceed correctly and safely so they have the best chance possible of achieving the desired outcome." Second, he states, "the healthcare delivery system is rapidly evolving and undergoing substantial redesign, which may introduce improvements but also new hazards." There is full agreement with these two statements. To be disputed and not substantiated by a critical analysis of the report is his position that "errors are responsible for an immense burden of patient injury, suffering, and death." This report lacks any semblance of scientific validity and is completely devoid of credible data to substantiate this conclusion. Simply put, the document constitutes a gross misrepresentation of the subject under consideration.

Completely lacking original data, and primarily relying on two previously published studies by the Harvard Medical Practice Study (HMPS) and a Utah and Colorado Hospital Survey (UC), sweeping recommendations are proposed predicated on the assumption that medical errors result in somewhere between 44,000 and 98,000 hospital deaths in the United States each year. Clearly, what has transpired is a combination of a subterfuge of semantics, exclusion of subtle but important nuances stated in the referenced reports, and extrapolation of referenced data that is clearly inaccurate, invalid, and not scientific.

A consideration of the semantics involved is crucial in determining and/or refuting the validity of the assertion that between 48,000 and 98,000 patients died as a result of medical errors while hospitalized. Error, as understood by the lay public, is clearly defined in Webster's Standard Dictionary as "something incorrectly done through ignorance or carelessness." The IOM bases their report on a definition of error "as a failure of a planned action to be completed as intended or the use of a wrong plan to achieve an aim." Clearly, the IOM's purpose of redefining this common term must be questioned. More striking is the fact that the two referenced studies on which the IOM report is based refer to adverse events, which they define as "an injury resulting from medical intervention . . . not due to underlying condition." Importantly, these articles further point out that "many patients who died after an adverse event had very serious underlying disease, and several surely had short life expectancies independent of their iatrogenic injury." The disparity between the assertion of 98,000 deaths due to "error" and deaths due to adverse reactions and their contributing underlying disease are neither delineated, nor dealt with.

A review of the two reports that the IOM based their assertion and conclusions regarding the occurrence of "medical errors" reveal them to be limited to retrospective chart reviews of hospitalized patients. Those of us involved in clinical studies are well aware of the unreliability and pitfalls associated with retrospective chart reviews. A credible and authoritative study must necessarily involve a prospective design and direct patient evaluation. In the studies that the IOM relied on, not one patient was interviewed, examined, or subject to a coherent evaluation. It is my view that the data relied upon is, for all intents and purposes, worthless.

The IOM determination of yearly occurrence of deaths due to medical errors is, to say the least, without logic. Basing their estimates on the UC and HMPS reports, it is stated that adverse events occurred in 2.9% and 3.7% of hospital admissions, respectively. It is stipulated that not all of these *adverse events,* defined as injury caused by medical management, were the result of *error* and "did not necessarily signal poor quality care." Of these *adverse events,* 8.8% and 13.6% led to death. Upon extrapolating *adverse events* resulting in death to over 33.6 million U.S. hospital admissions, "the results imply . . . that at least 44,000 Americans die each year due to *medical errors,*" as defined as failure of a planned action to be completed, and "the number may be as high as 98,000." Clearly the IOM converts apples to oranges *vis a vis adverse events* to *medical errors.* You figure!

To be noted, of the 19 members of the Committee on Quality Health Care in America who were signatories to the

report and the 11 reviewers, few are actually engaged in the clinical practice of medicine or surgery!

From this gross misrepresentation of the HMPS-UC data one can assume that the signatories to the IOM report either can't read, didn't read, or don't understand what they did read. However, we believe this assertion to be incorrect and can only assume that the data upon which the report is based was developed by inexperienced staff personnel. The outrageous misrepresentation of the data relied upon has appeared in an article in the *Philadelphia Inquirer* stating that "one of every two hundred hospital admissions in the United States results in death because of medical error." Taking on a life of its own, *USA Today* recently claimed 180,000 hospital deaths due to *"errors."*

The HMPS report upon which the IOM report is based clearly states that *"adverse events,"* which the IOM misrepresents as *errors,* "do not, of course, necessarily signal poor quality care." Also, they state, "elderly people are at a higher risk of an adverse event, and it may reflect in part the fact that older people are likely to have more complicated illnesses and often require more complicated intervention." To reiterate, "many patients who died after an adverse event had serious underlying disease" with "shortened life expectancies independent of their iatrogenic injury." In addition, the HMPS pointed out "many of the adverse events we identified were neither preventable nor predictable."

It is not denied that problems exist in the delivery of healthcare or that medical errors occur and can result in deaths. However, such problems must be identified and their solutions must be predicated on data obtained by accurate, reliable and appropriate scientific methodology. Congressional appropriation of 100 million dollars a year, as recommended by the IOM to deal with these issues is modest if it is appropriately and effectively spent, if problems are clearly identified and effective solutions implemented. This will not occur with the creation of another bureaucracy staffed by medical know-nothings. Contrary to this irresponsible and damaging report, the finest medicine with the most advanced technology and best-trained physicians and paramedical personnel is here in the United States. It is with this group that the responsibility of dealing with these issues lies.

Although a number of problems with healthcare delivery are mentioned by the IOM report and referenced studies, several other critically important issues were not addressed. These are issues that make it impossible for responsible members of the medical community to exert effective oversight and control regarding the dangerous and/or irresponsible behavior of the mentally, physically, or substance abuse impaired physician, the incompetent physician, or the economically motivated charlatan. It is with regard to these matters, a system of grievously flawed oversight and a jurisprudence that functions as an enabler that warrants attention.

The current system by which deviant practitioners are sanctioned is through peer review, a medical staff process protected from discovery with confidentiality being insured. It is my view that the peer review system as it functions today is grievously flawed. To expect members of a medical staff with emotional, economical, and political ties to an individual in question to be impartial and objective in their deliberation is unreasonable. Of equal importance, the investigative part of the peer review process starts at the department level where there is a lack of expertise, resources, and for reasons to be mentioned, commitment. Clearly, the initial phase of an investigative process of misconduct must be performed by individuals who have the proper resources at their disposal and no ties to the practitioner in question.

Recently, Senator Arlen Specter stated his intention to introduce legislation to fund research "that would help determine the best way to curb the tens of thousands of deaths each year nationwide that stem from medical error." Clearly, the Senator has also been misled by this spurious and inflammatory IOM report. According to press reports, he mentioned several mandatory-reporting scenarios, one of which would involve mandatory reporting of medical mistakes and require that patients be told of errors. I trust that the Senator is cognizant of the boondoggle that such a scenario would afford the plaintiff's bar. Clearly, in my mind, the major reason that physicians and hospital administrators are hesitant to declare errors, right or wrong, is that there prevails as a result of the existing jurisprudence system a lack of commitment on the part of most to participate in these matters for fear of litigious retribution. To become involved in an attempt to sanction a physician is a guarantee to be the subject of a law suit for purported slander, liable, defamation of character, interference with one's ability to make a living, etc. Quite frankly, who need the grief? To enact effective measures that will include participation of all responsible members of the medical community will necessitate safeguards to protect those who come forth from vindictive and spurious litigation.

In my view, the IOM report entitled "To Err Is Human" is an inflammatory document lacking creditable scientific format that intentionally or otherwise serves to demonize the medical profession.

References

1. Brennan, AB, et al. Incidence of Adverse Events and Negligence in Hospitalized Patients: Results of the Harvard Medical Practice Study I. *N Eng J Med* 1991; 324:370–376.
2. Leape, LL, et al. The Nature of Adverse Events in Hospitalized Patients: Results of the Harvard Medical Practice Study II. *N Eng J Med* 1991; 324:377–384.
3. Thomas, EJ, et al. Costs of Medical Injuries in Utah and Colorado. *Inquiry* 1999; 36:255–264.

Commentary

It's the Drugs, Stupid!

JOSEPH TORG, MD

Philadelphia, recently designated as the "next great American city," is in reality becoming its murder capital. The statistics are all too familiar: 330 homicides in 2004, 377 in 2005, and 406 in 2006 with 80% of the deaths resulting from gunshot injuries. Philadelphia has more murders per year than New York City with six times its population. Most alarming has been the fact that four Philadelphia police officers have been shot last October with Officer Cassidy dying from a gunshot wound to the head. Chaos reigns, the bad guys rule the streets, and by all appearances our governmental and civilian leaders appear confused and befuddled. Former Mayor Street announced a crackdown on curfew violations and begged the city's youth "to lay down their weapons." Police Commissioner Johnson has observed that there are "too many guns on the street" but laments that implementation of Mayor-elect Nutter's "stop and frisk" policy will result in civil discord and insurrection. And the gun nuts say that "guns don't kill people, rather people kill people" and unyieldingly maintain that the second amendment to the Constitution guarantees the right of the people to keep and bear arms and shall not be infringed, failing to recognize that the Constitution also guarantees freedom of speech but according to the Supreme Court that does not mean that one can yell "fire" in a crowded theatre. And talk show host Michael Smerconish, one of our town's clearer thinkers, only gets it half right. For reasons that are difficult to understand he opposes the ban on the sale of assault weapons. He believes that the solution to the problem lies in the home, a concept supported by Richard Gelles, Dean of the School of Social Policy at Penn who points out that the 1996 welfare reforms created the situation where single parents were put to work and the kids were left alone at home. Without proper supervision children are now being raised on the street. Smerconish emphasizes that it is the absence of the father in the family structure that is responsible for the mayhem and crime that is so pervasive in our society. Certainly this concept cannot be disputed, however solving the home problem is a long term project that pushes the time yield curve too far out to help the current situation. And the *Inquirer*'s editorial page states that "to reduce violent crime you must address the factors that produce it including unemployment, poverty and bad schools." Again long term projects that push the time yield curve too far out. Which brings us to Michael Nutter's stated intention of initiating a "stop and frisk" policy to remove guns from the street. Under the category of innovative police work, this tactic emanates from the classic study of criminologist and Penn professor Lawrence Sherman, who twenty years ago demonstrated that police enforcement of minor quality of life crimes, i.e. urination in public, jaywalking, turnstile jumping, etc. and in high crime "hot spots" resulted in discovery and confiscation of illegal concealed weapons. With fear of confiscation, the bad guys leave their guns at home and presumably the murder rates will decrease. Allegedly, this worked for Mayor Giuliani in New York City during the 1990s. The important question however, is whether this technique was actually responsible for the observed decrease in homicides. Steven Levett describes in his book Freakonomics the correlation of the Roe vs. Wade Supreme Court decision and the reduction of crime seen in the early and mid nineties. Accordingly, legalized abortion led to less child unwantedness, child unwantedness leads to higher crime and legalized abortion therefore leads to less crime. However, where New York City had 2,245 murders in 1990, it is on track to have less than 500 this year. Thomas A. Reppetto, a police historian and co-author of "NYPD: A City and its Police," observed that in the early 1990s the city's crack-cocaine epidemic was responsibility for many killed by bullets from battling drug gangs. Police action against the drug gangs has resulted in a marked decrease in the number of homicides.

It is my view that many, if not most, of gun related crimes and homicides are related to the use of both illegal and legally dispensed narcotic agents. Consider shootings associated with "a drug deal gone bad," drug dealers' turf battles, robberies to obtain funds to support the addict's habit, the irrationality and unpredictability of the deranged addict, and more recently those aimed at law enforcement officers. On October 30, 2007 a "perp" shot two men and one woman at 15th and Sansom Street, then shot a police officer at 22nd and Sansom and then proceeded to jump off the Chestnut Street Bridge and drowned. It is a reasonable assumption that the autopsy toxicology panel was positive for narcotics. John Lewis, who confessed to shooting and killing officer Chuck Cassidy, has a history of drug related violations. Again, it is a reasonable assumption that his robberies of the West Oak Lane Dunkin Donuts as well as the Feltonville Pizza Shop were to obtain funds to purchase drugs. The more recent shooting of two police officers in the Torresdale section drug bust is clearly more of the same.

To reiterate, it is primarily the drug problem that must be confronted and resolved to bring peace, safety and tranquility to the streets of Philadelphia. To do this there must be interdiction of the illegal drug supply chain and stringent control of legally prescribed narcotics and controlled agents.

Having practiced orthopaedics in this city for forty years, it is with regard to the latter issue that I believe that I can speak with some authority. Simply put, it is my view that there are both gross inadequacies in governmental narcotic controls as well as irresponsible dispensing and prescribing of controlled substances by duly licensed members of the medical profession. I believe that these two issues are major contributors to our crime problem and that clearly; these are two issues that are within our grasp to resolve.

The arrest and conviction of Philadelphia Eagles'coach Andy Reid's sons Garrett and Brett are a case in point with regard to what I perceive to be the medical community's irresponsible behavior in dispensing and prescribing narcotics. Montgomery County Judge Steven T. O'Neil was right on the mark when he stated "the medical community is just as much to blame for what happened to these two men . . . we live in a society where dangerous narcotics are highly overprescribed . . . so it is little wonder we are seeing them as drug addicts." Substantiating the judge's opinion is the fact that the younger Reid was prescribed Percocet "after he "cracked a vertebra" while lifting weights while in high school. This is a common condition that involves a stress defect in one of the lumbar vertebrae and under no circumstance would a responsible physician prescribe a narcotic. I see patients on a daily basis who have been inappropriately prescribed Percocet and Oxycontin by emergency room, family, and referring specialists. It is my opinion that the only two situations justifying the use of narcotics in the practice of orthopaedics are in the management of post-operative and fracture pain. Missing from the Reid story was an answer to the crucial question of how and why was OxyContin, a controlled substance regulated by the Drug Enforcement Agency (DEA) and requiring a physician's prescription so available to Garrett Reid. OxyContin, manufactured by Purdue Pharma and Percocet, manufactured by Endo Laboratories are not products of the Afghanistan poppy fields or the Columbian drug cartel. They are produced and distributed by companies here in the United States and their ubiquitous availability "on the street" clearly raises questions of these manufacturers' complicity. The culpability of Purdue Pharma for misleading the public regarding the abuse potential of OxyContin and their widespread security and record keeping problems at the company's manufacturing plants in Stamford, Connecticut resulted in three top Purdue executives pleading guilty to criminal charges that in May of 2007 and resulted in their paying a 634.5 million dollars in fines and payments. Also to be questioned is the role or lack thereof of the DEA in controlling the distribution of controlled substances.

Another major problem is the indiscriminate prescribing of narcotic agents by emergency room and primary care physicians. Simply put, the medical establishment has not defined clear indications and contra-indications for the use of these substances. With regard to OxyContin and Percocet, it is my view as an orthopedic surgeon that they should only be used to treat pain associated with major surgery, complex fractures, and terminal pain. The Reid's struggle represents but a tip of the iceberg, for much if not most of the mayhem and murder perpetrated on the streets of Philadelphia are clearly the result of drug activity and abuse. Until the drug problem is resolved mayhem and murder will prevail.

It is also interesting to note that it has been recently reported that "a loosely knit group of Philadelphia men roamed the suburbs at night for years, burglarized 47 Mom and Pop pharmacies and rural gun shops and then resold 400,000 stolen pain pills and 188 weapons on the city streets." Is this the tip of the iceberg? How do legally manufactured drugs such as Percocet by Endo Labs and Oxycontin by Prudue Pharma get to the illegal pushers on the streets? What are the sources of drugs that end up on the street and who is keeping track? Certainly this is something that can and should be controlled.

And what has the Drug Enforcement Agency been doing other than issuing licenses to physicians to prescribe controlled substances; the only requirements being that they not be convicted felons and pay a fee. The activities of the DEA must be more comprehensive. And that would include electronically monitoring the dispensing of controlled substances from secure vendors.

Murder, mayhem, shootings and stabbings will persist until it is understood that to paraphrase the Clintonesque mantra "It's the drugs, stupid!"

Commentary

Resiliency and Medicine — AKA: 'You Cannot Give What You Don't Have'

JOHN D. KELLY IV, MD

Medicine is a race — a marathon, 'Burnout,' or emotional exhaustion, is very common and affects about one third of physicians during their careers. Resiliency — the ability to 'bounce back' from difficulty, can be attained, even in the face of the most trying of times. Resiliency is really not about hours worked or hardships. It is about how you manage your *emotions and relationships.* It is about the 'call to character' and *choosing* actions which will ultimately sustain us (Sotile and Sotile). It is also about being mindful of energy flows in your life. Everything we do can 'drain or sustain.' Thus, one of the keys to resiliency is to minimize energy drains and maximize what replenishes us. The virtue of resiliency can be learned since the brain is a rather plastic organ. Certain maladaptive behaviors can be replaced with healthy ones such that the brain will be 'hard-wired' to perform healthy, energizing behaviors and to think 'good thoughts.' No matter what your background, genetics or station in life, you have the power to *choose* the life you want.

Steven Covey describes proactivity as basing behavior on *decisions,* not conditions. We can subordinate feelings to **Values.** We all have the power to choose our lives based on the values we revere, rather than our conditions or feelings. In other words, we are not our moods! I hope to share with you some thoughts on the values that will sustain you and how to attain a powerful mind and a resilient self. The principles that I would like to serve as 'take home points' are:

1) You cannot give what you do not have — happiness matters!
2) Emotions are contagious — be aware of what you spread around!
3) We can *choose* our actions, and therefore *create* the 'culture' at work and at home we desire.
4) The more we nourish relationships (especially our partner!) and the more 'uplifts' we can set place in our lives, the more resilient we will become.

When we make the choice to engage in healthy behaviors, we are slowly changing our brains. Behaviors once thought to be 'automatic' can be changed in time. When we change our behavior, we slowly eliminate maladaptive habits and *change our brain* (Schwartz) We literally 'inch closer' to forming a powerful mind!

In order to survive today's demands, one must cultivate a sense of self-nurturance and remember that *principles* govern our existence. In other words, as much as we would like to think otherwise, we cannot 'cut corners' with Mother Nature. Ask yourself the following questions to determine your 'risk' for burnout and anxiety/depression.

1) Do I get adequate sleep?
2) Do I go to the Doctor and dentist responsibly?
3) Do I have time to exercise?
4) Do I eat healthy meals?
5) Do I engage in a hobby?
6) Do I feed my soul with fine music, literature and art?
7) Do I feel close to my loved ones, especially my spouse?
8) Do I regularly connect to a Higher Power?

If the answer to any one of these questions is NO, you are neglecting some of your *basic* needs and not fueling your soul. Again, burnout does not correlate necessarily with hours worked as much as it does with meeting our basic human needs, especially the need for CONNECTION.

Let us look at energy drains and how JDKIV addresses them:

Demands of Contemporary Practice of Orthopedic Surgery

1) *Harried pace, dwindling resources result in having to see more patients, perform more surgeries, more paper work.*

   Those of us in urban, 'unfriendly' locales (such as Philadelphia) can be sued BID or TID. Surgeons have thus found themselves in a 'High demand-Low control' environment that can sap our energies dry. We feel at the mercy of insurers, patients and attorneys. The means to resiliency in these environs is to minimize the effects of the demanding world and to focus on the things *you can control and relinquish those you are powerless over.* A principle center, that is, having a changeless core in the midst of an ever-changing world, can introduce some measure of stability to your life and keep you energized. *You are in control of your actions* and they are in concert with your Values. Your energies are directed to doing the *right thing* in the *right way* in accordance to what you hold as morally correct. You can feel good at the end of the day knowing you did everything in your power to be true to what you hold as just. Living from a principle center is energizing; you are true to yourself! You are no longer at the mercy of 'what they must think' or what other less noble forces ask of you.

   Whenever you find yourself criticizing or complaining, you are in *negative energy* and focusing on things

for which you have *no control.* Criticizing someone else's behavior will accomplish nothing except undermine your mood. Complaining, similarly, will do nothing to effect positive change. Positive change occurs when we 'ask' for things for ourselves and focus on what we can control or influence. **Assertiveness** really means being fair to *yourself* and fair to *others.* Are you in a practice that is not FAIR to you? If you do not 'ask' for yourself, resentment will build and your energy will wane. I like the pneumonic **D.E.A.L.** when practicing assertiveness: **D**escribe the situation as you see it (use "I "statements). **E**xpress yourself and your feelings (again, "I" statements). **A**sk for changes (*demands* rarely work!) **L**ist the benefits (think 'win/win').

JDKIV solution: I have done my best to stay 'centered' and 'value based,' committed to try to do the right thing in the right way. I am in control of my actions which are *value based* and not prey to the whims of the 'world' I know my tendencies (OCD, ADD, 'touch' of bipolar) and I tend to 'please everyone.' However, I realize that *principles* are more important than 'being liked.' I choose my behavior based on the values and personal mission statement I have articulated for myself. My values and mission statement are written in a notebook and I refer to them often so I can stay 'on track' — *no matter how I feel.* If your 'core' or 'center' is spiritually based, the 'world' can only do so much to hurt you! A good part of my mission statement includes 'to look for the good in myself, others, the world and the future.'

The whole notion of looking for the GOOD or 'gift' each situation brings us can be life transforming. You will find yourself living in more positive energy. Whenever an issue arises in the hospital that may have negative consequences, I ask myself "what can **I do** about this to effect *positive* change?" Or 'What good can arise from this, what lesson is to be learned?'

Lastly, I try to approach patients with the mindset 'who is my God sending me today? How can I *help* this person? What **good** can I see in this person in pain? What **good** can I effect?' Rather than viewing each patient as a potential litigant or 'the enemy,' I try to get out of my self-absorption and focus on this "Divine Moment" whereupon I am called to effect a positive change for someone. I look for the **good** in the situation and devote my focus to this.

2) *Perfectionism and the pursuit of an illusory goal.*

How about your standards? Medicine attracts perfectionists who are accustomed to harshly criticizing themselves and creating expectations that are unrealistic. If you always feel that you are 'missing the mark,' you will be continually disappointed and **drained.** Furthermore, perfectionism throttles the creative, life force within us. It is nearly impossible to be creative and produce innovative and novel work when one is continually feeling the pressure to perform at superhuman levels. By 'letting it flow,' you will not only find creativity is nurtured, but productivity skyrockets.

JDKIV solution: I recognize that *perfection is an illusion* and only leads to frustration and wounding of self-esteem. I have learned much about myself and realize I am plagued by OCD (Obsessive Compulsive Disorder) and I can drive myself crazy striving for a 'perfect surgery.' I have learned to recognize, accept and label the 'voice of OCD' and practice detachment from the 'voices.' I *choose* instead to act on my value of 'daring to be average' and 'letting it flow.' I remind myself daily that HAPPY DOCTORS ARE HEALTHIER, GIVE BETTER CARE AND ARE MORE PRODUCTIVE. I am not advocating complacency, and I still strive for excellence, but I set realistic goals and listen to the gentle voice of fulfillment and satisfaction for a job well done. I try to nurture myself so I can better take care of the next patient. I tackle problems 'head on' — problems that my perfectionist voice tells me to 'avoid until I am ready.' I realize that unfinished tasks consume enormous energy (William James).

2a) *Clutter*

Part of the perfection and obsessive trait is the ease at which clutter infiltrates our lives. Unnecessary items and lack of order drains us and stifles creativity. I struggle with this but have found the following helpful regarding objects that clutter our lives: a) if you haven't *worn* or *used* it within a year, give it to someone who can. Giving frees us to receive and energizes our spirit by helping us recognize all that we *do have* and that our abundance will help someone else. b) clear off your desk. Handle things as they come the best you can and delay only those things that need considerable attention. However, by 'daring to be average' if you just breathe and try to 'just do it' you will be astounded at your productivity. Ten 'good works' are far better than one 'Mona Lisa.'

2c) *Journals*

In this day and age of online access, there is no need to pore over and store every publication imaginable. I do my best in scanning journals for relevant articles and focus on that which will help me the most. The 'Parieto Principle' dictates that 80% of what we need to know in life is discovered, on average, by 20% of our efforts. The challenge, therefore, is to discern what is truly good and useful and ignore the rest. Eliminate clutter from your office and discard old journals. You can access them online!!!

3) *Anxiety/Depression.*

It is truly difficult not to get into a 'funk' with all the responsibilities of Orthopedic Surgery. It is certainly normal to feel 'blue' when a surgery does not go particularly well or when a complication develops. However, anxiety and depression are not *normal* responses to stress and are largely the result of *distorted thinking.*

JDKIV solution: With the help of a cognitive therapist, I have learned how to better respond to the distorted thoughts which lead to emotional unrest. Again, I practice 'detachment' and love the pneumonic **AWARE:** a) **A**ccept the unwanted thought because fighting intrusive thoughts gives them strength. b) **W**atch the thought from a distance — learn to stand apart from your hurtful thoughts. c) **A**ct according to your values (no matter how you feel, and remember that if you change your behavior, you will change your brain!). d) **R**epeat the process. e) **E**xpect the best (look for good).

Whenever I am plagued by an emotional rut (I am Irish, these do occur!), I DO NOT BELIEVE A THING MY MIND TELLS ME. Learn to become an impartial spectator to your thoughts and recognize when they are distorted or harmful. When you can detach and look at harmful thoughts as *not being you,* but merely your mind *playing tricks on you,* you are on your way to developing a **strong mind.** For example, while in the OR, after I have attained that very good reduction, I have learned to label the 'voice of perfection' which has, in the past, prompted me to do and undo many a very good reduction. I **a**ccept the 'voice,' **w**atch it from a distance, and then **a**ct on my value of patient safety and expeditious surgery. I **r**epeat this as often as necessary and **e**xpect the best!!! Since I have learned to detach from my harmful thoughts, my OR times are but a fraction of what they were several years ago. I leave the operating room more satisfied and my patients are doing very well!!!

I also journal regularly and write down recurrent or especially troubling distorted thoughts and respond to them. I find these thoughts arise whenever stressors are greatest or when major decisions are to be made. I use F.A.S.T. (MacDermott) when dissecting thoughts. What are the **F**acts or evidence to feel this way? What is an **A**lternative way to look at the evidence? **S**o what if it is true. (What is the worst that can happen?). **T**oll. What is the effect on my thinking?

When I am anxious, I realize distorted thinking is to blame and also recognize that anxiety is ENERGY. I also use **AWARE** and I try to use this energy to face the problem I may be avoiding. I also try to practice mindfulness, or living in the present (Divine Moment), and/or meditate whenever I feel anxious, since anxiety is about fear of what may occur in the **future.** Staying in the present lessens anxiety greatly.

Mindfulness tip: focus on the breath in and out you nostrils. I use a prayer with this concerning gratitude. JDKIV mantra "Father (inhale) Thank You (exhale)" and I conclude each breath with a thought of something I am grateful for (Marie, Ann Marie, Mary etc.) By being aware of one's breath, you can 'stay in the moment' and enjoy more peace.

Final JK tip: get help when needed. June 2003, JDKIII died, practice was 'out of control' and lawsuit 'du jour' was pending. I couldn't sleep for three months. DEPRESSION. I consulted a psychiatrist friend, and started low dose meds. In addition, I saw a cognitive therapist and went back to *fundamentals* in order to recover — God, as I knew Him, relationships and self-nurturance.

Now that we have addressed energy consumers, we will discuss energy sources. How do you replenish yourself? In order to stay resilient, we need to continually stay connected to the things that give us passion, interest, meaning and 'uplifts.' In addition to focusing on our basic human needs, such as sleep, nutrition, exercise, we all need to encourage 'connection' — with our staff, patients, families and higher power.

What we spread around will help us or hurt us. We truly do 'reap what we sow.' Humans are hard wired to respond predictably to love and affirmation. Positive actions reap positive responses. Also, when we choose to look for the good, our mood is boosted. We are entering positive energy! Good and bad exist in every person, situation or thing. What matters is what we *choose* to focus our energies on.

When we go to work in the morning, do we greet our staff or do we mumble or complain about the latest practice "issue." Do we bless others or criticize them? I can assure you; if you look for the good you will find it and in the process *bless* your life as well. We all need to make the proactive decision to be a love finder, not a fault finder. We need to look for the good in ourselves, others and the future. We can affirm and bless all we meet, not condemn them. Again, whatever you reap you will sow. When we look for the good and bless others (no matter how we feel) we will fashion a 'culture' that exudes positive energy that will help sustain us. As Drs. Wayne and Mary Sotile have elegantly stated in their writings on physician stress, resiliency is not about absence of hassles. It is about presence of 'uplifts.' Emotions are truly contagious!!!! Also remember, happiness matters. If we boost our mood, our productivity will increase. Further, happy doctors give better care, have more compliant patients and are less likely to be named in malpractice suits!

Humor is a wonderful way of staying in positive energy. When we look at the light side, we are affirming that things will be OK and that nothing is so bad that we can't at least

joke about it. Humor must be positive to be truly effective and can never be at someone's expense nor can it be a weapon. Complimentary humor, or making light of someone's strengths, is a wonderful tool for spreading around positive energy. Lines like 'she is so smart . . . her IQ is higher than my malpractice premium' convey both affirmation and humor. Keep humor positive and see what it can do to a gathering!

JDKIV method: I try to greet the office staff and OR staff with good humor *before* the day starts. I am generous with compliments and use *humor* to especially ease tensions in the OR. I am quick to affirm a resident's performance and liberally praise (when indicated) ancillary staff. I also strive to be gentle with myself and regularly refer to a list of surgeries and accomplishments that I have done well. (Give *yourself* uplifts!)

The greatest affirmation we can receive is from our **partner. 'No single thing will bring you more happiness than investment in your marriage'** (*Fighting for Your Marriage,* Markman, Stanley, Blumberg). Marital problems are the number one cause of depression in America. Emotional connection and support of spouse/partner is essential for resiliency. Everything *good* flows from the union with your partner — security, intimacy, positive feedback, a beautiful secure family culture and the overall sense that you are not alone in facing the world. Investment in marriage is truly an investment in your happiness and fulfillment. Work on 'Living in Love' and *hang in there!* 72% of 'miserably married' couples, when questioned 5 years later, are happy!

Likewise, investment in *families* has huge dividends in one's quest for peaceful living. The *Value* one places on family will largely determine one's peacefulness and resistance to stress. NO ONE WILL 'COVER YOUR BACK' LIKE YOUR FAMILY! ". . . what I call your 'spiritual security' — knowing that your family will be there watching out for you. Nothing else will give you that. Not money. Not fame." Morrie Schwarz from Mitch Albom's "Tuesdays with Morrie."

Remember, we enter this world and leave this earth with our families. No amount of material success will ever surpass the joy of a rich family life. We must prioritize our family life and carve out time daily to affirm and sow intimacy with our loved ones! Want to leave your 'mark' on the world? Start with your family!!!!

Lastly, friendships outside of our family are crucial to feeling the emotional 'connection' needed to remain resilient. Friends outside of medicine in particular, help us to see the world differently and experience life in ways unknown to 'medical families.'

JDKIV method: I try to prioritize and value my marriage more than anything — even more than the children! My wife and I spend regular time with other couples who affirm marriage. We are actively engaged in a church program that fosters 'living in love.' We pray together and compliment and affirm each other daily.

My children and I talk every day and I try to drive them to school two days a week. I help with homework often and encourage 'one on one' time whenever possible. If I am stuck in the OR, I am sure to call or 'text message' them. I stay actively *engaged* in their lives although I do not make 'every game.' I have listed my close friends on my cell phone menu and call them regularly to and from work. My wife and I try to visit at least one friend from the community each weekend.

Another source of energy is our interests and 'Passions.' We need to stay close to what really interests us and moves us. When we gravitate to our interests *and* look for a greater good in the process, then we will be doubly energized. *Taking* from the world to meet selfish desires will lead to depletion. Giving back and looking to change the world for the better will lead to sustainable energy. *Causes,* or crusades to make the world better, truly motivate. That is not to say we can ignore our basic needs of living, loving and learning. (Remember, the heart feeds the coronary arteries *first* before it nourishes the rest of the body.) However, if you truly want to contribute to the well being of your brothers and sisters on the planet, you will be blessed with fuel for the journey! Steve Farber, in his book, *The Radical Leap,* expounds on this further by listing the following 'energy generators':

Love
Great ideas
Noble principles
'Leaping' goals (goals which 'leap over' your self imposed limits)
Interesting work
Exciting challenges
Compelling vision of the future

Trying to approach each day expecting to make a difference and 'change the world' will get your blood flowing like nothing else.

JDKIV method: I have learned to reconnect with my passion for teaching and try to lecture residents as frequently as possible. I also limited my practice more on my two loves — arthroscopy of the shoulder and knee, and have been better able to serve my patients in the process. I also *try* to approach talks, scientific papers and research with the intent of 'making a difference' and appealing to a higher purpose, rather than 'hog the limelight.' (Hard at times for a performer!) I try to feed my passion for writing as much as I can. I have dedicated much time to improving the lives of the youth of North Philadelphia and am actively campaigning against gun violence.

Next, let us look at another energy generator: hobbies or interests outside of medicine. We need to feed our souls with activities that are just fun — period. The medical mind, which feels the need to continually produce, will ultimately languish when there is no more 'juice.' Resiliency requires regular hobbies that **rest our nervous system,** which allow us to experience *pleasures,* not just work aversion. The bonus is that by regularly engaging in a fun hobby, your productiv-

ity will INCREASE. Every successful surgeon I know, who has enjoyed long term productivity, has a hobby for which they feel passionate about.

JDKIV method: I try to do the 'comedy thing' whenever I can. I listen to jokes on 'satellite radio' and try to write new material and perform regularly. In the summer, I engage in ocean distance swimming and particularly feel removed from the stresses of medicine whenever I am in the water. I play the piano whenever I can!

Lastly, for lasting energy and resiliency, we need to connect to our Higher Power. Individuals who pray and worship are more resilient — period. Communion with a Loving Presence is the ultimate source of energy. Belief in a Loving presence also gives *meaning* to the seemingly senseless tragedies we witness regularly. Want to feel charged? Plug in to the ultimate source of energy as often as possible. Your Higher Power, the Loving presence in the Universe, will give you a sense of security that no worldly thing can ever match. While connecting to your 'source,' recognize *three things a day* to be grateful for. By living a life centered on Faith and gratitude you will dwell more and more in *positive energy.* Remember, positive emotions are contagious and positive people truly have more to give to the planet!!!

JDKIV method: I try to read spiritual literature daily and pray as often as I can throughout the day. I try to be mindful of the Divine Presence on all I do. I thank my Higher Power every day, first thing in the morning for my family and try to also meditate on the Blessings in my life as I drive to work. I regularly try to reflect on how much my Higher Power loves me, regardless of what I do or fail to do!!!! I also have a list of "power quotes" and affirming phrase to which I refer often. I did not receive much affirmation from my parents so I do my best to get it any way I can!!!

The resilient life is the byproduct of choices you make. Write your values, write your mission with the awareness that *relationships* (God, family, colleagues) determine your happiness. **Decide** to act on your values *no matter how you feel* and you will sow the seeds of resiliency. Separate yourself from thoughts that hurt and direct your thoughts to what is **good** in your life. Now, go find your partner and giver her/him a **hug** — whether you feel like it or not. You will never regret it!!!!!!

Suggested Reading

The Resilient Physician: Effective Emotional Management for Doctors and Their Medical Organizations. WM Sotile and MD Sotile.
The Feeling Good Handbook. David Burns, MD
Seven Habits of Highly Effective People. Steven R. Covey
Brain Lock. Jeffrey Schwartz, MD
How to Fight for Your Marriage. Markman, Stanley, Blumberg
Wherever You Go, There You Are: Mindfulness Meditation in Everyday Life (Paperback). Jon Kabat-Zinn
The Radical Leap. Steve Farber
Feel the Fear and Do It Anyway. Susan Jeffers
The Secret. Rhonda Byrne

Clinical Research

The Importance of Surgical Sequence in the Treatment of Femur Fractures with Concomitant Vascular Injury: A Meta-Analysis

John Fowler, MD,[1] Shawn Leslie, MD,[2] John P. Gaughan, PhD,[3] Saqib Rehman, MD[1]

[1]*Department of Orthopaedic Surgery,* [2]*School of Medicine,* [3]*Biostatistics Consulting Center, Temple University School of Medicine, Philadelphia, PA*

Abstract

Objective: The optimal sequence of surgical repair for femoral fractures with associated vascular injuries is unclear. Advocates of performing the vascular repair prior to fracture fixation argue that reversal of ischemia in the limb is the most important factor in limb survival and should take precedence. Advocates of fracture fixation prior to revascularization worry that the manipulation during fixation could disrupt the vascular repair and that total ischemia time is more relative than absolute. A meta-analysis of the available literature could help decision making in this regard.

Methods: A literature search was performed to identify studies with the following criteria: adult population, femoral fracture with associated vascular injury, an intervention of fracture fixation prior to revascularization and/or revascularization prior to fracture fixation, and amputation as an outcome measurement. Meta-analysis was performed.

Results: 934 articles were identified and narrowed to 18 articles through exclusion criteria. Meta-analysis of the data shows no statistical difference in regards to the incidence of amputation between fracture fixation prior to revascularization and revascularization prior to fracture fixation.

Conclusion: Femoral fractures with associated vascular injury are an uncommon injury representing 0.3–3% of trauma admissions. There has been a widespread but unsupported belief that manipulation and traction during fracture fixation will disrupt the vascular repair. Ischemic time should be considered a relative, but not absolute predictor of amputation. Soft tissue injury and neurologic deficits have been found to be highly correlated with disability and amputation. Cooperation between the orthopedic surgeon and vascular surgeon is very important. Surgical sequence has not been shown to affect the rate of amputations in this injury in this meta-analysis.

Introduction

Fractures of the femur with associated vascular injury are relatively rare, accounting for 0.3–0.4% of fractures,[1–2] but have an amputation rate of 20–50% in some series.[3] Prior to 1960, patients who had femoral fracture with vascular injury almost always had an above the knee amputation.[4] Experience gained from the Vietnam War led to aggressive attempts at limb salvage through vascular repair with promising results.[5] Limb salvage in civilian injuries is now the rule rather than the exception with salvage rates reported near 100% in recent series.[7] Debate still continues, however, over the surgical sequence in these injuries. Should fracture fixation precede vascular repair or vice versa.

McHenry described two major considerations in the determination of surgical sequence: effect of ischemia time on limb viability and the effect of fracture stability on the vascular repair procedure.[7] Those advocating initial fracture fixation have argued that fixation performed after vascular repair may disrupt it. In accordance with this hypothesis, Iannacone et al. suggested that immediate external fixation allows the vascular repair to be performed in a controlled environment to protect the completed vascular repair from disruption.[14] Others have argued that the vascular injury should be repaired first because reversal of limb ischemia takes precedence. Connolly,[5] Starr et al.,[12] and Ashworth et al.[20] showed that the vascular repair was able to withstand longitudinal traction during fracture fixation and that no disruption of the vascular repair occurred in their series. There are valid arguments on both sides of the issue and the goal of this meta-analysis is to determine if there is a difference in amputation rates between the two treatment groups.

Materials and Methods

Eligibility Criteria

Studies included in this meta-analysis needed to have a target population of adults who sustained femoral fractures with associated vascular injury. The studies needed to have

an intervention of either fracture fixation followed by vascular repair or vascular repair followed by fracture fixation. Studies also needed to have amputation as an outcome measurement. Prospective randomized trials, case series, and retrospective reviews were included. Review articles without patient data were excluded.

Identification of Studies

We performed a PubMed Search using MeSH from 1966–2006 using the following MeSH words: "Wounds, Gunshot" [MeSH] AND "Femoral Fractures" [MeSH]; "Blood Vessels/Injuries" [MeSH] AND "Femoral Fractures" [MeSH]; "Blood Vessels/Injuries" [MeSH] AND "Fracture Fixation"[MeSH]; "Femoral Fractures" [MeSH] AND "Ischemia"[MeSH]; "Femur" [MeSH] AND "Fractures, Bone" [MeSH] AND "Blood Vessels/Injuries" [MeSH]; "Blood Vessels/Injuries" [MeSH] AND "Leg Bones"[MeSH]; "Wounds, Gunshot" [MeSH] AND "Femoral Fractures" [MeSH].

A Cochrane Database search was also conducted as well as a review of reference lists of all articles to be included in the meta-analysis in an attempt to find more potentially relevant articles. We also reviewed the abstracts presented at the Orthopedic Trauma Association Meetings from 1999–2005.

Highest Available Evidence

The highest level of evidence is retrospective cohort studies, Level III.

Statistical Methods

The rate of amputation was calculated separately for each study. Composite average rates of amputation are presented for the two treatment modalities. In addition, weighted averages based on sample size of each study were calculated. To model the between-study heterogeneity and synthesize the results appropriate for meta-analysis, we used a weighted mixed effects linear model with "study" analyzed as a random effect and treatment modality as a fixed effect using the binomial distribution (SAS PROC GLIMMIX, version 9.1, SAS Institute, Cary, NC). The composite odds ratio was calculated along with the 95% confidence interval. The significance of treatment modality was tested using a type III F test with statistical significance set at ≤.05.

Results

Literature Search

The PubMed MeSH search yielded 934 results. The Cochrane Database search did not yield any results. The reference review of all articles included in the meta-analysis did not yield any additional studies, nor did the search of abstracts from the OTA meetings from 1999–2005. Article titles were reviewed independently by two reviewers (JF and SL). 234 articles were excluded because there was no femoral fracture. 449 articles were excluded because a non-related disease process was being studied. 130 articles did not have a vascular injury. Eleven articles were review articles without patient data, two articles were excluded because they dealt with a pediatric population, and two single case reports were excluded. Using these guidelines for exclusion, 111 potentially relevant articles were chosen for abstract review. The abstracts of the 111 potentially relevant articles were again reviewed by JF and SL and 18 articles were chosen to be included in the meta-analysis. 22 articles were excluded because they were duplicates. 50 articles were excluded after abstract review and an additional 21 articles were excluded after a full article review (see Figure 1 for breakdown of exclusion). Assessment of agreement between JF and SL was performed and a kappa value of 0.67 was achieved, signifying very good agreement.[19]

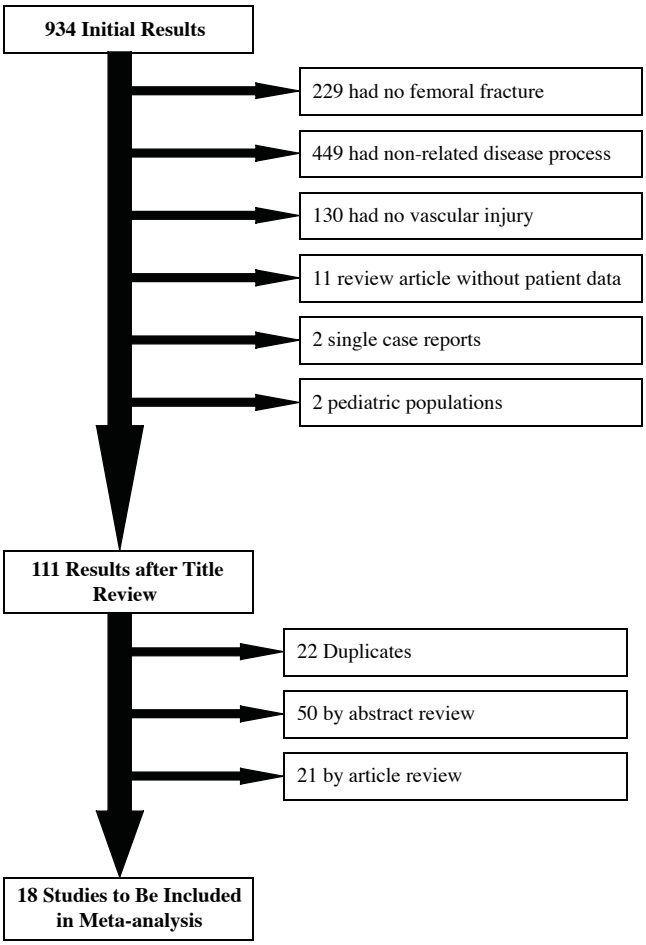


Figure 1

Data

Our meta-analysis allowed us to achieve an N of 516 patients, which is nearly five times the size of any current study (please refer to Table 1). 325 patients underwent

Table 1

Article Title	Journal	Authors	N	LE	F	V	Amp F	Amp V
Fractures of the Limbs Complicated by Ischemia Fur to Lesions of the Major Vessesls	*Italian Journal of Orthopedics and Traumatology* 1984 June;10(2):163–185	Guercio, Orsini	56	24/56	24/24	0/24	2/24	
The Management of Open Fractures Associated with Arterial Inury Requiring Vascular Repair	*The Journal of Trauma* 1994 Dec;37(6): 938–40	Seligson, Ostermann, et al.	72	58/72	72/72	0/72	7/72	
Vascular Injuries Associated with Fractures of the Femur	*Arch Surg* Vol 110, May 1975	Rosental et al.	19	19/19	6/19	13/19	2/6	0/13
Concomitatnt Orthopedic and Vascular Injuries as Predictors for Limb Loss in Blunt Lower Extremity Trauma	American Surgeon; Jan. 1997, Vol 63, Issue 1, p 24	Moniz, Ombrellaro	23	23/23	0/23	23/23	0/23	11/23
Fractures with Major Vascular Injuries from Gunshot Wounds: Implications of Surgical Sequence	*J Trauma* Volume 53 No 4, Oct 2002, pp 717–721	McHenry et al.	27	17/27	5/27	22/27	0/5	0/22
Treatment of Femur Fracture with Associated Vascular Injury	*J Trauma* Volume 40 (1), January 1996, pp 17–21	Starr et al.	26	26/26	10/26	13/26	0/10	2/13
Improved Results in the Treatment of Civilian Injuries Associated with Fractures and Dislocations	*J Vasc Surg* 1986; 3:707–711	Bishara, Pasch et al.	38	31/38	30/38	8/38	1/30	0/8
Early Exchange Intramedullary Nailing of Distal Femoral Fractures with Vascular Injury Initially Stabilized with External Fixation	*J Trauma* 1994, Vol 37 No 3	Iannacone, Delong et al.	6	6/6	6/6	0/6	0/6	
Lower Limb Fractures with Associated Vascular Injury	*JBJS British Edition* 1990; 72-B: 116–120	Makin and Howard	35	35/35	15/35	20/35	5/15	2/20
Femur Fractures with Femoral or Popliteal Injuries in Blunt Trauma	*Journal of Orthopedic Trauma* Vol 8 No 6, pp 494–503	DiChristina et al.	13	13/13	10/13	3/13	1/10	1/3
Blunt Vascular Injury Associated with Closed Mid-shaft Femur Fracture: A Plea for Concern	*Journal of Trauma* 1994, Vol 6 No 2	Kluger, DiChristina et al.	10	10/10	10/10	0/10	0/10	
Upper and Lower Limb Fractures with Concomitant Arterial Injuries	*JBJS* March 1992, Vol 74-B No 2	Schlickewei et al.	113	76/113	113/113	0/113	27/113	
Major Vascular Lesions Associated with Orthpaedic Injuries	*Journal of Orthopedic Trauma* Vol 6 No 2, pp 180–85	Karavias, Korovessis et al.	17	12/17	17/17	0/17	3/17	
Femoral Shaft Fracture with Injury of the Superficial Femoral Artery in Civilian Accidents	*Surg Gynecol Obstet.* 1976 Mar;142(3): 399–403.	Kootstra, Schipper et al.	8	8/8	5/8	3/8	1/8	0/3
Combined Skeletal and Vascular Injuries of the Lower Extremities	*Am Surg.* 1984 Apr;50(4):189–97.	Weaver, Rosenthal et al.	31	31/31	0/31	31/31		7/31
Femoral and Tibial Fractures Combined with Injuries to the Femoral or Popliteal Artery	*J Bone Joint Surg Am.* 1971 Jan;53(1):56–68	Connolly, Whittaker et al.	14	14/14	0/14	14/14		3/14
Major Arterial Injury Complicating Fracture of the Femoral Shaft	*JBJS* May 1963, Vol 45-B No 2	Kirkup	3	3/3	0/3	3/3		0/3
Arterial Injury Associated with Closed Femoral-Shaft Fracture	*JBJS* December 1975, Vol 57-A No 8	Isaacson et al.	5	5/5	2/5	3/5	0/2	0/3

LE = number of injuries that were of lower extremity
F = fracture fixation performed first
V = vascular repair performed first
Amp F = amputations when fracture fixation performed first
Amp V = amputations when vascular repair performed first

fracture fixation followed by vascular repair with amputation occurring in 49 (15%). 153 patients underwent vascular repair followed by fracture fixation with amputation occurring in 26 (17%). Table 2 shows the number of patients who underwent each treatment in each study and the number of amputations. Many authors experienced no amputations in their series while others had rates as high as 47%. The injuries were not homogeneous, with some authors treating mostly closed, blunt trauma and others treating Grade III C open fractures. Table 3 shows the analysis of the treatment options based on the number of amputations for each treatment. The group that had fracture fixation performed first had a mean amputation rate of 11.4% (±12.3) while the group that had vascular repair performed first had a mean amputation rate of 12.3% (±16.0). This difference was not statistically significant. The maximum percentage of amputations in the fracture fixation first group was 33.3% and 47.8% in the vascular repair group. Table 4 shows the percentage of amputations weighted for the number of patients in each treatment group. The weighted mean for the fracture fixation group was 15.1% (±48.9) and the weighted mean for the vascular repair group was 16.3% (±60.4).

Table 2

Study	Treatment	N	N Amputation	% Amputation
1	F	24	2	8.3
2	F	72	7	9.7
3	F	6	2	33.3
3	V	13	0	0
4	V	23	11	47.8
5	F	5	0	0
5	V	22	0	0
6	F	10	0	0
6	V	16	2	12.5
7	F	30	1	3.3
7	V	8	0	0
8	F	6	0	0
9	F	15	5	33.3
9	V	20	2	10
10	F	10	1	10
10	V	3	1	33.3
11	F	10	0	0
12	F	113	27	23.9
13	F	17	3	17.6
14	F	5	1	20
14	V	3	0	0
15	V	31	7	22.6
16	V	14	3	21.4
17	V	3	0	0
18	F	2	0	0
18	V	3	0	0

F = fracture fixation performed first
V = vascular repair performed first

Table 3

Sequence	N	Mean Amp (%)	Max Amp (%)	Std Dev
F	14	11.4	33.3	12.3
V	12	12.3	47.8	16.0

F = Fracture fixation was performed first
V = Vascular repair was performed first
Mean amp = average percentage of amputations in the treatment group
Max amp = the most amputations in any one study

Table 4

Sequence	N	Weighted Mean (%) Amp	Max Amp (%)	Std Dev
F	14	15.1	33.3	48.9
V	12	16.4	47.8	60.4

F = Fracture fixation was performed first
V = Vascular repair was performed first
N = number of studies
Weighted Mean Amp = mean percent amputations weighted based on number of patients in each treatment group
Max amp = the most amputations in any one study

Discussion

This is the first meta-analysis comparing outcomes of surgical sequence in the repair of femur fractures with associated vascular injury. Our data shows that the two treatment groups (fracture fixation followed by vascular repair and vascular repair followed by fracture fixation) are not significantly different in our outcome measure of amputation. Overall ischemia time has been proposed as the major determinant of limb survival. It has long been believed that rapid revascularization to reverse ischemia should be a major goal of the repair. Miller and Welch,[21] in their experiment with dogs, showed that an ischemia limit of less than six hours led to a 90% limb salvage rate, but an ischemia time of greater than twelve hours led to an amputation rate of greater than 50%. Other authors, however, have demonstrated limb survival even after 20 hours of ischemia.[4] The extent of tissue injury resulting from the ischemic time period is dependent on the proficiency of the collateral circulation and absolute ischemia limits should be avoided.[16]

McHenry et al.[7] in 2002 performed a retrospective review of 27 patients, 17 of which had lower extremity fractures with the objective of determining the optimal surgical sequence for the repair of fractures with major vascular injuries. 22 of the 27 patients underwent vascular repair prior to fracture fixation while the remaining five had fracture fixation first. McHenry documented an increase in the need for fasciotomy in the group that had fracture fixation first, but this difference was not statistically significant. No amputations were performed in this retrospective review. McHenry has concluded that vascular repair should be performed first and had no disruptions of the vascular repair in his review. McHenry stated that the consequences of surgical sequence are often clouded by other injuries and factors in the multiply injured trauma patient.

Weaver and Waterhouse[16] performed a review of 31 patients with fractures and concomitant vascular injury, 16 of which had femoral fractures. The authors recommend vascular repair first and confirm the observations of Conolly, Starr, and McHenry that the vascular repair is not disrupted by subsequent fracture fixation. Weaver and Waterhouse believe that the proficiency of collateral circulation is an important factor affecting ischemia time and that it is difficult to measure. 12/31 patients underwent amputation due to vascular disruption and secondary soft tissue infection. This emphasizes the need for a clean, viable soft tissue environment. The authors found a frequent association between this type of injury and permanent neurologic deficits and felt that fractures should be stabilized externally in most cases. The authors recommended frequent and early post-operative debridement of non-viable soft tissue with early coverage or closure to prevent soft tissue/bony infection. The authors concluded that amputation was more likely due to soft tissue issues than ischemia.

Schlickewei[1] performed a large retrospective review of 113 patients with fracture and vascular injury. 30 of these patients had a femoral fracture with associated vascular injury and underwent fracture fixation before revascularization. In this series, 27 amputations were performed, although the author did not specify the location. The interesting aspect of this study was the analysis done on the patients who underwent amputation. 51.8% of the amputations occurred in limbs with an ischemia time of greater than six hours. 81.4% of amputations occurred in limbs with major soft tissue injury. 85.2% of amputations occurred in limbs with open fractures. Schilckewei has shown that soft tissue injury and open fractures may be better predictors than ischemia time for amputation. These patients were a particularly complicated group with multiple injuries, with 11/113 deaths.

Kootstra and Schipper[4] published a case series of eight patients with femoral fracture and vascular injury who underwent internal fixation followed by vascular repair. The patients experienced an average ischemia time of 22 hours. One patient underwent an above the knee amputation and one patient underwent a below the knee amputation. The authors concluded that a delay in revascularization has a relative, but not absolute significance and that repair should be attempted even after a significant ischemia time.

Drost and Rosemurgy[22] reviewed over 10,000 trauma admissions and found 22 patients with combined orthopedic and arterial injuries of the lower extremity. The authors excluded immediate primary amputations from their study, instead focusing on salvageable limbs. Fracture fixation was performed prior to revascularization in eleven of the 22 patients and revascularization was performed first in the rest. No vascular disruptions occurred in the group that underwent vascular repair prior to fracture fixation. Drost and Rosemurgy found that the mechanism of injury, injury severity score, sequence of vascular and orthopedic procedures, length of ischemia time, and presence of open fracture did not affect limb salvage or outcome. However, the presence of neurosensory impairment, soft tissue loss, and injuries distal to the popliteal artery were predictors of disability and amputation. Amputations were performed in eight of the twenty two patients. In the amputation group, the average ischemia time was 8.8 ± 3.8 hours, 75% had a neurosensory deficit, 100% had open fractures, and 75% had soft tissue injury. In the limb salvage group, the average ischemia time was 10.2 ± 4.2 hours, 50% had a neurosensory deficit, 86% had an open fracture, and 21% had a soft tissue injury. The authors attribute four of the amputations to a failed vascular repair and four to soft tissue loss. It appears again that ischemia time does not adequately assess vascularization and is not an accurate predictor of amputation. Drost and Rosemurgy also looked at the long term functional capabilities of their patients. Seven of the eight patients who underwent amputation were "doing well" and working, while only six of the fourteen patients who had limb salvage were doing the same. The authors want to challenge the notion that limb salvage should be the only acceptable goal of treatment.

Iannacone and DeLong[14] reported on their case series of six patients who sustained femoral fractures with vascular injury who were initially stabilized with external fixation and later converted to intramedullary nail. In this series, the authors felt that initial external fixation had the advantages of rapid application, restoration of skeletal stability, and protection of the soft tissues while allowing access for subsequent vascular repair and protecting that repair once it has been performed. Because external fixation had been shown to increase the occurrence of delayed union, the authors used primary exchange to intramedullary nail. The average ischemia time in this series was five hours and the time needed for external fixation was 40 minutes. The authors feel that since external fixation can be performed this rapidly, it does not significantly increase the ischemia time and therefore the benefits outweigh the disadvantages. No amputations were done in this series.

Starr and Hunt's[12] retrospective analysis of 26 patients studied internal versus external fixation of femoral fractures with associated vascular injury. Fracture fixation was performed first in sixteen cases and vascular repair was performed first in nine cases. The authors experienced no disruptions of the vascular repair in patients who had revascularization prior to fracture fixation. The study was not randomized and the patients who had external fixation prior to vascular repair were more hemodynamically unstable and tended to have poorer outcomes. The authors feel that the orthopedist must make a realistic judgment as to whether the planned skeletal stabilization can be performed quickly enough to avoid approaching the ischemic threshold. Immediate skeletal fixation not only has the advantage of creating a stable environment for the vascular repair, but has also been shown to reduce the pulmonary complications in multiple trauma patients. In this study, poor outcomes were significantly associated with a mangled extremity severity score of greater than six, rather than ischemia times.

Bishara and Pasch reported a limb salvage rate of 97% in 38 patients with fractures in a variety of extremitites and venous or arterial injuries. Fracture fixation was performed prior to revascularization in 79% of cases. Average ischemia time was 19 hours, again reflecting the relative nature of ischemia times and the importance of collateral circulation. Only six of the 38 patients in this series had injury to the superficial femoral artery, with none of these patients undergoing amputation.

Kluger and DiChristina[2] reviewed 765 trauma admissions and found that 1.3% had acute vascular injuries with comminuted femoral fractures. Nine patients underwent internal fixation prior to revascularization and one patient underwent external fixation prior to revascularization. No amputations were performed. The authors felt that mechanical protection of the vascular repair was mandatory for success and made this a priority. The average time for ORIF in the series was 30–45 minutes.

Moniz and Ombrellaro[11] reviewed a total of 52 cases of vascular injury in the lower extremity, 65% of which had a fracture. Revascularization was accomplished before fracture fixation in all cases. The femoral artery was injured in 23 of the 52 cases. Fourteen above the knee amputations were needed as well as 2 below the knee amputations. The authors found that long ischemia times did not influence the rate of amputation. Patients often had a vascularized, yet non-functional limb secondary to neurologic or soft tissue injury. Two or more bone fractures were predictive of amputation.

Rosental[10] studied 21 patients with femoral fracture and vascular injury to determine a difference in the outcomes between internal and external fixation. External fixation was performed after vascular repair in eleven cases. Internal fixation was performed prior to vascular repair in six cases and after vascular repair in two cases. The internal fixation group and the external fixation group each had two amputations. Both amputations in the internal fixation group had vascular repair before fracture fixation. Rosental reported no disruptions of the vascular repair[10] from traction during fracture fixation and stated that there is a widespread, but unsupported belief that without fixation of the fracture, the vascular repair will fail. He felt that the delay between injury and revascularization wasn't the critical factor in limb salvage since the average ischemia time in limb salvage cases was fifteen hours while it was 14 hours in the amputation cases. The preservation of the limb was most directly related to the success of the arterial repair and the extent of soft tissue injury. The dissection necessary for internal fixation leads to soft tissue disruption and venous disruption and could be the etiology of poorer outcomes in the internal fixation groups.

Guercio and Orsini[8] performed a retrospective analysis of 68 patients with vascular injury and concurrent fracture. 26 patients in this analysis had a fracture of the femur and underwent fracture fixation prior to revascularization. The authors felt that the brief prolongation ischemia caused by immediate fracture fixation did not affect the general outcome of the treatment. Stabilization of the fracture facilitates the vascular repair and causes little or no aggravation of the already damaged vascularity of the limb. The authors performed two amputations. A delay of treatment for greater than twelve hours was the most common cause for amputation in their experience.

Connolly and Whittaker[5] reviewed 36 patients with femoral or popliteal vascular injuries with associated fracture to look at internal versus external fixation. Arterial repair was performed first in all patients within eight hours. The authors report no damage to the vascular repair with subsequent fracture fixation and explained that the resistance of soft tissues serves to absorb the majority of forces in skeletal traction. The authors recommended 4.5–6.8 kilograms of skeletal traction. Two of six patients undergoing internal fixation required amputation while one of seven patients undergoing external fixation required amputation. Connolly felt that absolute ischemia time should not be established. Length of delay prior to treatment, the extent of collateral circulation, the amount of soft tissue damage, and the presence of infection were identified as factors predictive of outcome. The authors stressed the importance of adequately treating the soft tissue injury.

DiChristina[3] studied thirteen blunt femoral fractures with vascular injury where fracture fixation was performed first in ten of thirteen cases and accomplished in approximately thirty minutes in each case. Amputation was required in ten percent of the cases in which fracture fixation occurred first and in one third of the cases in which vascular repair occurred first. Twelve of the thirteen cases had ischemia times of greater than six hours. Prophylactic fasciotomies were performed in all cases. The functional outcomes depended on the soft tissue damage.

Conclusion

Femoral fractures with associated vascular injury are an uncommon injury representing 0.3–3% of trauma admissions. Limb salvage has increased in recent years, likely due to an increased index of suspicion for vascular injury and better cooperation between orthopedic and vascular surgeons. There has been a widespread but unsupported belief that manipulation and traction during fracture fixation will disrupt the vascular repair. Ischemic time should be considered a relative, but not absolute predictor of amputation. Soft tissue injury and neurologic deficits have been found to be highly correlated with disability and amputation. Cooperation between the orthopedic surgeon and vascular surgeon is very important as the orthopedic surgeon must make a clinical judgment as to whether his fixation can be accomplished quickly enough to avoid prolonged ischemic times. Surgical sequence has not been shown to affect the rate of amputations in this injury.

References

1. Schlickewei W, Kuner EH, Mullaji AB, Gotze B. Upper and lower limb fractures with concomitant arterial injury. *J Bone Joint Surgery Br* 1992;74(2):181–8.
2. Kluger Y, Gonze MD, Paul DB, DiChristina DG, Townsend RN, Raves JJ, Young JC, Diamond DL. Blunt vascular injury associated with closed mid-shaft femur fracture: a plea for concern. *J Trauma* 1994; 36(2):222–5.
3. DiChristina DG, Riemer BL, Butterfield SL, Burke CJ 3rd, Herron MK, Phillips DJ. Femur fractures with femoral or popliteal artery injuries in blunt trauma. *J Orthop Trauma* 1994;8(6):494–503.
4. Kootstra G, Schipper JJ, Boontje AH, Klasen HJ, Binnendijk B. Femoral shaft fracture with injury of the superficial femoral artery in civilian accidents. *Surg Gynecol Obstet* 1976;142(3):399–403.
5. Connolly JF, Whittaker D, Williams E. Femoral and tibial fractures combined with injuries to the femoral or popliteal artery. A review of the literature and analysis of fourteen cases. *J Bone Joint Surg Am* 1971;Jan;53(1):56–68.
6. Kirkup JR. Major arterial injury complicating fracture of the femoral shaft. *J Bone Joint Surg Br* 1963;45-B:337–43.
7. McHenry TP, Holcomb JB, Aoki N, Lindsey RW. Fractures with major vascular injuries from gunshot wounds: implications of surgical sequence. *J Trauma* 2002;53(4):717–21.
8. Guercio N, Orsini G. Fractures of the limbs complicated by ischaemia due to lesions of the major vessels. *Ital J of Orthop Traumatol* 1984; 10(2):163–85.
9. Seligson D, Ostermann PA, Henry SL, Wolley T. The management of open fractures associated with arterial injury requiring vascular repair. *J Trauma* 1994;37(6):938–40.
10. Rosental JJ, Gaspar MR, Gjerdrum TC, Newman J. Vascular injuries associated with fractures of the femur. *Arch Surg* 1975;110(5):494–9.
11. Moniz MP, Ombrellaro MP, Stevens SL, Freeman MB, Diamond DL, Goldman MH. Concomitant orthopedic and vascular injuries as predictors for limb loss in blunt lower extremity trauma. *Am Surg* 1997; 63(1):24–8.
12. Starr AJ, Hunt JL, Reinert CM. Treatment of femur fracture with associated vascular injury. *J Trauma* 1996;40(1):17–21.
13. Bishara RA, Pasch AR, Lim LT, Meyer JP, Schuler JJ, Hall RF Jr, Flanigan DP. Improved results in the treatment of civilian vascular injuries associated with fractures and dislocations. *J Vasc Surg.* 1986;3(5): 707–11.
14. Iannacone WM, Taffet R, DeLong WG Jr., Born CT, Dalsey RM, Deutsch LS. Early exchange intramedullary nailing of distal femoral fractures with vascular injury initially stabilized with external fixation. *J Trauma* 1994;37(3):446–51.
15. Howard PW, Makin GS. Lower limb fractures with associated vascular injury. *J Bone Joint Surg Br* 1990;72(1):116–20.
16. Weaver FA, Rosenthal RE, Waterhouse G, Adkins RB. Combined skeletal and vascular injuries of the lower extremities. *Am Surg* 1984; 50(4):189–97.
17. Karavias D, Korovessis P, Filos KS, Siamplis D, Petrocheilos J, Androulakis J. Major vascular lesions associated with orthopaedic injuries. *J Orthop Trauma* 1992;6(2):180–5.
18. Isaacson J, Louis DS, Costenbader JM. Arterial injury associated with closed femoral-shaft fracture. Report of five cases. *J Bone Joint Surg Am* 1975;57(8):1147–50.
19. Guggenmoos-Holzmann I. The meaning of kappa: probabilistic concepts of reliability and validity revisited. *J Clin Epidemiol* 1996;49(7): 775–82.
20. Ashworth EM, Dalsing MC, Glover JL, Reilly MK. Lower extremity vascular trauma: a comprehensive, aggressive approach. *J Trauma* 1988;28:329–336.
21. Miller HH, Welch CS. Quantitative studies on the time factor in arterial injuries. *Ann Surg* 1949;130:428.
22. Drost TF, Rosemurgy AS, Proctor D, Kearney RE. Outcome of treatment of combined orthopedic and arterial trauma to the lower extremity. *J Trauma* 1989;29:1331–1334.

Clinical Research

PediGuard™: A Solution for the Challenges of Pedicle Screw Placement

Randal R. Betz, MD,[1] Amer F. Samdani, MD,[1] Mladen Djurasovic, MD,[2] Stewart I. Bailey, MD,[3] Courtney Brown, MD,[4] JahanGir Asghar, MD,[1] Linda P. D'Andrea, MD,[5] John Dimar, MD,[6] Harry L. Shufflebarger, MD,[7] John Gaughan, PhD[8]

[1]*Shriners Hospitals for Children, Philadelphia, PA,* [2]*Leatherman Spine Center, Louisville, KY,* [3]*Westminster Hospital, London, Ontario, Canada,* [4]*Panorama Orthopedics and Spine Center, Golden, CO,* [5]*Brandywine Institute of Orthopaedics, Pottstown, PA,* [6]*Department of Orthopaedic Surgery, University of Louisville, Louisville, KY,* [7]*Miami Children's Hospital, Miami, FL,* [8]*Department of Biostatistics, Temple University School of Medicine, Philadelphia, PA*

Conflict of interest statement: Supported by a research grant from SpineVision, Inc.

Abstract

Pedicle screw fixation is not without complications, one of which is pedicle perforation, with rates ranging as high as 40%. Much of the variation in perforation rates in the literature depends on the method used to determine the perforation. Studies using a postoperative CT scan reviewed by independent or blinded reviewers show higher rates of perforation than those determined by radiograph. Despite all of the available techniques used to minimize perforation, there is still a need for an efficient, simple, and cost effective device which will help the surgeon to more safely drill a pilot hole for placement of a pedicle screw. In a US clinical randomized trial, preliminary analysis of patients having had surgery for degenerative conditions with titanium screws between T12 and S1 shows a significant clinical trend in reduction of breach (by 8%) using the PediGuard™ device and a six-fold reduction in medial breaches. In a separate cohort of patients comparing PediGuard™ and a fluoroscopic technique, the average radiation exposure was reduced by approximately 30% with PediGuard™.

Introduction

Pedicle screw fixation has been shown to be superior to other methods of instrumentation of the spine for spinal fusion and correction of spine deformity.[4, 7, 9–11, 15, 18, 20] In a meta-analysis of the literature by Yahiro[22] of 5,756 patients reported in 101 articles, the success of fusions with pedicle screws was 94.8%, attesting to the clinical usefulness of this technique.

Pedicle screw fixation is not without complications, one of which is pedicle perforation, with rates ranging as high as 40%.[1] Perforations can further lead to complications such as dural tear,[19] nerve root injuries,[19] paraplegia,[6, 16, 19, 23] or vascular injury.[8]

Much of the variation in perforation rates in the literature depends on the method used to determine the perforation. Studies using a postoperative CT scan reviewed by independent or blinded reviewers show higher rates of perforation than those determined by radiograph.

Many surgeons rely on plain radiographs to assess screw perforation postoperatively. However, the number of malpositioned screws are underestimated. In an article by Learch, et al.[13] using cadaver specimens of the lumbar spine, only 63% of the screw positions were correctly identified on radiograph as compared to 87% with CT scan.

When inserting screws in the pedicle, surgeons rely on various methods to ensure accurate placement. The gold standard is manual probing, often with or without fluoroscopy. The "freehand technique" is based on knowledge of spinal anatomy.[14] This technique results in the least radiation exposure to the patient and surgeon but is less accurate in placing contained pedicle screws as compared to imaging techniques.[12]

A fluoroscopic technique may provide more consistent results but carries some risks associated with radiation dose, especially to young patients[17, 21] and to the surgeon.[21]

Three dimensional image-guided surgery (IGS) can result in better screw accuracy. Surgeons have also used various electrophysiological monitoring techniques such as EMG and somatosensory evoked potentials (SEP) for assessing nerve root function and pedicle screw placement.[12, 17] Clements, et al.[5] report thresholds above 10 mA as being associated with no postoperative nerve root radiculopathies.

Despite all of the above mentioned techniques, there is still a need for an efficient, simple, and cost effective device which will help the surgeon to more safely drill a pilot hole for placement of a pedicle screw.

In 2006, a study group was assembled to investigate the effectiveness of the PediGuard™ device for placement of the pedicle screw pilot drill hole, reducing pedicle screw breaches during thoracic and lumbar pedicle screw fixation of the spine. The first hypothesis is that the PediGuard™ would be more accurate for pedicle screw placement as compared to other standard manual techniques of pedicle screw insertion. The second hypothesis is that the PediGuard™ will not be inferior to fluoroscopic techniques for pedicle screw insertion; however, the radiation dose will be less in the PediGuard™ group.

Materials and Methods

PediGuard™ is a wireless electronic handheld pedicle screw pilot hole preparation instrument designed to continuously monitor the electrical conductivity of the tissue at its tip throughout the drilling process. It provides audible and visual feedback in response to local tissue conductivity changes. This feedback allows the surgeon to discriminate between different types of tissue in contact with the tip, detecting possible vertebral cortex perforations. PediGuard™ has received FDA 510(k) clearance for commercial distribution in the US.

PediGuard™ features bipolar electrodes that avoid any shunting effect and keep the measured electrical conductivity independent of the insertion depth. When in the same medium, the electrical conductivity remains constant while the instrument is advanced into the vertebral pedicle. Variation occurs when the instrument passes through a boundary between two different media; for example, bone vs. blood. As shown in Figure 1, PediGuard™ consists of an awl instrument with a hollow handle that accepts a built-in electronic printed circuit board. The electronic components allow performing measurements, with translation to audible signal and colored LEDs (Light Emitting Diodes) to be used as feedback to the surgeon.

Surgical Techniques Using PediGuard™

Determination of the size and style of the probe. First, the surgeon determines in which area of the spine the pedicles will be drilled. In the lower lumbar spine, generally a 4.0-mm diameter tip would be most advantageous. If one needs to go to L1 and L2 and, on radiograph, the pedicles look extremely small, one may wish to use 3.2 mm tip. If one is instrumenting most of the thoracic spine, the 3.2-mm or the 2.5-mm probe will be most advantageous.

There are two different styles of tip. The four-edge probe is much duller and is best used where there is soft cancellous bone within the pedicle. This would in most cases occur with degenerative spine in older patients. Where the cancellous bone is harder, it is recommended that one use the tri tip. Because the tri tip provides better control without having to push, it is widely preferred by surgeons.

The PediGuard™ is used in an anticipatory function during drilling of the vertebral pedicle. Due to the shape of the electromagnetic field at the tip of the device, the pitch and cadence of the sound emitted slightly changes before the nature of the bone or tissue changes.[2] When first entering the cancellous bone, keeping firm pressure is necessary to get a sense of the rate and pitch of the sound for that particular pedicle. As one advances, if the rate and pitch slow, then one is probably near or up against cortical bone. One can then gently reangle the tip, keeping firm pressure to look for the original sound of the cancellous bone. Once the sound of the original cancellous bone is heard, then one should advance the PediGuard™ in that direction. It is extremely important to not decrease pressure of the tip on the bone, or blood will intervene, and then a very high pitch and rate of sound will result. In addition, if one angles the tip too far in any one direction, then blood will seep in and surround the electrode tips, and a high pitched, high cadence sound will be heard as a consequence of the tip measuring blood.

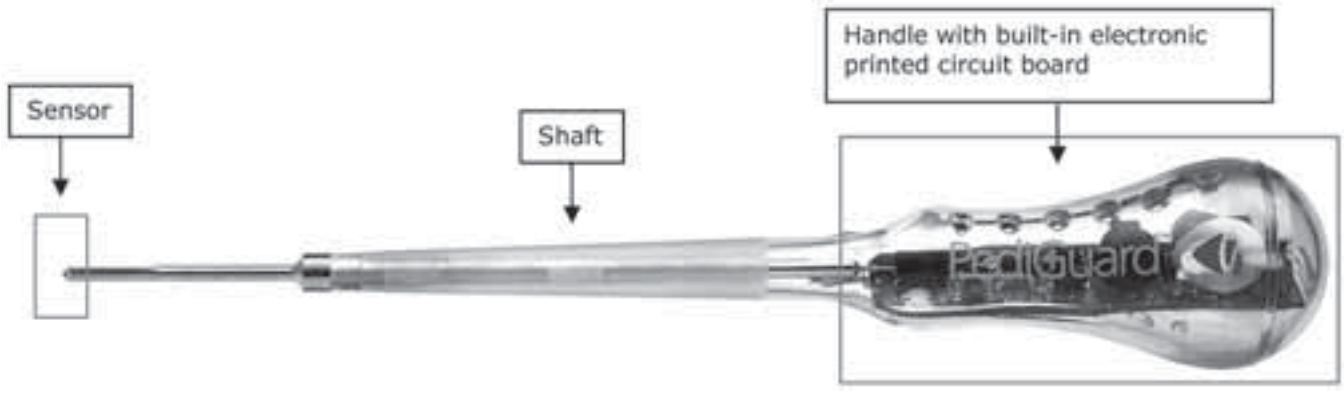


Figure 1. PediGuard™ Device

In difficult pedicle screw placements, this anticipatory function can also be used for placing a drill hole going from the outside in, especially in the thoracic spine. In this scenario, one may wish to slide down the lateral side of the transverse process and upper lateral wall of the pedicle. One can then assure that cortical bone has been reached by the slow rate and low pitched sound. Then, one can drill through the lateral cortex of the pedicle and enter the cancellous bone of the pedicle and then on to the vertebral body, assuring that the tip is contained within bone.

If one does perforate outside of the pedicle wall, either medially or laterally, the device will detect this with a high rate, high pitched sound. When this happens, the PediGuard™ device should be removed. One can still use bone wax or FloSeal or any other anticoagulant to try to decrease the bleeding out of the pedicle hole. One should then take a ball tip probe and palpate the walls of the pedicle to confirm the location of the breach. Sometimes, palpating the breach may be difficult, as the PediGuard™ is so accurate that only the very tip of the probe may perforate into the soft tissue before a large hole is made. Either way, if one can determine the location of the breach, one can redirect the PediGuard™ and create a new pedicle drill hole. One just reinserts the PediGuard™ device and puts it up firmly against cancellous bone and then begins drilling again. If the breach location is known (medial, lateral, superior, inferior), the surgeon can direct away from that. Otherwise, he or she should just continue to listen to the sound carefully and advance as appropriate. There are times when the surgeon cannot advance past the medial and lateral wall without perforation due to the starting hole entry point. It may be necessary on occasion to move the starting hole more laterally, even to the point of an outside-in technique, in order to pass through the pedicle morphology at that level.

Study Design

The study design includes a randomized process of pedicle screw insertion in which the surgeon alternates between the pedicle drill hole being placed using PediGuard™ versus his or her other standard technique, either manual or fluoroscopic. The randomization occurs with the first hole drilled. Then, the insertion technique (PediGuard™ versus surgeon's standard technique) alternates with each additional screw going left to right and proximal. Once the pedicle drill hole is placed, all other aspects of the pedicle screw insertion, including tapping, screw insertion, and electrical stimulation, are the same for both techniques. As part of standard of care, a postoperative CT scan is performed on every patient. The CT scans were reviewed by a team of five surgeons very familiar with pedicle screw insertion, and consensus on the placement of each screw was required.

Data Collection

Subjects who were scheduled to undergo thoracic and/or lumbar pedicle screw fixation during spine surgery were recruited from the clinical practices of the six participating surgeons. Written IRB-approved informed consent was obtained during a pre-surgery office appointment and prior to randomization.

The technique for drilling the pedicle screw pilot hole developed by Dr. Harry Shufflebarger begins with obtaining a true AP image of the spine by rotating the fluoroscope and/or the patient. An awl is employed to initiate the starting hole. A 2.5 mm or 2.7 mm drill bit is utilized. The starting point is just lateral to the lateral wall of the pedicle, with drilling directed toward the medial pedicle wall. The angle of the drill varies with the vertebral rotation. The depth before passing medial to the medial wall of the pedicle is approximately 18–20 mm, assuring that one is past the spinal canal. The surgeon must determine the length of the flutes on the drill bit to enable determination of the depth of penetration of the drill. After the drill tip passes the medial pedicle cortex, it may be advanced a few mm further into the cancellous bone of the vertebral body. There is no set number of fluoro shots taken during this procedure; it is done according to the anatomy of each different level. For the side utilizing the PediGuard, a starting point image is obtained on the fluoroscope, and then the PediGuard is used to navigate the pedicle. Position and passage medial to the medial wall is still confirmed on the fluoroscope. In most circumstances, fewer fluoro shots are needed because the PediGuard provides its own feedback with regards to location within the pedicle. The pedicle screws are then inserted in a standard fashion. For this study, the number of fluoro shots were counted for each pedicle hole drilling, whether done with the standard method or with PediGuard.

Results

US Clinical Trial

Utilizing this consensus data, a group of 7 patients had titanium screws between T12 and S1 for degenerative surgical procedures, with 62 screws placed by a manual technique and 60 with the current PediGuard™. With the manual technique, 79% of screws were within 2 mm and 21% of pedicle screw breaches were out by greater than 2 mm. Using the PediGuard™, there was a trend toward significant improvement, with 86.7% being within 2 mm and 13.3% being out greater than 2 mm. This 8% improvement with PediGuard™ appears to be a significant clinical trend (Table 1).

Table 1. Breaches T12 to S1, Titanium Screws, Degenerative Cases

	PediGuard™ N = 60	Manual N = 62
Anterior	3 (5%)	4 (6.5%)
Lateral	3 (5%)	3 (5%)
Medial	1 (1.5%)	6 (9.5%)
Superior	1 (1.5%)	0
Total	8 (13%)	13 (21%)

An analysis of the direction of the breach shows a very significant reduction in medial breaches (Table 1). With the standard manual technique, 6 of 62 screws (9.5%) were out medially versus only 1 of 60 screws (1.5%) with the PediGuard™. Lateral and anterior breaches were similar. This finding of a six-fold reduction in medial breaches becomes more significant when considering that all screws were tested with EMG monitoring and recorded above 10 mA.

A study by Ul Haque, Shufflebarger et al.[21] on radiation exposure with all screw constructs in adolescent idiopathic scoliosis showed that a nonclassified radiation worker (i.e. the surgeon) inserting approximately 2,800 screws under fluoroscopic guidance received in one year the ten-year equivalent of allowable radiation for a nonclassified worker.

In the US clinical trial of PediGuard™, we analyzed deformity cases with titanium screws between T11 and S1 and compared screws inserted following drilling with fluoroscopic drilling alone versus PediGuard™. CT assessment of screws demonstrated breaches greater than 2 mm to be equal in both groups (Table 2). These data are encouraging because the perforation rate greater than 2 mm is equal by both techniques, the average time per screw is reduced by approximately 10%, and the average radiation exposure is reduced by approximately 30% with PediGuard™ (Table 3).

Table 2. Percentage of Breaches: Deformity Cases T11-S1, Titanium

	In	Out > 2 mm
PediGuard™	81.4	18.5
Fluoroscopy	80.7	19.2

Table 3. Radiation Exposure

	Time (seconds)	Number of Fluoro Shots
PediGuard™	211	3.2
Fluoroscopy	229	4.5

Discussion

Other clinical studies have demonstrated the safety and efficacy of the PediGuard™ device. Bolger et al.[3] reported a clinical study of 28 patients with 147 screws to determine cortical perforations. A total of 23 (16%) vertebral cortex perforations out of the 147 manual pedicle drillings were confirmed. Of these 23 perforations, 22 (95.7%) were detected by the PediGuard™ during the procedure. A total of 12 vertebral cortex perforations (52.2%) were detected by the PediGuard™ but not by the physician.

During the second phase of this study, Bolger et al.[3] reported on an additional 374 pedicle drillings performed on 69 patients. Postoperative CT imaging showed 41 confirmed breaches (41 of 374, or 11%). The PediGuard™ had correctly detected 100% of the breaches. Pearson's correlation coefficient was 374.000 ($P < 0.001$). Three false positives occurred where there was an increase in the frequency of the beats; however, no break was detected in the pedicle cortex on postoperative CT scan. This so-called false positive can occur, as only the tip of the PediGuard™ goes through the cortex and a true hole is not made. The PediGuard™ drill hole can be redirected such that the final position of the screw on CT scan is then in a correct position.

Conclusion

Preliminary analysis of patients having had surgery for degenerative conditions with titanium screws between T12 and S1 shows a significant clinical trend in reduction of breach (by 8%) using the PediGuard™ device and a six-fold reduction in medial breaches. In patients with deformity having titanium screws, performance between PediGuard™ and a fluoroscopic technique for creating a drill hole for pedicle screw insertion appears to be equal. However, data suggest that the average time per screw is reduced by approximately 10% and also the number of fluoro shots per screw are significantly reduced with the PediGuard™, reducing the average radiation exposure by approximately 30%.

References

1. Belmont Jr PJ, Klemme WR, Robinson M, Polly Jr DW. Accuracy of thoracic pedicle screws in patients with and without coronal plane spinal deformities. *Spine.* 2002; 27:1558–66.
2. Bolger C, Bourlion M. Pedicle navigation in spondylolisthesis, ch. 28. In: Gunsburg R, Szpalski M. Spondylolysis, Spondylolisthesis, and Degenerative Spondylolisthesis. Philadelphia: Lippincott Williams & Wilkins; 2005.
3. Bolger C, Brayda-Bruno M, Kaelin A, Lazennec JY, Le Huec JC, Logroscino C, Saillant G, Zeller R. Electrical conductivity measurement: a new technique to detect iatrogenic initial pedicle perforation. *Eur Spine J,* in press.
4. Burton DC, Asher MA, Lai SM. Scoliosis correction maintenance in skeletally immature patients with idiopathic scoliosis. Is anterior fusion really necessary? *Spine.* 2000; 25:61–8.
5. Clements DH, Morledge DE, Martin WH, Betz RR. Evoked and spontaneous electromyography to evaluate lumbosacral pedicle screw placement. *Spine.* 1996; 21:600–4.
6. Donovan DJ, Polly Jr. DW, Ondra SL. The removal of a transdural pedicle screw placed for thoracolumbar spine fracture. *Spine.* 1996; 21:2495–8.
7. Hackenberg L, Link TM, Liljenqvist U. Axial and tangential fixation strength of pedicle screws versus hooks in the thoracic spine in relation to bone mineral density. *Spine.* 2002; 27:937–42.
8. Jendrisak MD. Spontaneous abdominal aortic rupture from erosion by a lumbar spine fixation device: a case report. *Surgery.* 1986; 99:631–3.
9. Kim YG, Lenke LG, Bridwell KH, Kim KL, Steger-May K. Pulmonary function in adolescent idiopathic scoliosis relative to the surgical procedure. *J Bone Joint Surg Am.* 2005; 87:1534–41.
10. Kim YJ, Lenke LG, Bridwell KH. Comparative analysis of pedicle screw versus hook instrumentation in posterior spinal fusion of adolescent idiopathic scoliosis: a matched cohort analysis. Scoliosis Research Society annual meeting, Quebec City, Canada, September 10–13, 2003.
11. Kuklo TR, Lenke LG, O'Brien MF, Lehman Jr RA, Polly Jr DW, Schroeder TM. Accuracy and efficacy of thoracic pedicle screws in curves more than 90 degrees. *Spine.* 2005; 30:222–6.
12. Laine T, Makitalo K, Schlenzka D, Tallroth K, Poussa M, Alho A. Accuracy of pedicle screw insertion: a prospective CT study in 30 low back patients. *Eur Spine J.* 1997; 6:402–5.
13. Learch TJ, Massie JB, Pathria MN, Ahlgren BA, Garfin SR. Assessment of pedicle screw placement utilizing conventional radiography and computed tomography: a proposed systematic approach to improve accuracy of interpretation. *Spine.* 2004; 29:767–73.

14. Lenke LG, Rinella A, Kim Y. Freehand thoracic pedicle screw placement. *Sem Spine Surg.* 2002; 14:48–57.
15. Liljenqvist U. Comparative analysis of pedicle screw and hook instrumentation in posterior correction and fusion of idiopathic thoracic scoliosis. *Eur Spine J.* 2002; 11:336–43.
16. Papin P, Arlet V, Marchesi D, Rosenblatt B, Aebi M. Unusual presentation of spinal cord compression related to misplaced pedicle screws in thoracic scoliosis. *Eur Spine J.* 1999; 8:156–9.
17. Perisinakis K, Theocharopoulos N, Damilakis J, Katonis P, Papadokostakis G, Hadjipavlou A, Gourtsoyiannis N. Estimation of patient dose and associated radiogenic risks from fluoroscopically guided pedicle screw insertion. *Spine.* 2004; 29:1555–60.
18. Suk S-I, Choon KL, Won-Joong K, Yong-Jin C, Yong-Bum P. Segmental pedicle screw fixation in the treatment of thoracic idiopathic scoliosis. *Spine.* 1995; 20:1399–405.
19. Suk S-I, Kim W-J, Lee S-M, Kim J-H, Chung E-R. Thoracic pedicle screw fixation in spinal deformities: are they really safe? *Spine.* 2001; 26:2049–57.
20. Suk S-I, Lee CK, Min HJ, Cho KH, Oh JH. Comparison of Cotrel-Dubousset pedicle screws and hooks in the treatment of idiopathic scoliosis. *Internat Orthop (SICOT).* 1994; 18:341–6.
21. Ul Haque M, Shufflebarger HL, O'Brien MF, Macagno A. Radiation exposure during pedicle screw placement in adolescent idiopathic scoliosis: is fluoroscopy safe? *Spine.* 2006; 31:2516–20.
22. Yahiro MA. Comprehensive literature review. Pedicle screw fixation devices. *Spine.* 1994; 19:S2274–S8.
23. Yalcin S, Guven O. Reversible anterior cord syndrome due to penetration of the spinal canal by pedicular screws. *Paraplegia.* 1995; 33:423–5.

Clinical Research

Sagittal Plane Deformity During Femoral Lengthening

James J. McCarthy, MD,[1] Richard S. Davidson, MD,[2] Michael Ast, MS,[3] Gina Bundy, MS[3]

[1]*Department of Orthopaedic Surgery, Shriners Hospital for Children, Philadelphia, PA,*
[2]*Department of Orthopaedic Surgery, Children's Hospital of Philadelphia, Philadelphia, PA,*
[3]*School of Medicine, Temple University, Philadelphia, PA*

Introduction

Limb lengthening procedures are commonly performed in children primarily to correct limb length inequality due to a variety of etiologies.[1–4] Although these techniques are commonly successful at achieving their primary goal of limb length equality and angular correction, complications are common.[5–10] Complication rates vary depending on the underlying etiology, location of the limb lengthening, degree of lengthening, definition of "complication," and experience of the medical team.[1, 11–14] Angular deformities have typically been assessd in the coronal plane. This data is extracted from a series of papers that address the multitude of complications that occur during limb lengthening. Typically they address only residual deformity and do not attempt to define how or when the deformities occur and none have address angular deformities as they occur in the sagittal plane. This manuscript has focused exclusively on the angular deformity that occur after femoral lengthenings. We hypothesis that angular deformities are uncommon, and occur primarily in the coronal plan with lengthening, ie that they drift into varus as the laterally placed fixator lengthens. The purpose of this study is to determine the incidence and degree of sagittal plane deformity that occurs during limb lengthening of the femur.

Methods

This is an IRB approved retrospective review of patients that underwent a femoral lengthening at our institution. A chart review was performed to determine the demographic data, diagnosis, procedure and complications. Radiographic assessment was performed to assess degree of angulation and displacement at the level of the corticotomy from the lateral radiographs. Radiographs were assessed perioperatively, after lengthening and at the latest follow up.

21 patients (25 limbs) were identified that met the above criteria, 10 females, 11 males, 13 left and 12 right limbs. The diagnosis was proximal femoral focal deficiency in 8, fibular hemimelia (with associated short femur) in 3 and femoral hypoplasia in the remaining 14. The mean age at the time of lengthening was 10.2 years (range 4 to 19 years). The limbs were lengthened a mean of 6.1 cm (range 3.5–9 cm), and the time in the fixators averaged 8.1 months (range 4–13 months). Mean follow up was 1.5 years post operatively.

Statistical analysis was performed using a paired t-test, with $p < 0.05$ being considered significant.

Results

The initial (immediate post op) mean deformity in the sagittal plane was 8.3° (range 3–18°). This deformity did not progress during lengthening, with mean sagittal deformity measurements of 6.8° (range 0–21°) at follow up ($P < 0.05$). There were 2 patients with angular deformities >10°. Mean displacement measured in the sagittal plane (either anterior or posterior) was 3.1 mm (range 0–22 mm).

The initial (immediate post op) mean deformity in the coronal plane was 9.6° (range 0–26°). This deformity did not progress during lengthening, with mean sagittal deformity measurements of 8.2° (range 0–26°) at follow up ($P < 0.05$). There were 6 patients with angular deformities >10°. Mean displacement measured in the sagittal plane (either anterior or posterior) was 4.0 mm (range 0–18 mm).

Discussion

Angular deformities, although typically small, can occur in the sagittal plane, and may be accompanied by displacement. These deformities are usually present immediately post operatively and typically do not worsen significantly with lengthening.

Clinically there appears to be little limitation in function, but often the underlying condition, in this case congenital femoral deficiency, may have functional limitations that mask any small changes in function. Despite this, 20% of limbs had angular deformities of >10 degrees. Therefore a fixator that would allow for multi-plane correction during the lengthening would be a benefit in this population.

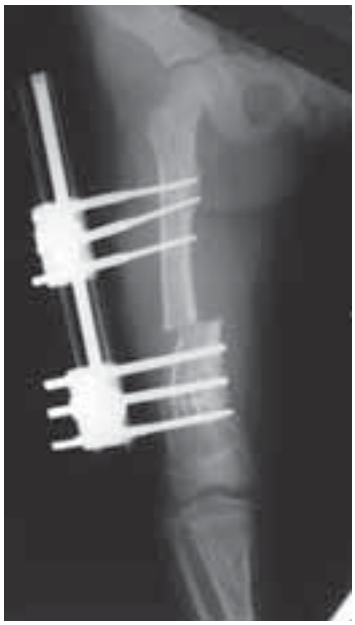


Figure1. Right femur immediately post-placement of external fixator.

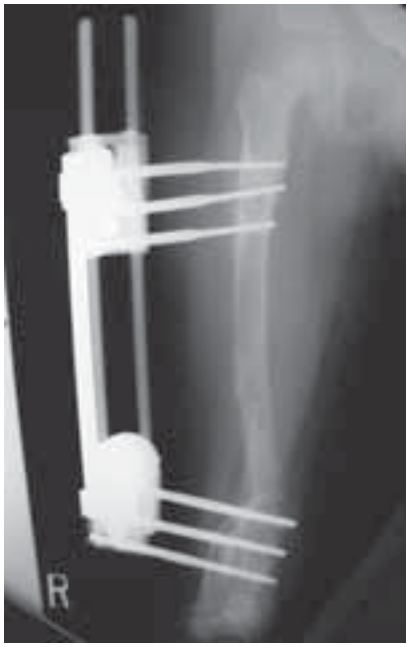


Figure 2. Right femur at end of limb lengthening prior to fixator removal.

Figure 3. Example of the technique used to measure the sagittal deformity of the femur. Note that a midpoint of the angulation was found and intersecting lines created an angle representative of the deformity.

References

1. Aldegheri R. Distraction osteogenesis for the lengthening of the tibia in patients who have limb-length discrepancy or short stature. *J Bone Joint Surg Am* 1999;81:624–634.
2. Manning C. Leg lengthening. *Clin Orthop* 1978;136:105–110.
3. Paley D. Current techniques of limb lengthening. *J Pediatr Orthop* 1988;8:73–92.
4. Velazquez RJ, Bell DF, Armstrong PF, et al. Complications of use of the Ilizarov technique in the correction of limb deformities in children. *J Bone Joint Surg Am* 1993;75:1148–1156.
5. D'Aubigne M, Dubousset J. Surgical correction of large length discrepancies in the lower extremities of children and adults. *J Bone Joint Surg Am* 1971;53:
6. Eldridge JC, Bell DF. Problems with substantial limb lengthening. *Orthop Clin North Am* 1991;22:625–631.
7. Galardi G, Comi G, Lozza L, et al. Peripheral nerve damage during limb lengthening. Neurophysiology in five cases of bilateral tibial lengthening. *J Bone Joint Surg Br* 1990;72:121–124.
8. Green SA. Complications of external skeletal fixation. *Clin Orthop* 1983;180:109–116.
9. Malhis TM, Bowen JR. Tibial and femoral lengthening: a report of 54 cases. *J Pediatr Orthop* 1982;2:487–491.
10. Naudie D, Hamdy RC, Fassier F, et al. Complications of limb-lengthening in children who have an underlying bone disorder. *J Bone Joint Surg Am* 1998;80:18–24.
11. Danzinger MB, Kumar A, DeWeese J. Fractures after femoral lengthening using the Ilizarov method. *J Pediatr Orthop* 1995;15:220–223.
12. Johnson EE. Acute lengthening of shortened lower extremities after malunion or non-union of a fracture. *J Bone Joint Surg Am* 1994;76: 379–389.
13. Stanitski DF, Bullard M, Armstrong P, et al. Results of femoral lengthening using the Ilizarov technique. *J Pediatr Orthop* 1995;15:224–231.
14. Stanitski DF, Shahcheraghi H, Nicker DA, et al. Results of tibial lengthening with the Ilizarov technique. *J Pediatr Orthop* 1996;16:168–172.

Clinical Research

Arthroscopic "Mumford" for the Treatment of Patellar Tendonitis — A Retrospective Study

JOHN D. KELLY, IV, MD

Department of Orthopaedic Surgery, Temple University, Philadelphia, PA

Introduction

Patellar tendonitis, or jumper's knee, is a common affliction in athletes who participate in rigorous running and jumping sports, such as basketball and volleyball.[1, 6, 7] The pathoanatomy of this condition has been described as cumulative micro- tearing of tendon fibers, which manifest with an inadequate healing response culminating with tissue demonstrating mucoid degeneration and fibrinoid necrosis. Popp et al. examined histologic specimens of affected tendon and characterized the tissue as "angiofibroblastic tendinosis."[16] The injured tissue has been demonstrated to lie on the deeper, undersurface of the tendon where pain nociceptors reside. Since most tendon injury is thought to occur from eccentric loading, it is noteworthy that the pathologic tissue in patellar tendonitis lies on the deep or dorsal "compressive" side of the tendon. Furthermore, the pathoanatomy of the diseased tissue is consistent with reaction to a compressive load.[8] Thus, some authors propose that impingement of the distal, non-articular pole of the patella, which can be quite prominent (Fig. 1), is implicated in the pathophysiology of patellar tendonitis.[3, 5, 9, 12]

Figure 1. Elongated distal pole patella

The treatment of this condition is largely conservative, with most athletes responding to rest, eccentric strengthening, and various modalities.[10] A considerable number of patients, however, do not adequately respond to non-operative measures. Operative treatments have been described and principally involve open debridement of the usually deep, devitalized tissue. Drilling, curettage, or removal (apicotomy) of the distal pole has also been proposed as a means to enhance healing. Romeo and Larson described an arthroscopic approach to surgical treatment of patellar tendonitis, reporting the successful return of two patients to athletics.[17] Subsequently, Ogon et al. described an arthroscopic paratenon "release" and bone denervation for chronic tendinopathy, although these investigators did not remove injured tendon or bone.[13] Most recently, Willberg et al. described an arthroscopic "dorsal release" of the neovessels and nerves on the dorsal tendon surface.[22]

For approximately the past six years, the senior author has been treating patellar tendonitis with arthroscopic debridement of the painful, abortively healed tendinous tissue coupled with excision of the non-articular distal bony patellar excrescence ("arthroscopic mumford"). The rationale for the bone excision and the author's hypothesis is that removal of any potential source of bony impingement and the introduction of local bleeding, replete with growth factors, would render results superior to open treatment. Furthermore, the ablation of free nerve endings, located at the bone tendon junction, may better ensure pain relief.[19] The purpose of this study is to report the clinical results of arthroscopic debridement and distal patellar pole excision for treatment of refractory patellar tendonitis.

Materials and Methods

This retrospective study included nine patients with refractory patellar tendonitis who underwent the "arthroscopic mumford" procedure. Patients who underwent arthroscopic tendinous debridement with concomitant distal pole excision were included. One patient underwent an additional lateral retinacular release at the time of surgery and was included. Patients were chiefly high school or collegiate athletes who had demonstrated failure to respond to at least three months of conservative treatment for jumper's knee. All patients underwent a trial of physiotherapy along with a guided rest program. All patients complained of persistent

pain at the distal aspect of the patella and all patients demonstrated marked tenderness with palpation on an everted distal pole preoperatively ('Bassett Sign').[15]

Surgical Technique

All patients underwent arthroscopic evaluation under general or regional anesthesia. Portals were created in line with the distal pole with the knee in extension. Portals were also placed as far medially and laterally as possible, so that visualization of the distal pole would be enhanced. A shaver was used to excise the local fat pad and enhance visualization of the distal pole of the patella. An electrothermal device was similarly used to further improve exposure of the non-articular distal portion of the patella. A spinal needle was used to localize the tendon if necessary. Once the proximal tendon was visualized, a small shaver was used to debride devitalized tissue. Once the medial and lateral borders of the tendon were delineated, attention was directed chiefly to the portion of the tendon that was most painful to palpation, as noted in the preoperative exam. Usually, the involved, diseased tendon segment demonstrated a more yellowish hue than the surrounding healthy tissue. The shaver was used to excise devitalized and abnormally appearing tissue. Both medial and lateral portals were used to complete the debridement and rarely a 70-degree arthroscope was employed. Following tendon debridement, a small oval burr was introduced and approximately 4–5 mm of the distal pole of the patella was excised. Care was employed to ensure a full thickness excision of bone was removed and no excrescences abutting the tendon remained (Fig. 2).

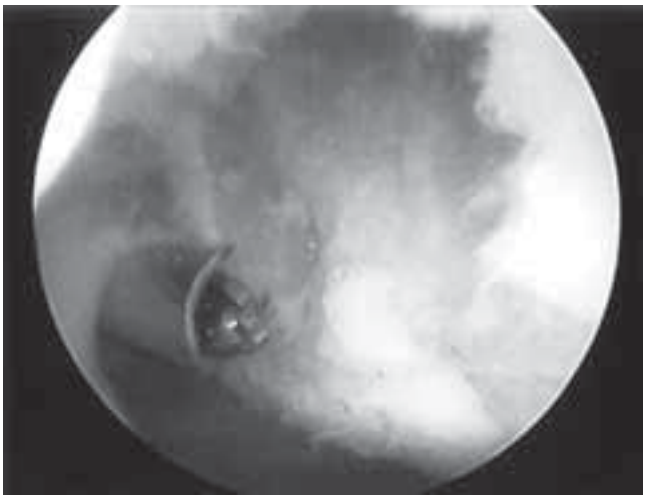


Figure 2. Arthroscopic excision distal pole patella

Postoperatively, patients were placed in a knee immobilizer and allowed to weight bear in extension for approximately three weeks. Early passive motion was encouraged and formal physical therapy was instituted after weight bearing commenced. Once the patient attained full range of motion and attained approximately 85% quadriceps strength of the contralateral knee, return to activity was permitted.

The chief determinant of treatment success was tenderness of the distal pole of the patella to palpation, which has been shown to be a reliable indicator of patellar tendinopathy.[2] Tenderness was graded as non-tender, slightly tender, moderately tender and severely tender. All patients exhibited severe tenderness preoperatively. All patients were evaluated at least approximately 3 months postoperatively and thereafter for distal pole tenderness. Follow-up ranged from approximately 3 months to 5 years.

Results

Nine patients underwent the arthroscopic Mumford from 2001 to 2006 and all were evaluated at least three months postoperatively for point tenderness at the distal pole. Eight of nine demonstrated no tenderness at the distal pole with the ninth patient demonstrating mild tenderness initially but returning to full activity without symptoms (basketball). This patient admittedly was noncompliant with postoperative rehabilitation protocol but had no complaints when contacted by phone.

Discussion

The treatment of jumper's knee can sometimes be frustrating for the clinician with slow resolution of symptoms often common. Refractory cases historically were treated surgically with open debridement with complete relief attained in only 63–80% of patients.[5, 7, 12, 14, 16, 18] Romeo first introduced arthroscopic treatment in 1999, reporting on complete relief in two patients.[17] Subsequently, Coleman compared open versus arthroscopic treatment of this affliction with the arthroscopic group demonstrating earlier return to sports.[4] However, only half of patients were able to return to competition in each group.

Arthroscopic treatment of patellar tendonitis affords the advantages of faster recovery, less pain, and less likelihood of introducing peripatellar fibrosis and paratenon violation. Furthermore, recent imaging investigations indicate that the damaged tendinous fibers lie deep to the paratenon and lie adjacent to the joint.[3] The involved dorsal tendon fibers have also been found to be richly endowed with neovessels and nerves.[22] Further, Sanchis-Alfonso, using immunohistochemical analysis of retrieved degenerative patellar tendons, demonstrated that the tendon bone junction was well innervated and often exhibited "nerve sprouting" indicative of free nerve ending growth.[19] Arthroscopic approaches to debridement are therefore inherently advantageous, since access to the deeper tendinous surface is enhanced.

The presence of bony impingement as a possible etiologt in the pathogenesis of jumper's knee was developed by Johnson et al. who posited that a prominent distal patellar pole was an etiologic factor for chronic patellar tendonosis.[9] This "impingement" theory has been more recently contested by

Schmid et al. using MRI images.[21] These investigators showed no material difference in distal patellar pole size in symptomatic versus controls. Yet, they did concede that symptomatic patients demonstrated a more posterior insertion of the tendon than asymptomatic controls. Furthermore, Shalaby and Almekinders did find evidence of a "long inferior pole" in patients with symptoms, although correlations with portions of involved tendon were inconsistent.[20] Lastly, Hamilton posited that the hypoechoic lesions observed in tendinosis are the result of an adaptation to compressive load.[8] While we cannot confirm the true role of the "impingement lesion," we submit that once tendonitis is established, the removal of bony excrescence may enhance healing of diseased tendon by removal of any potential compressing bony elements and the introduction of bleeding — r*egardless of etiology.* In addition, removal of bone may more effectively ablate the free nerve endings present at the bone tendon junction described by Sanchis-Alfonso.[19]

Of the nine patients evaluated, only one had any residual tenderness on early exam. The one singular symptomatic patient was contacted by phone at approximately 12 months later and did not report any limitations to activity. These results compare favorably with both surgical and conservative regimes.[2, 4, 10, 11]

Weaknesses of the study include the retrospective nature and the reliance on a singular test — point tenderness on the distal patellar pole — as a means of assessing improvement. However, the authors felt that the absence of tenderness to palpation is a reliable sign to indicate recovery.

Conclusions

We conclude that debridement of the patellar tendon coupled with arthroscopic "mumford" is a reasonably successful treatment approach to refractory patellar tendonitis. This treatment appears to compare favorably to open means of surgical treatment. We cannot, however, state that it is superior to arthroscopic debridement of the devitalized, richly innervated dorsal tissue alone.

References

1. Blazina ME, Kerlan RK, Jobe FW, Carter VS, Carlson GJ. Jumper's Knee. *Ortho Clinic N. America.* 1973;4:665–78.
2. Bahr R, Fossan B, Loken S, Engebretsen L. Surgical treatment compared with eccentric training for patellar tendinopathy (Jumper's Knee). A randomized, controlled trial. *J Bone Joint Surg Am.* 2006. Aug. 88 (8):1689–98.
3. Bodne D, Quinn SF, Murray WT, et al. Magnetic resonance images of the chronic patellar tendonitis. *Skeletal Radiol.* 1988;17:24–28.
4. Coleman BD, Khan KM, Kiss ZS, Bartlett J, Young DA, Wark JD. Open and arthroscopic patellar tenotomy for chronic patellar tendinopathy. A retrospective outcome study. *Am J Sports Med* 28(2):183–90, Mar-Apr. 2000.
5. Colosimo AJ, Bassett FH. Jumper's knee: diagnosis and treatment. *Orthop Rev.* 1990;19:139–149.
6. Cook JL, Khan KM, Kiss ZS, Purdham CR, Griffiths L. Reproducibility and clinical utility of tendon palpation to detect patellar tendinopathy in young basketball players. *Br J Sports Med* 2001;35:65–69.
7. Ferretti A, Conteduca F, Camerucci E, Morelli F. Patellar Tendinosis: A follow-up study of surgical treatment. *J Bone Joint Surg Am* 2002; 84:2179–2185.
8. Hamilton B, Purdam C. Patellar tendinosis as an adaptive process: a new hypothesis. *Br J Sports Med.* 2004 Dec; 38(6):758–61.
9. Johnson DP, Wakeley CJ, Watt I: Magnetic resonance imaging of patellar tendonitis. *J Bone Joint Surg* 78B:452–457, 1996.
10. Jonsson P, Alfredson H. Superior results with eccentric compared to concentric quadriceps training in paitents with jumper's knee: a prospective randomized study. *Br J Sports Med.* 39(11):847–50, Nov. 2005.
11. Martens M, Wouters P, Burssens A, Mulier JC. Patellar tendonitis: pathology and results of treatment. *Acta Orthop Scand.* 1982;53: 445–50.
12. Maffulli N, Binfield PM, Leach WJ, King JB. Surgical management of teninopathy of the main body of the patellar tendon. *Clin J Sport Med.* 1999 Apr, 9(2);58–62.
13. Ogon P, Maier D, Jaeger A, Suedkamp NP. Arthroscopic patellar release for the treatment of chronic patellar tendinopathy. *Arthroscopy,* 22(4): 462.e1–5, 2006.
14. Orava S, Osterback L, Hurme M. Surgical treatment of patellar tendon pain in athletes. *Br J Sports Med.* 1986 Dec; 20(4):167–9.
15. Osbahr, DC, Speer, KP. Patellar Tendinitis: Evaluation and arthroscopic management. *Techniques in Knee Surgery.* 2(3):160–165, September 2003.
16. Popp JE, Yu JS, Kaeding CC. Recalcitrant patellar tendinitis: Magnetic resonance imaging, histologic evaluation and surgical treatment. *Am J Sports Med.* 1997;25:218–222.
17. Romeo A, Larson R. Arthroscopic treatment of infrapatellar tednonitis. *Arthroscopy.* 15(3):341–5, April 1999.
18. Roels J, Martens M, Mulier JC, Burssens A. Patella tendonits (jumper's knee) *Am J Sports Med* 1978;6:362–8.
19. Sanchis-Alfonso V, Rosello-Sastre E, Subias-Lopez A. Neuroanatomic basis for pain in patellar tendinosis (jumper's knee): a neuoimmunohistochemical study. *Am J Knee Surg.* 2001 Summer; 14(3):174–7.
20. Shalaby M, Almekinders LC. Patellar tendonitis: The significance of magnetic resonance imaging findings. *Am J Sports Med* 1999;27: 345–348.
21. Schmid MR, Hodler J, Cathrein P, Duewell S, Hilaire A, Jacob C, Romero J. Is Impingement the Cause of Jumper's Knee? *Am J Sports Med* 2002;30:388–395.
22. Willberg L, Sunding K, Ohberg L, Forssblad M, Alfredson H. Treatment of jumper's knee: promising short term results in a pilot study using a new arthroscopic approach based on imaging findings. *Knee Surg Sports Traumatol Arthrosc.* Dec. 2006.

Basic Science Research

Characterization of a First Thoracic Rib Ligament: Anatomy and Possible Clinical Relevance

Kristofer S. Matullo, MD,[1] Ian Duncan, MD,[1] John Richmond, MD,[1]
Katharine Criner, BA,[3] Carson Schneck, MD, PhD,[2] F. Todd Wetzel, MD[1]

[1]*Department of Orthopaedic Surgery,* [2]*Department of Anatomy and Cell Biology,* [3]*School of Medicine, Temple University, Philadelphia, PA*

Abstract

Introduction: Preclavicular entrapment of the T1 ventral ramus can lead to radiculopathy, neurogenic thoracic outlet syndrome, or both, as a "double crush" phenomenon. The usual sites of entrapment include the neural foramen, the interscalene interval, an aberrant cervical rib, the first rib itself, or any apical thoracic mass (e.g. Pancoast tumor). We describe a previously undocumented intracostal ligament that limits the potential space through which the T1 ventral ramus may pass prior to crossing the superior aspect of the first rib.

Materials and Methods: Forty-two shoulders from 21 embalmed cadavers (13 male, 8 female) were dissected. The presence of the ligament was noted and its anatomic characteristics were measured with digital calipers by three independent investigators. Means, ranges, and standard deviations were calculated.

Results: The average ligament length was 31.0 mm (SD 4.3). The ligament was trapezoidal in shape wider anteriorly. The mean anterior width was 7.1 mm (SD 3.8), midsubstance width 3.6 mm (SD 1.5), and posterior width 3.5 mm (SD 1.3). The mean thickness was 0.5 mm (SD 0.3), and the maximal opening through which the T1 nerve passed between the first rib and the ligament was 6.3 mm (SD 1.6). The ligament was present on at least one side in 81% of individuals (67% of shoulders): 52% bilateral (62% males, 38% females) and 29% unilateral (23% male, 38% female).

Conclusion: This previously undescribed ligament is a robust structure, present on at least one side in over 80% of the individuals studied. When present, the ligament creates a narrow interval between the ligament and the first rib that the T1 ventral ramus traverses prior to crossing the first rib superiorly and contributing to the inferior trunk of the brachial plexus. While the actual clinical significance has not been demonstrated, this ligament may represent another entrapment site for the T1 ventral ramus.

Introduction

Neurogenic or vascular thoracic outlet syndromes involve compression of the brachial plexus and/or subclavian vessels. Neurovascular structures may be compressed by the first thoracic rib, an aberrant cervical rib, a displaced clavicle fracture, an anomalous cervical band from the C7 transverse process, a constricted anterior/middle scalene interval, the pectoralis minor tendon, the coracoid, or a posterior sternoclavicular joint dislocation.[3, 7, 11, 16] Patients typically present with pain in the apical, scapular, or suprascapular regions of the limb with radiation down the limb. Weakness in the hand or arm may be present as well. These symptoms change with abduction and extension or when carrying objects with the effected extremity.[15]

Thoracic outlet syndrome may be neurogenic, vascular, or both. Involvement of the T1 ventral ramus may lead to radicular symptoms within the T1 sclerodermotomal distribution or intrinsic hand muscle weakness. The C8 ventral ramus also contributes to hand intrinsic muscle function; this weakness is variable. The dermatomal distribution of the T1 spinal nerve includes the medial aspect of the brachium and the axilla. T1 also contributes to the median and ulnar nerve, and pain may also radiate to their respective dermatomes, further complicating the clinical scenario.

In the course of gross anatomic instruction, one senior author noted an aberrant ligament crossing the first thoracic rib (Figures 1–3). This ligament has not been previously described, and may act as another compression point of the first thoracic ventral ramus. The prevalence and characteristics of this ligament are described.

Methods and Materials

Twenty-one embalmed cadavers were utilized for the study. There were 13 males (26 shoulders) and 8 females (16 shoulders). A right sided exposure was performed to visualize all structures of the anterior and posterior triangles of the neck. The left shoulders were dissected through a supraclavicular approach to the brachial plexus. The T1 ventral ramus was identified distal to its passage through the ante-

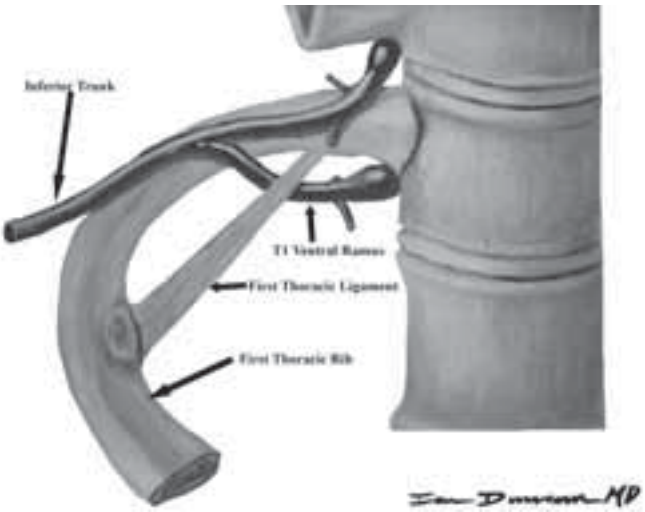


Figure 1. Artist's drawing of the first thoracic rib ligament and it's relation to the C7 and T1 ventral ramus.

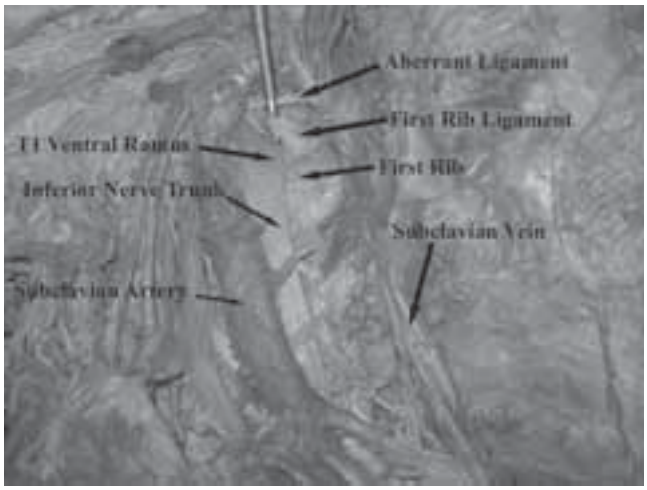


Figure 2. Anterolateral view of the first rib ligament with surrounding anatomic structures. Note the presence of an additional aberrant ligament which was only present in this particular specimen.

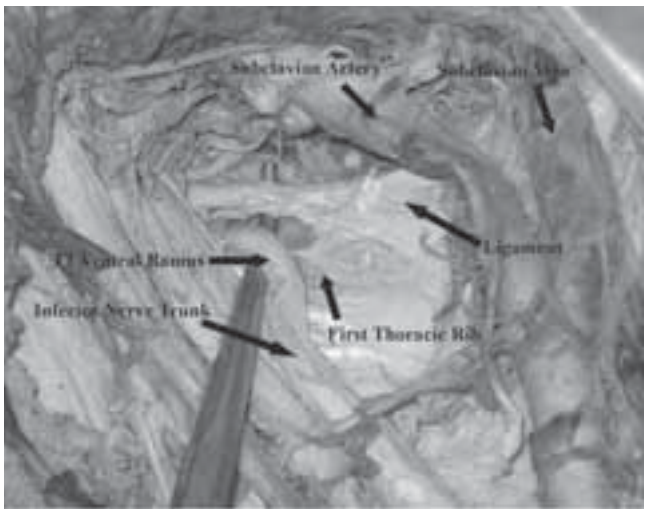


Figure 3. Close-up of dissected first rib ligament in another cadaveric specimen.

rior and middle scalene muscles, then traced proximally to the neural foramen. The first rib was evaluated for the presence of the ligament.

After identification of the ligament, the length (defined as the value from the posteromedial origin on the first rib to the anterolateral insertion on the first rib), width at the most anterior, middle, and most posterior portions, and thickness were measured. The T1 ventral ramus was dissected out and the distance from the lateral border of the ligament at its midsubstance to the medial border of the first rib was measured. This opening distance is the interval at its widest portion that the T1 ventral ramus must pass through prior to crossing the superior aspect of the first thoracic rib (Figure 4).

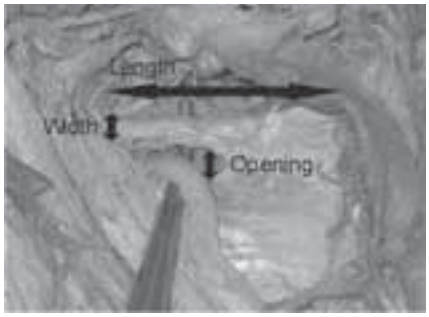


Figure 4. Dimensional characteristics of the first rib ligament that were evaluated in this study.

Three separate investigators took three independent measurements of these dimensions with electronic digital calipers (Absolute Digimatic, Mitutoyo Corp., Japan) accurate to 1/100th of a millimeter. Interobserver variability was determined by comparing individual measurements and the means. The total average of the three investigator's measurements for length, width (anterior, middle, and posterior), thickness, and opening distance were calculated, as well as the range and standard deviation for each measurement. Statistics were performed with Microsoft Excel (Microsoft, Washington, 2007).

Results

This ligament runs from the posteromedial aspect of the rib (starting just anterior to the end of the transverse process) to the anterolateral part of the rib, directly posterior to the scalene tubercle. When this ligament is present, the proximal T1 ventral ramus is initially inferior to this ligament, then passes through a narrowed interval between the lateral edge of the ligament and the medial edge of the first thoracic rib, finally crossing superior to the first thoracic rib joining the C8 ventral ramus to form the inferior trunk of the brachial plexus.

The ligament was present on at least one side in 17 out of 21 subjects for a total incidence of 81%. The ligament was present bilaterally in 11/21 (52%), unilaterally in 6/21 (29%), and not present in 4/21 (19%) of people. An aberrant liga-

ment was found in 1/42 shoulders (2%), but was significantly smaller (Figure 1). If each shoulder is considered individually, the ligament was present in 28/42 shoulders for a total incidence of 67% per shoulder.

Analyzing the difference between male and female subjects, the ligament was present in 11/13 male specimens (85%). In males, the ligament was bilateral in 8/13 (62%), unilateral in 3/13 (23%), and not present in 2/13 (15%). Considering each shoulder individually, it was present in 19/26 male shoulders for a total of 76%. In females, the presence of a ligament was found in 6/8 for a total incidence of 75%, bilateral in 3/8 (38%), unilateral in 3/8 (38%), and it was not present in 2/8 (25%). When considering each shoulder individually, it was present in 9/16 female shoulders for a total of 56%. Data are summarized in Table 1.

Table 1

	Numbers	Percent Incidence
Total Number of Specimens	21	
Male Specimens	13	
Female Specimens	8	
Male Shoulders	26	
Female Shoulders	16	
Total Number of Ligaments	28	
Total Number of Shoulders	42	
Incidence of Ligament per Shoulder	28/42	67
Incidence of Ligament in Male Shoulders	19/26	73
Incidence of Ligament in Female Shoulders	9/16	56
Total Specimens with Ligament Present Unilaterally or Bilaterally	17/21	81
Specimens with Bilateral Ligaments	11/21	52
Specimens with Unilateral Ligaments	6/21	29
Specimens with No Ligament	4/21	19
Males with Ligament Present Unilaterally or Bilaterally	11/13	85
Males with Bilateral Ligaments	8/13	62
Males with Unilateral Ligaments	3/13	23
Males with No Ligament	2/13	15
Females with Ligament Present Unilaterally or Bilaterally	6/8	75
Females with Bilateral Ligaments	3/8	38
Females with Unilateral Ligaments	3/8	38
Females with No Ligament	2/8	25

The ligament is trapezoidal in shape (Figure 3) wider anteriorly than posteriorly (measured medial to lateral. Due to the semicircular shape of the rib, the ligament (defined as the distance measured anterior to posterior) is longer on the medial side. The average length of the medial side of the ligament is 31.9 mm (standard deviation 4.7 mm), and the average length of the lateral side measuring 30.1 mm (standard deviation 4.1 mm). The average length of the center of the ligament (mean of average lateral and medial length) is 31.0 mm (SD 4.3 mm). The average anterior width is 7.1 mm (SD 3.8 mm), with a middle width of 3.6 mm (SD 1.5 mm) and posterior width of 3.5 mm (SD 1.3 mm). The thickness of the ligament measured 0.5 mm (SD 0.3 mm).

The distance from the lateral border of the ligament at its midsubstance to the medial border of the first rib averaged 6.3 mm (standard deviation 1.3 mm). This is the size of the maximal opening between the lateral edge of the ligament and the medial edge of the first rib through which the T1 ventral ramus passes. All measurements are summarized in Table 2. Note that some ligaments had substantially smaller dimensions than those depicted in Figures 1–3. An appreciation of how small the ligament can be is illustrated in Figure 4.

Discussion

Upon leaving the cord, the T1 ventral ramus passes through the T1-2 neural foramen, the interval between the anterior and middle scalene muscle, and then runs superior to the first rib prior to combining with the C8 ventral ramus to form the inferior trunk of the brachial plexus. All of these loci could serve as potential entrapment sites. We have described a previously undocumented ligament of the first thoracic rib present in 81% of individuals (67% of shoulders) that may be another site of encroachment upon the T1 ventral ramus. This ligament is variable in size (Figures 3 and 5); one cadaveric specimen also contained an aberrant second ligament. However, this ligament was significantly smaller in size (Figure 2). When the new ligament is present, it runs from a posteromedial to anterolateral direction, and thus alters the course of the T1 ventral ramus.

Neurogenic syndromes, such as thoracic outlet syndrome or radiculopathy, may be caused by direct compression, stenosis of an interval through which a nerve must pass, or tenting of the nerve fibers. The presence of this ligament could affect the T1 ventral ramus in a variety of ways. Medially, the ligament creates a roof-like structure over the ventral ramus, allowing any potential compressive lesion growing from inferiorly (e.g. a Pancoast tumor) to compress the T1 ventral ramus against the undersurface of the ligament. Laterally, the ligament creates an interval through which the T1 ventral ramus must pass. This is a potential area of stenosis which measured as little as 3.1 mm in our series. Any pathologic condition that causes tendinous hypertrophy, such as diffuse idiopathic skeletal hyperostosis (DISH)[13] or amyloidosis,[4, 8, 10, 18] may further narrow this interval.

Clinically, compressive neuropathy of a peripheral nerve can cause symptoms of neuropathic pain, paresthesia, anesthesia, muscular weakness, decreased proprioception, or, in long standing cases, allodynia. The spinal canal, the neural foramen, the interval between the anterior and middle scalene muscle, and an aberrant cervical rib have been identified as possible areas where the T1 nerve may be compressed.[3, 6, 8, 12] Neurogenic thoracic outlet syndrome is a positional radiculopathy caused by compression of the nerve distal to the neural foramen. Multiple clinical tests have been

Table 2

Cadaver #	Length		Average Length	Thickness Middle	Width			Opening Middle
	Laterally	Medially			Anterior	Middle	Posterior	
1 R	36.4	40.4	38.4	0.4	14.5	4.3	4.1	8.4
L	32.3	37.3	34.8	0.4	11.8	3.5	3.4	7.1
2 R	35.4	38.9	37.1	0.4	4.7	1.9	2.0	6.9
L	40.4	42.2	41.3	0.2	4.3	1.6	2.2	6.3
3 R	26.2	30.5	28.4	0.1	3.2	1.4	1.2	5.6
L	28.1	30.6	29.4	0.2	2.8	2.0	2.3	6.4
4 R	27.2	32.0	29.6	0.3	5.2	3.8	2.6	7.8
L	27.5	31.0	29.3	0.2	2.9	1.9	2.8	8.2
5 R	23.3	25.5	24.4	0.5	4.0	2.6	1.8	8.4
L	—	—	—	—	—	—	—	—
6 R	30.6	29.0	29.8	0.3	2.2	1.8	3.7	4.6
L	26.3	27.5	26.9	0.3	2.7	2.4	2.3	4.7
7 R	27.5	28.0	27.7	0.3	9.7	5.1	3.8	6.3
L	30.9	30.0	30.5	0.5	3.7	3.1	3.6	5.0
8 R	32.0	34.8	33.4	0.8	10.1	5.7	5.7	3.7
L	31.6	31.9	31.8	0.8	6.8	5.5	5.8	8.2
9 R	31.5	33.1	32.3	0.9	12.1	6.5	6.8	7.1
L	—	—	—	—	—	—	—	—
10 R	28.7	31.5	30.1	0.7	7.7	3.8	2.7	6.1
L	30.5	30.8	30.6	0.7	2.2	2.9	4.2	6.3
11 R	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—
12 R	—	—	—	—	—	—	—	—
L	28.6	26.3	27.5	0.7	5.1	2.8	3.6	3.1
13 R	33.3	34.6	34.0	0.7	9.5	4.5	4.3	7.8
L	—	—	—	—	—	—	—	—
14 R	37.9	41.2	39.5	0.7	14.4	6.8	4.4	5.4
L	28.9	28.4	28.6	0.3	4.3	3.2	3.0	8.1
15 R	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—
16 R	27.0	29.2	28.1	0.2	8.0	3.2	1.8	8.6
L	27.8	30.1	28.9	0.5	6.8	3.9	3.4	6.9
17 R	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—
18 R	26.2	30.3	28.3	0.9	12.5	4.9	4.2	3.6
L	22.6	22.4	22.5	0.7	8.0	3.8	4.7	3.8
19 R	—	—	—	—	—	—	—	—
L	—	—	—	—	—	—	—	—
20 R	31.3	34.3	32.8	1.1	9.7	4.3	4.3	5.3
L	—	—	—	—	—	—	—	—
21 R	—	—	—	—	—	—	—	—
L	31.7	30.8	31.2	0.1	9.5	4.8	4.1	7.6
Average	30.1	31.9	31.0	0.5	7.1	3.6	3.5	6.3
Std Dev	4.1	4.7	4.3	0.3	3.8	1.5	1.3	1.6
Min	22.6	22.4	22.5	0.1	2.2	1.4	1.2	3.1
Max	40.4	42.2	41.3	1.1	14.5	6.8	6.8	8.6

All values are in millimeters. When no value is recorded, the ligament was not present.

described to diagnose this condition and its vascular variant.[17] An upper thoracic radiograph can aid in the diagnosis of an aberrant cervical rib or Pancoast's tumor. Currently, however, there is no diagnostic study or physical examination maneuver that is specific to the diagnosis of T1 entrapment. T1 radiculopathy typically presents with pain in the inferior brachium and decreased sensation in the involved axilla. Unfortunately, neither nerve conduction velocities[19–21] nor somatosensory evoked potentials[12] are diagnostic.

Radiographs can help visualize potential entrapment sites of the T1 nerve root (i.e. aberrant cervical rib, first thoracic rib, malunited clavicle fracture, sternoclavicular dislocation, or cervical/thoracic stenosis). The use of MRI may help as well. Narrowing of the scalene interval between the anterior and middle scalene muscle, as well as aberrant ligamentous structures are not well delineated with MRI; however, it is possible to visualize a diminished costoclavicular distance, thicker subclavius muscles, and a narrowed retropectoralis

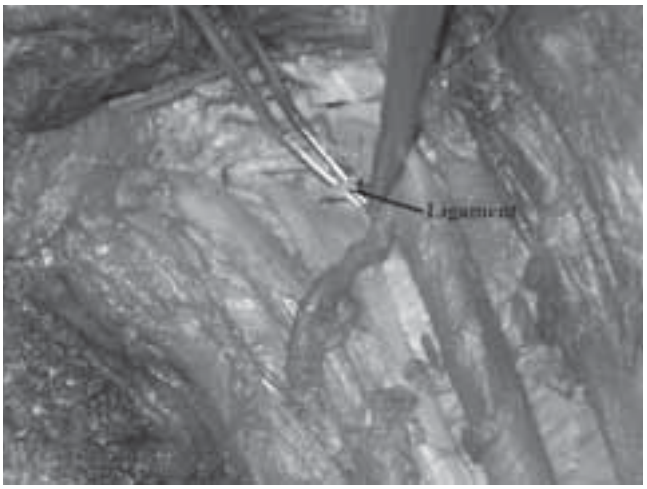


Figure 5. Lateral view of another cadaveric specimen demonstrating the substantial variability in size of the first rib ligament which a surgeon should be cognizant of in searching for this ligament.

minor space.[5] Vascular compression or occlusion leading to vascular thoracic outlet syndrome may be delineated with postural venography or arteriography.[3]

Typical treatment of thoracic outlet syndrome is primarily nonoperative. Conservative treatment of thoracic outlet syndrome was reported by Novak in 1995 which included physical therapy, education, aerobic conditioning, and correction of posture and positions of discomfort. Of the 42 patients in his study, complete resolution of symptoms occurred in 3 patients, near complete resolution in 16, improvement in 6, no change in 10, and worsening in 7. While the frequency of symptoms improved, the duration of symptoms did not seem to be related to the outcome of conservative therapy.[15]

Surgical intervention involves release of the scalene muscles, resection of the first thoracic rib, or removal of an aberrant cervical rib. These procedures are performed through either a supraclavicular or transaxillary approach. In cases of first rib resection, either open or thoracoscopically, there have been reports of ligamentous structures that must be released to complete the resection.[6] There is even a documented case of recurrent thoracic outlet syndrome secondary to a "ectopic ligament," however, the characteristics of the ligament have not been identified.[2]

The results of release of an aberrant cervical rib or thoracic rib for thoracic outlet historically are variable. Donaghy reported a 90% decrease in pain and sensory disturbance, but only a 50% improvement in motor symptoms. In this series, there was resection of the first thoracic rib or a fibrous ligament in 18 of 49 patients.[6] O'Brien reported a primary success rate (defined as a 50% or more relief in pain or return to work) in 46.5% of patients undergoing primary first rib resection with lower scalenectomy, and a 64.2% success rate for previously operated cases treated with upper scalenectomy.[16] Hempel reported 59% excellent results and 27% good results in 770 of cases treated with supraclavicular scalenectomy and rib resection.[9] Maxey noted a resolution of symptoms in 63.9%, a partial response in 23.6%, and no change in 12.5% of patients treated with a supraclavicular approach and decompression.[14] Barkhordarian correlates the length of the remaining first rib after resection, as well as lack of adequate release of all fibrous structures, periosteum, and scalene muscles with surgical failure.[3] First rib resection has also been described through video assisted thorascopy.[1] Complications from a first rib resection include pneumothorax, subclavian vein injury, long thoracic nerve injury, internal mammary artery injury or suture granuloma.[16]

Clinically, the diagnosis of neurogenic thoracic outlet syndrome should be included in the differential diagnosis in a patient with a suggestive history, positional radicular symptoms and a positive provocative test. Ligaments and other fibrous restraints have been demonstrated to cause peripheral nerve entrapments in many parts of the body. Examples include the transverse scapular ligament, ligament of Struthers, bicipital aponeurosis, arcade of struthers, cubital tunnel, or the soleal arch.

Despite the intimate relationship of the ligament with the T1 ventral ramus, its exact clinical significance is unknown. Overall, the results of first rib resection to treat thoracic outlet range from 40–70% success.[14, 16] While it would be tempting to suggest that failures of surgery could be explained by failure to recognize and release this ligament — perhaps analogous to the "fibrous ligament" identified by Donaghy[6] as a potential cause for surgical failure — this cannot be supported by the present study and remains an object of future anatomic, clinical, and biomechanical study.

References

1. Al-Sayyad, M. J.; Crawford, A. H.; and Wolf, R. K.: Video-assisted thoracoscopic surgery: the Cincinnati experience. *Clin Orthop Relat Res,* (434):61–70, 2005.
2. Ambrad-Chalela, E.; Thomas, G. I.; and Johansen, K. H.: Recurrent neurogenic thoracic outlet syndrome. *Am J Surg,* 187(4):505–10, 2004.
3. Barkhordarian, S.: First rib resection in thoracic outlet syndrome. *J Hand Surg [Am],* 32(4):565–70, 2007.
4. D'Agostino, A. N.; Mason, M. S.; and Quinn, S. F.: Lumbar spinal stenosis and spondylosis associated with amyloid deposition in the ligamentum flavum. *Clin Neuropathol,* 11(3):147–50, 1992.
5. Demondion, X.; Bacqueville, E.; Paul, C.; Duquesnoy, B.; Hachulla, E.; and Cotten, A.: Thoracic outlet: assessment with MR imaging in asymptomatic and symptomatic populations. *Radiology,* 227(2):461–8, 2003.
6. Donaghy, M.; Matkovic, Z.; and Morris, P.: Surgery for suspected neurogenic thoracic outlet syndromes: a follow up study. *J Neurol Neurosurg Psychiatry,* 67(5):602–6, 1999.
7. Fujita, K.; Matsuda, K.; Sakai, Y.; Sakai, H.; and Mizuno, K.: Late thoracic outlet syndrome secondary to malunion of the fractured clavicle: case report and review of the literature. *J Trauma,* 50(2):332–5, 2001.
8. Harats, N.; Worth, R.; and Benson, M. D.: Spinal claudication in systemic amyloidosis. *J Rheumatol,* 16(7):1003–6, 1989.
9. Hempel, G. K.; Shutze, W. P.; Anderson, J. F.; and Bukhari, H. I.: 770 consecutive supraclavicular first rib resections for thoracic outlet syndrome. *Ann Vasc Surg,* 10(5):456–63, 1996.
10. Honig, S., and Murali, R.: Spinal cord claudication from amyloid deposition. *J Rheumatol,* 19(12):1988–90, 1992.
11. Jain, S.; Monbaliu, D.; and Thompson, J. F.: Thoracic outlet syndrome caused by chronic retrosternal dislocation of the clavicle. Successful treatment by transaxillary resection of the first rib. *J Bone Joint Surg Br,* 84(1):116–8, 2002.

12. Komanetsky, R. M.; Novak, C. B.; Mackinnon, S. E.; Russo, M. H.; Padberg, A. M.; and Louis, S.: Somatosensory evoked potentials fail to diagnose thoracic outlet syndrome. *J Hand Surg [Am],* 21(4):662–6, 1996.
13. Laroche, M.; Moulinier, L.; Arlet, J.; Arrue, P.; Rousseau, H.; Cantagrel, A.; and Mazieres, B.: Lumbar and cervical stenosis. Frequency of the association, role of the ankylosing hyperostosis. *Clin Rheumatol,* 11(4): 533–5, 1992.
14. Maxey, T. S.; Reece, T. B.; Ellman, P. I.; Tribble, C. G.; Harthun, N.; Kron, I. L.; and Kern, J. A.: Safety and efficacy of the supraclavicular approach to thoracic outlet decompression. *Ann Thorac Surg,* 76(2): 396–9; discussion 399–400, 2003.
15. Novak, C. B.; Collins, E. D.; and Mackinnon, S. E.: Outcome following conservative management of thoracic outlet syndrome. *J Hand Surg [Am],* 20(4):542–8, 1995.
16. Obrien, M. J., Dreese, J. C.: Thoracic Outlet Syndrome. *Curr Opin Orthop,* 17(4):331–334, 2006.
17. Reider, B.: The Orthopaedic Physical Examination. Edited, 402, Philadelphia, W.B. Saunders Company, 1999.
18. Roche, P. H.; Figarella-Branger, D.; Malca, S.; Bouvier, C.; Soumare, O.; and Pellet, W.: [Lumbar canal stenosis caused by amyloidosis of the yellow ligament]. *Neurochirurgie,* 45(2):91–7, 1999.
19. Urschel, H. C., Jr.: Management of the thoracic-outlet syndrome. *N Engl J Med,* 286(21):1140–3, 1972.
20. Urschel, H. C., Jr.; Razzuk, M. A.; Wood, R. E.; Parekh, M.; and Paulson, D. L.: Objective diagnosis (ulnar nerve conduction velocity) and current therapy of the thoracic outlet syndrome. *Ann Thorac Surg,* 12(6):608–20, 1971.
21. Wilbourn, A. J., and Lederman, R. J.: Evidence for conduction delay in thoracic-outlet syndrome is challenged. *N Engl J Med,* 310(16):1052–3, 1984.

Basic Science Research

The Relationship of the Coracoid Process to the Glenoid: An Anatomic Study

ALLEN THAM, MD, ROBERT PURCHASE, MD, JOHN D. KELLY, IV, MD

Department of Orthopaedic Surgery, Temple University Hospital, Philadelphia, PA

Abstract

Purpose: To define the spatial relationship of the coracoid process to the glenoid cavity.

Type of Study: Anatomic study in cadavers.

Methods: Using 20 cadaver shoulders, the location of the tip of the coracoid process was assessed based on the clock face of the glenoid.

Results: In all shoulders, the tip of the coracoid process was between 1:24 and 2:18 o'clock with an average of 1:47 +/– 0:15 o'clock. The distance of the coracoid process tip to the nearest portion of the glenoid labrum was 21.5 +/– 3.6 mm.

Conclusion: Our analysis of the anatomic relationship of the coracoid to the glenoid provides the shoulder arthroscopist with essential information regarding the location of the coracoid tip during coracoplasty.

Introduction

Coracoid impingement is a syndrome of anterior shoulder tenderness and pain with adduction, flexion, and rotation; moreover, it is becoming a progressively more diagnosed entity.[1, 2] The treatment of coracoid impingement which has failed conservative management is decompression of the coracohumeral space, otherwise known as coracoplasty.[3]

An arthroscopic method of coracoplasty has recently been described.[4] Before arthroscopic coracoplasty can be performed, the coracoid tip must be first located. The coracoid tip is usually found anterior to the upper border of the subscapularis.[5] However, with tears of the subscapularis, the relationship of the coracoid tip to the upper subscapularis tendon is altered with distal retraction of the tendon. In this circumstance, arthroscopically finding the precise location of the coracoid tip may be challenging and incur excessive soft tissue ablation with consequent bleeding.

Knowledge of the bony anatomy may assist in locating the coracoid tip arthroscopically; yet, the coracoid's relationship to the anatomic structures of the glenohumeral joint has never been described. This cadaveric study evaluated the distance of the coracoid to the glenoid as well as its relationship to the clock face of the glenoid.

Materials and Methods

Twenty shoulders from 18 cadaver specimens were evaluated. The glenohumeral joint and coracoid were exposed using sharp dissection. The humeral head was disarticulated. The acromion process was also removed to provide unobstructed measurement of the glenoid. The center of the glenoid and the 12 o'clock position on the glenoid labrum were marked (Figure 1). A straight line from the center of the glenoid to the tip of the coracoid was made. The glenoid labrum was marked at its intersection with this line, designated point A (Figure 2). A degree measurement was obtained from the two marks on the glenoid rim using the center of the glenoid as the vertex (Figure 3). Then, the distance in millimeters from the coracoid tip to point A on the glenoid labrum was determined (Figure 4).

Mean and standard deviation were calculated for the degree values as well as the distance values. The degree values were then converted to hours: minutes in reference to the right shoulder.

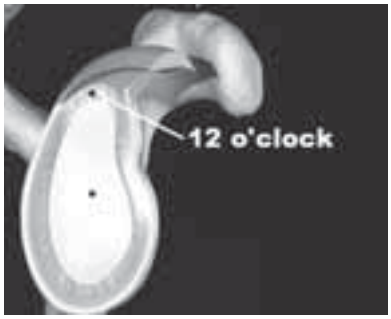


Figure 1. Center of glenoid and 12 o'clock position.

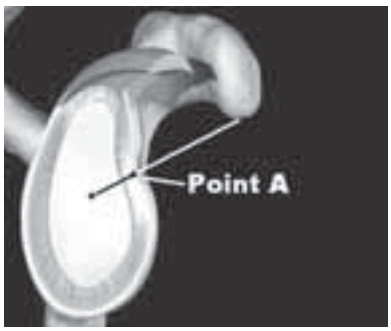


Figure 2. Intersection of line from center of the glenoid to the coracoid and the labrum, designated point A.

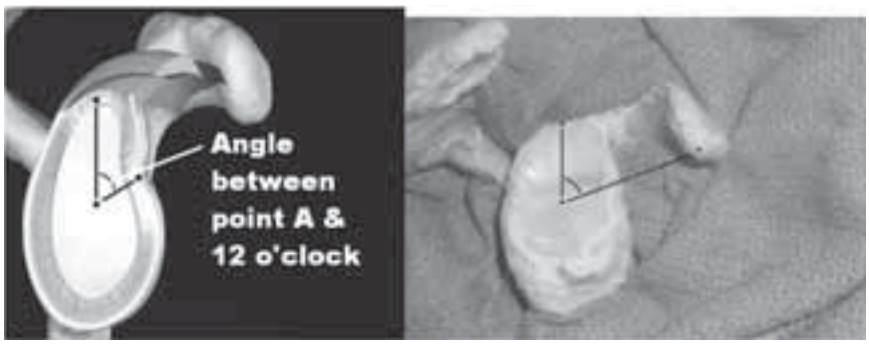


Figure 3. Angle between point A and 12 o'clock.

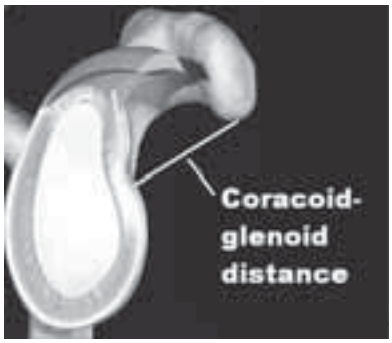


Figure 4. Distance between coracoid and glenoid.

Results

In all shoulders, the tip of the coracoid process was between 1:24 and 2:18 o'clock with an average of 1:47 +/– 0:15 o'clock. The distance of the coracoid process tip to the nearest part of the glenoid labrum was between 14 and 30 mm with and average of 21.5 +/– 3.6 mm.

Discussion

Arthroscopic coracoplasty has become a valuable technique for the treatment of coracoid impingement.[1] Further, decompression of the coracohumeral space is commonly performed in conjunction with arthroscopic repair of the subscapularis. Observing the coracoid's relationship to the humeral head and tendon of the subscapularis can be used to diagnose coracoid impingement.[4] However, a quantitative relationship of the coracoid to the clock face of the glenoid has never been described in the literature (using medline 1950–present English literature, human subjects with "glenoid" and "coracoid" search terms, no similar studies have been performed). We described this relationship and found that it is fairly consistent. This information can be used clinically to access the coracoid from the glenohumeral joint during shoulder arthroscopy. This information may prove especially useful in massive, retracted tears of the subscapularis, when the upper subscapularis tendon can no longer be used as a reference point for the coracoid tip. Using the information from this study, a universal approach to locating the coracoid using intra-articular markers could be developed.

One shortcoming of this study is that it was a cadaveric study with no history given for each specimen. It is possible that in shoulders with known coracoid impingement, the bony anatomy of the coracoid in relation to the glenoid may be different. Nevertheless, our findings provide anatomical information useful in subsequent studies designed to locate the coracoid from an intra-articular location.

Arthroscopic coracoplasty is a newer technique for the treatment of coracoid impingement and tears of the upper subscapularis. This study presents some of the anatomy and surgical relationships of the coracoid to the glenoid, useful for arthroscopic coracoplasty. Future studies may determine the clinical utility of these results.

References

1. Ferrick MR. Coracoid impingement: A case report and review of the literature. *Am J Sports Med.* 2000; 28:117–119.
2. Arrigoni P, Brady PC, Burkhart SS. Calcific Tendonitis of the Subscapularis Tendon Causing Subcoracoid Stenosis and Coracoid Impingement. *Arthroscopy.* 2006; 22,10:1139–1139.
3. Ide J, Tokiyoshi A, Hirose J, and Mizuta H. Arthroscopic Repair of Traumatic Combined Rotator Cuff Tears Involving the Subscapularis Tendon. *J Bone Joint Surg Am.,* 2007; 89:2378–2388.
4. Lo IK, Burkhart SS. Arthroscopic coracoplasty through the rotator interval. *Arthroscopy.* 2003; 19:667–71.
5. Burkhart SS, Brady PC. Arthroscopic Subscapularis Repair: Surgical Tips and Pearls A to Z. *Arthroscopy.* 2006; 22,9:1014–1027.

Basic Science Research

Upper Limb Movement Degradation with Performance of Repetitive Reaching in a Rat Model

David M. Kietrys,[1, 2] Mary F. Barbe,[2, 3] Mamta Amin,[2] Michele Y. Harris,[2]
Frank K. Bempong,[2] Ann E. Barr[4]

[1]*Department of Physical Therapy, UMDNJ, Stratford, NJ,*
[2]*Department of Physical Therapy, Temple University, Philadelphia, PA,*
[3]*Department of Anatomy and Cell Biology, Temple University Medical School, Philadelphia, PA,*
[4]*Department of Physical Therapy, Thomas Jefferson University, Philadelphia, PA*

Abstract

This study examined the induction of upper limb behavioral changes with performance of low or high repetition tasks in young adult, female, rats. Forty-nine young (12–24 weeks) female Sprague-Dawley rats were used. Rats performed either a low repetition negligible force reaching task, or a high repetition negligible force task, or a high repetition high force task for over 6 weeks. Rats were videotaped at the end of weeks 1, 3 and 6 weeks; representative reaches were quantified with video motion analysis. Reach rate, task duration, reach time, grasp time and movement reversals were determined and analyzed with repeated measures ANOVA within groups. Reach rate and task duration did not change in the LRNF group, but there were significant declines in both in the HRNF and HRHF groups compared to week 1. There was also a rebound in task duration in the HRNF group in week 6 compared to the HRHF group, which showed a persistent decline. The number of movement reversals, forelimb total reach time and grasp time increased from week 1 to 6 in the HRHF group only. Our results are consistent with the development of uncoordinated movement patterns in the early stages of repetitive motion injury that is dose-dependent.

Introduction

Risk factors in the work place that may contribute to the development of work-related musculoskeletal disorders include highly repetitive and/or highly forceful movements. We have developed a rat model of a repetitive and forceful voluntary reaching and pulling task in the rat, which enables us to monitor both tissue pathophysiology and behavioral changes. In previous studies, we have shown that there is a dose-dependent increase in tissue injury, inflammation and fibrosis that involves muscle, tendon, bone and peripheral nerve.[1–4] At low repetition and negligible force, minimal tissue damage and inflammation occurred, and task pace was maintained. In contrast, at high repetition and high force, a progressive worsening of tissue effects and task performance was evident.[2–3] One early observation was that rats resorted to uncoordinated raking movements of the reach limb that corresponded to tissue inflammation.[1] We are interested in these motor changes, because they are observable behaviors that may assist in early detection of subclinical tissue pathophysiology.

Our overall goals are to examine factors that contribute to the development of work-related musculoskeletal disorders (WMSD), including repetitive and/or forceful movements. The purpose of this study was to quantify exposure-dependent forelimb reach changes in a rat model of WMSD, comparing low repetition negligible force (LRNF), high repetition negligible force (HRNF), and high repetition high force (HRHF) tasks.

Methods

Subjects and Task Regimen. Forty-nine, young adult (12–24 weeks) Sprague-Dawley rats were used. All procedures were approved by the Temple University IACUC in accordance with NIH guidelines for the care and use of laboratory animals. Rats were trained to perform a reaching task at three exposure levels: low repetition negligible force (LRNF, n = 16, cued every 30 seconds to retrieve a 45 mg spherical food pellet in an apparatus shown in Figure 1A), high repetition negligible force (HRNF, n = 16, cued every 15 seconds to retrieve a 45 mg food pellet, Figure 1A), and high repetition high force (HRHF, n = 17, cued every 15 seconds to exert an isometric pull on a handle at 60% of maximum voluntary force in an apparatus shown in Figure 1B,C). Maximum voluntary force as measured with a miniature tension-compression load cell (Model LSB 200; 1 lb capacity, Futek Advanced Sensor Technology, Inc., Irvine, CA). Load cell output was sampled continuously at 100 Hz during task sessions. Rats performed the tasks for 2 hrs/day and 3 days per week for 6 weeks. At the end of weeks 1 and 6, lateral view video recordings at 60 Hz were collected (JVC Model TK-C1380 interfaced with Panasonic Desktop editor Proline, Model AG-1980), and 5 representative reaches for

each rat at each weekly endpoint were digitized to create 2D fore-aft Cartesian trajectories of the distal forelimb (Peak-Motus Version 8.2, Vicon-Peak).

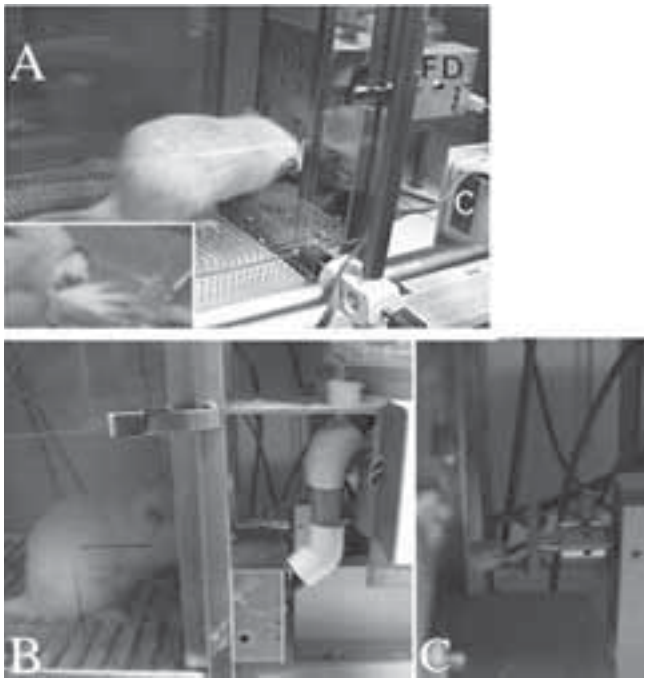


Figure 1. (A) Lateral and close up views of a rat performing food pellet retrieval during the low force tasks (LRNF and HRNF tasks), Inset shows the forepaw entering the tube through the opening in the side of the training pen. The food dispenser (FD) dispensed pellets at high or low frequencies. A video camera **(C)** recorded upper limb movements from the lateral aspect for motion analysis. **(B)** Lateral and close up views of the grasp phase of the high force reaching task (HRHF task) showing the rat grasping the handle attached to the force transducer.

Behavioral Analysis. The effects of the task on motor performance were evaluated at the ends of weeks 1, 3 and 6 using two variables reach rate (reaches/min) and task duration (hours per day) described previously.[1, 3] We also examined a quantitative movement pattern analysis of reach movement reversals using a JVC CCD video camera (Model TK-C1380, 60 Hz) to record the reach limb from a lateral view. A landmark on the forelimb was digitized and then tracked at 60Hz (X and Y coordinates) and a graphic display of this landmark coordinate was visually assessed to determine if (and how many) movement reversals occurred. Rats were video taped for 15 minutes at the end of weeks 1, 6, 9 and 12. Five representative videotaped reaches were selected for each weekly endpoint using a systematic procedure shown in Figure 3A,C. First, a representative reach was defined as a reach sequence beginning with the reach paw in a fixed position and the snout in the tube opening and ending with the consumption of a food pellet. The start of the sequence was the first frame in which the forepaw began its ascent toward the tube opening, and the end of the sequence was the first frame in which the head moved away from the forepaws following consumption of the food pellet. The grasp period was defined by the first frame in which the reach forepaw entered the tube opening until the first frame in which the reach forepaw exited the tube opening with the food pellet. Each 15 minute videotape was divided into 5 equal (3 minute) segments, and the first reach sequence in each 3 minute segment that satisfied the above criteria was digitized in order to determine the average number of reach movement reversals (fore-aft displacements) performed by the forearm segment using video motion analysis (VMA) (Vicon Motus v.8.0, Vicon, Centennial, CO) as shown in Figure 3A. The point chosen for digitization was on the proximal forearm segment just below the elbow joint, as this was easily visualized on the videotape throughout the reach sequence (Figure 3C). The number of reach movement reversals (fore-aft movements of the forelimb) was used as an indicator of motor dysfunction (e.g. diminished fine motor coordination) and/or discomfort (e.g. self-regulation of exposure).

Data Analysis. Mixed model ANOVA was used to compare reach rate and task duration at weeks 3 and 6 to week 1 within groups; and to compare reach movement reversals, total reach time, and grasp time at weeks 1 and 6 between groups. Post hoc analyses were performed using the Bonferroni method ($\alpha = 0.05$).

Results

Reach rate (RR) and task duration (TD) did not change in the LRNF group, but there were significant declines in RR in week 6 and TD beginning in week 3 in both the HRNF and HRHF groups ($p < 0.05$) compared to week 1 (Figure 2). There was also a return toward baseline of task duration in the HRNF group in week 6 as compared to the HRHF group, which showed a persistent decline (Figure 2B). The number of movement reversals increased from week 1 to week 6 in the HRHF group only ($p < 0.05$) compared to week 1 of these same rats (Figure 3B). Forelimb total reach time (RT) and grasp time (GT) increased from week 1 to week 6 in the HRHF group only ($p < 0.05$) compared to week 1 (Figure 4).

Discussion

Our results are consistent with the development of uncoordinated movement patterns in the early stages of repetitive motion injury that is exposure-dependent. Such exposure dependent results are consistent with our previous studies examining tissue pathology, which also showed the greatest changes in the animals performing the HRHF task.[1–4] At a low reach rate and negligible force level, task performance and movement quality is maintained. With increasing reach rate and reach force, performance and movement quality decline. The development of an uncoordinated grasp in which fore-aft submovements increase in the HRHF group contributes to a longer grasp phase.

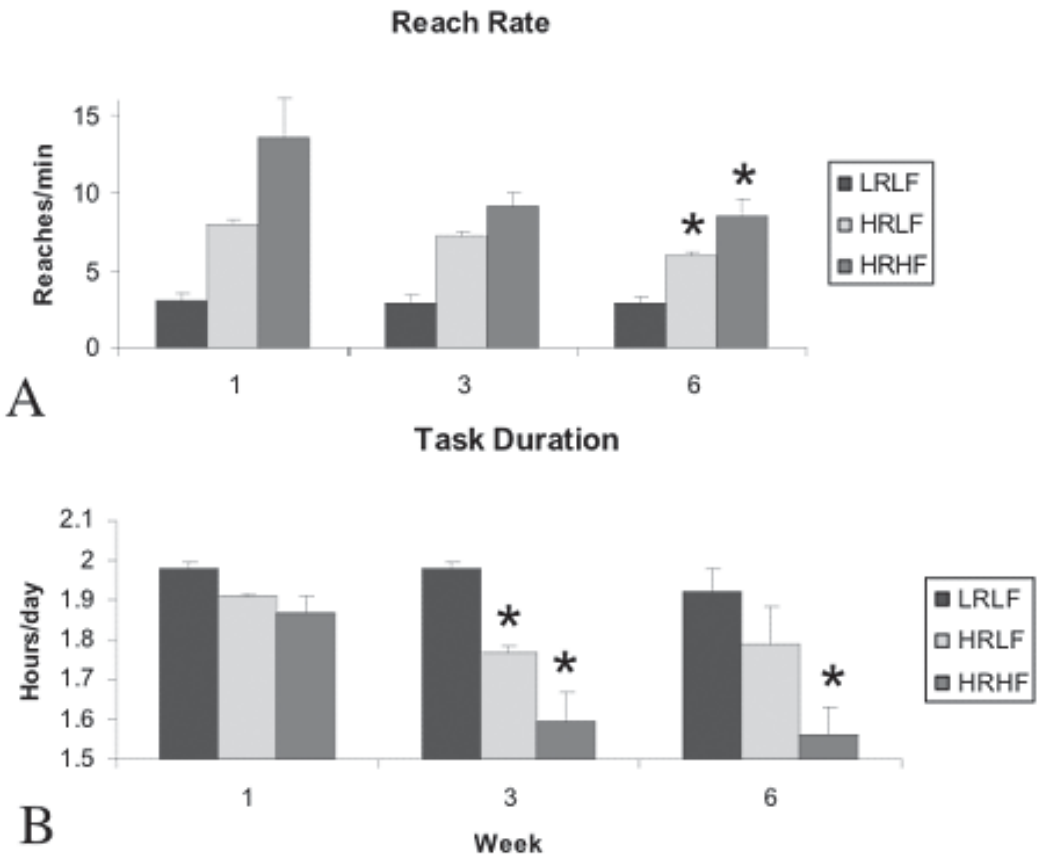


Figure 2. (A) Reach rate (+SEM). **(B)** Task duration (+SEM). *p < 0.05 compared to week 1.

Reduction in reach rate and task duration in the HRHF group was countered by the increased number of submovements within each reach, thereby maintaining risk exposure at a relatively high level of repetition. Such disordered movement patterns may further increase risk for repetitive motion disorders, and may also provide an outwardly observable sign of underlying tissue pathophysiology.

Acknowledgements

This work was supported by CDC-NIOSH grant to M.F.B. (OH 03970 Barbe) and NIH-NIAMS to A.E.B. (AR051212).

References

1. Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J Orthop Res* 2003 21:167–176.
2. Barr AE, Barbe MF. Inflammation reduces physiological tissue tolerance in the development of work-related musculoskeletal disorders. *J Electromyo Kines* 2004, 14:77–85.
3. Clark BD, Al-Shatti TA, Barr AE, Amin M, Barbe MF. Performance of a High-repetition, high-force task induces carpal tunnel syndrome in rats. *J Orthop Sports Phys Ther,* 2004, 34(5):244–254.
4. Clark BD, Barr AE, Safadi FF, Beitman L, Al-Shatti T, Barbe MF. Median nerve trauma in a rat model of work-related musculoskeletal disorder. *J Neurotrauma,* 2003, 20(7):681–695.

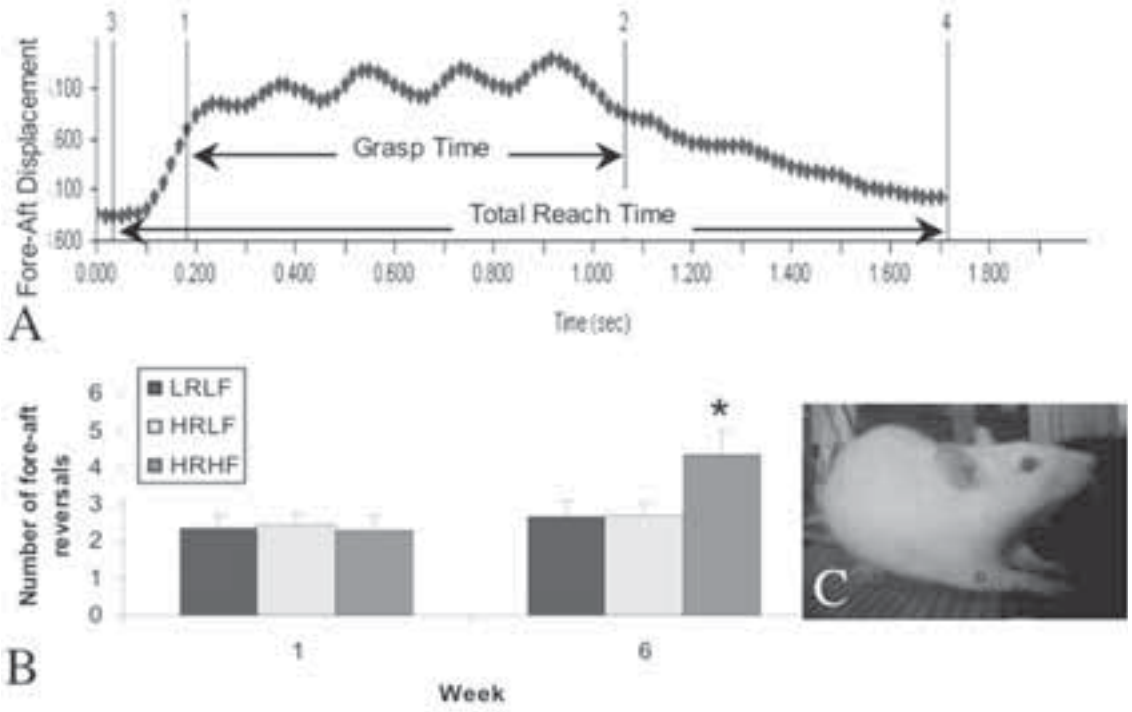


Figure 3. (A) Fore-aft displacement of digitized point depicted in panel A. Vertical lines numbered 3 and 4 indicate the beginning and end of an individual reach, respectively. Line 1 indicates the moment the forepaw exits the opening at the beginning of the grasp phase and 2 indicates the moment it reenters the opening at the end of the grasp phase. Movement reversals are counted as extra oscillations in the curve (4, in this case). Total reach time and grasp time are indicated. **(B)** The number of forelimb movement reversals as defined in Figure 6 during the grasp phase of the reach (+SEM). *p < 0.05 compared to week 1. **(C)** Single frame of video showing location of digitized landmark (circle) on the reach limb of an animal trained to perform the reaching task. The animal is positioned with the snout in the opening in the first frame of a reach sequence, just before the reach paw is lifted toward the opening.

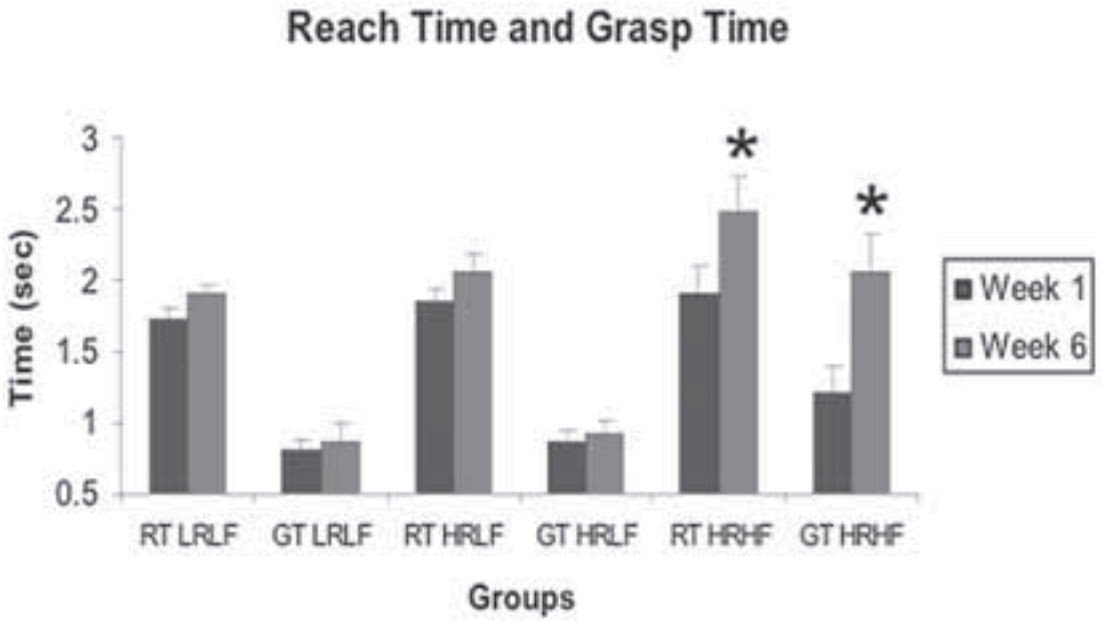


Figure 4. Total reach time and grasp time (+SEM) comparing weeks 1 and 6 in the LRNF, HRNF and HRHF groups. *p < 0.05 compared to week 1.

Basic Science Research

Characterization and Function of Osteoactivin in Osteoblasts

Samir M. Abdelmagid,[1] Mary F. Barbe,[1, 2] Mario C. Rico,[1] Israel Arango-Hisijara,[1] Abdel-Hafez Selim,[1] Michael G. Anderson,[3] Simon W. John,[4] Thomas A. Owen,[1] Steven N. Popoff,[1] Fayez F. Safadi[1]

[1]*Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA,*
[2]*Department of Physical Therapy, Temple University, Philadelphia, PA,*
[3]*Department of Molecular Physiology and Biophysics, University of Iowa, Iowa, IW.*
[4]*Jackson Laboratories, Bar Harbor, MN*

Abstract

Osteoactivin (OA) is a novel glycoprotein that is highly expressed during osteoblast differentiation. Using Western blot analysis, our data showed that the OA protein has two isoforms, one is transmembranous and the other is secreted into the conditioned medium of primary osteoblasts cultures. Fractionation of osteoblast cell compartments showed that the mature, glycosylated OA isoform of 115 kDa is found in the membranous fraction. Both OA isoforms (secreted and transmembrane) are found in the cytoplasmic fraction of osteoblasts. Overexpression of EGFP-tagged OA in osteoblasts showed that OA protein accumulates into vesicles for transportation to the cell membrane. We examined OA protein production in primary osteoblast cultures and found that OA is maximally expressed during the third week of culture (last stage of osteoblast differentiation). Glycosylation studies showed that OA isoform of 115 kDa is highly glycosylated. We also showed that retinoic acid (RA) stimulates the mannosylation of OA protein. In contrast, tunicamycin (TM) strongly inhibited N-glycans incorporation into OA protein. The functional role of the secreted OA isoform was revealed when cultures treated with OA antibody showed decreased osteoblast differentiation compared to untreated control cultures. Gain-of-function in osteoblasts using the pBABE viral system showed that OA overexpression in osteoblast stimulated their differentiation and function. The availability of a naturally occurring mouse mutant of OA with a truncated protein provided further evidence that OA is an important factor for terminal osteoblast differentiation and mineralization. Using bone marrow stromal cells derived from OA mutant and wild-type mice and testing their ability to differentiate into osteoblasts showed that differentiation of OA mutant osteoblasts was significantly reduced compared to wild-type osteoblasts. Collectively, our data suggest that OA acts as a positive regulator of osteoblastogenesis in vitro.

Introduction

The initial identification of osteoactivin (OA) emerged from studies using an animal model of osteopetrosis.[1] Other groups have also identified the same protein in different species, and have designated different names, such as glycoprotein nmb (gpnmb) in melanoma cell lines,[2–6] and melanocytes,[7, 8] dendritic cell heparan sulfate proteoglycan integrin dependent ligand (DC-HIL) in dendritic[9, 10] and human hematopoietic growth factor inducible neurokinin (HGFIN) in tumor cells.[11] OA has high homology to Pmel-17, a melanosomal protein that is well characterized in melanocytes and plays a role in melanin fibril formation.[12–19] These similarities suggest that OA may belong to the same gene family as Pmel-17. The OA protein is a type I transmembrane protein with two isoforms, one is membranous and the other is secreted.[1, 9, 10, 20–23]

Recent reports demonstrated the cellular functions of OA showing that OA has the ability to regulate cell proliferation, adhesion, differentiation and synthesis of extracellular matrix (ECM) proteins in various cell types, in normal and pathological conditions.[1–3, 6–10, 20–31] Some animal models have been generated to demonstrate OA function in different tissues. OA transgenic (Tg) mice that overexpress OA under the CMV promoter showed increased muscle mass and enhanced expression of MMP-3 and MMP-9 in fibroblasts from denervated skeletal muscle model.[30] Another study in transgenic rats that overexpress OA in liver cells showed that OA attenuates the development of hepatic fibrosis.[29] The most exciting animal model is the natural mutation of OA gene in the mouse causing a premature stop codon that results in the generation of a truncated OA protein.[7, 8, 32, 33] These mice develop an eye phenotype with iris pigmentary dispersion and iris stromal atrophy. They also have increased macrophage function.[34] With the development of these animal models, there has been an increased focus on OA and its effects on different cellular and pathological processes. However, there is still a great deal of work that needs to be done to determine the functions of osteoactivin and its mechanism(s) of action.

In bone and using the *osteopetrotic (op)* rat as a model to examine differential gene expression in bone from normal and osteopetrotic rats, we discovered that OA mRNA expression was significantly increased in osteopetrotic bone.[1] Our group was the first to report the expression and function of OA in bone. Previously, we demonstrated that OA mRNA and protein are expressed by human and rodent osteoblasts and its expression exhibited a temporal pattern during osteoblast differentiation reaching highest levels during the later stages of matrix maturation and mineralization.[1, 20, 22, 23]

OA and Pmel-17 are heavily glycosylated proteins with O- and N-linked glycans.[20, 35] Glycosylation of proteins plays a crucial role in cell differentiation and function.[36] Understanding the mechanism mediating OA protein processing and glycosylation will shed light on its mechanism(s) of action. While processing and regulation of Pmel-17 in melanocytes has been well described by different laboratories.[35, 37, 38] There are no reports that characterize OA processing and secretion by osteoblasts. Here we provide evidence that OA is synthesized and secreted by osteoblast during differentiation. There are two isoforms of OA one is transmembrane and the other is secreted and the secreted isoform is heavily glycosylated that plays a role in osteoblast differentiation and function. We also present evidence that OA glycosylation is regulated by retinoic acid and tunicamycin. These data will help to elucidate the mechanism/s of action of OA protein in osteoblast differentiation and function.

Materials and Methods

Bioinformatic Analysis

The amino acid sequence for OA protein was obtained in FASTA format from SWISSPORT database (http://us.expasy.org/sprot/). Signal peptide sequence of OA protein was analyzed by SignalP server. Trans-membrane hydrophobic sequence of OA protein was analyzed by TransMemb server. O-glycosylation sites on OA protein were analyzed by net OGlyc server. All servers were provided by the Center for Biological Sequence Analysis database.

Osteoactivin Mutant Mice

Mice mutant for osteoactivin (DBA/2J) were purchased from Jackson laboratory. Wild type mice (DBA) were purchased from Teconic laboratory. Mutant and wild type mice were bred and maintained at Temple University School of Medicine Central Animal Barrier Facility according to the guidelines of the Institutional Animal Care and Use Committee (IACUC).

Generation of OA Antibody

Anti-OA antibody (OA-551) was raised against the peptide sequence of amino acids 551 to 568 and anti-OA antibody (OA-35) was raised against the peptide sequence of amino acids 35.

Both peptides were selected because of its potential antigenicity and were screened against the protein database to ensure lack of homology with other sequences. Chickens were immunized, and the precipitated crude IgY was purified by affinity chromatography on Sepharose 4B derivatised with the immunizing peptide (Cambridge Research Biochemicals, Stockton-Tees, UK).

Primary Osteoblast and Bone Marrow Cultures

Primary osteoblasts were isolated and cultured as described previously.[23] Briefly, Neonatal rat pups were decapitated; the calvaria were harvested and placed into a Petri dish with 20 ml isolation media. The calveria were cut into smaller pieces and placed into a siliconized flask with digestion media. Cells were digested three times in a medium containing collagenase-P as described previously.[1, 23] The supernatants were collected from all 3 digestions and centrifuged. The cell pellets were re-solubilised into 5 ml of fresh washing media. Cells were then plated in a 100 mm Petri dish at a density of 500,000 cells with 10 ml initial plating medium and incubated at 37°C with 5% CO_2. Differentiating factors (10 mM β glycerol phosphate + 50 μg/ml ascorbic acid) were added on day 3 and every time culture media was changed.

For osteoblast differentiation using bone marrow stormal cells, bone marrow from 8 weeks old osteoactivin mutant and wild type mice was flushed using femurs and tibea. Bone marrow cells were harvested, counted and plated overnight. Adherent cells were cultured for different time points in osteogenic media containing αMEM supplemented with 10% FBS, 10^{-8}M dexamethasone, 70ng/ml L-ascorbic acid and 8mM β-glycerol phosphate.

Generation of OA-pBABE Viral Vector Stable MC3T3-E1 Cell Line

A pBabe viral vector containing OA cDNA was provided to us from Dr. Jeremy Rich at Duke University. For the generation of OA-pBabe viral vector, please refer to reference 21. For propagating the OA-pBabe viral vector, OA-pBabe retroviral vector or control pBabe (empty vector) were co-transfected with a PCL10-A1 packaging vector, into subconfluent 293 HEK (human embryonic kidney) cell line using the calcium chloride method.[21] Virus-containing supernatant was harvested after 48 hours and was used to infect MC3T3-E1 murine osteoblastlike cell line. For generation of stable virus producing cell line, infected MC3T3-E1 cells were splitted and selected by replacing the medium with Bleomycin antibiotic (500 μg/ml) containing medium. The medium was changed after 72 hours with continued selection. After 5 days, the antibiotic resistant colonies were selected and used for further cultures.

Co-localization of OA and Endoplasmic Reticulum (ER) in Primary Osteoblasts

Primary osteoblasts were cultured in chamber slides at a density of 5000 cells/well. On the second day of culture, cells were fixed, washed and double labeled with OA using anti-OA antibody and 3,3'-dihexyloxacarbocyanine iodide

($DiOC_6(3)$, a green-fluorescent, lipophilic dye (Invitrogen), followed by anti-chicken-Cy3-conjugated secondary antibody. Cells were washed with PBS and visualized using E600 Nikon fluorescent microscope.

Transfection of EGFP-tagged-OA and Cellular Labeling

Primary osteoblasts were cultured in 2-chamber slides at a density of 5000 cells/well. On the second day of culture, cells were transfected with either GFP empty vector or GFP-tagged CMV-OA construct using Lipofectamine 2000 (Invitrogen, Carlsbad, CA). On day 3, cultured cells were fixed with 4% paraformaldehyde in 1x PBS for 15 minutes at R.T. Cells were washed 3 times (10 minutes each) with 1x PBS, and cover slipped using 80% glycerol in PBS. Slides were then examined using confocal laser scanning microscope. For co-localization of GFP-OA protein in the plasma membrane, cells were transfected above and the cell membrane was labeled using lipophilic tracer DiD (Molecular Probes, Eugene, OR) in a 5 μM working concentration.

Cells were incubated with DiD dye for 5 minutes at 37°C and then for an additional 15 minutes at 4°C, then washed with 1x PBS. Slides were cover slipped using 80% glycerol in PBS. Slides were examined using confocal laser scanning microscope.

RNA Isolation

RNA was isolated as described previously.[23] Briefly, cell cultures were harvested then homogenized in Trizol, separated into organic and aqueous layer by chloroform, and RNA was recovered from the aqueous layer by isopropyl alcohol precipitation. Pellets were washed with 70% ethanol and concentration of RNA was calculated using spectrophotometer. For the evaluation of RNA integrity, 1 μg total RNA was run on formaldehyde gel and stained with Ethedium bromide.

RT and Quantitative (q)PCR Analysis

RT-PCR analysis for OA and G3PDH was performed as previously.[23] Briefly, 2 μg of total RNA were reverse transcribed to cDNA. Two microliters of the generated cDNA was amplified in 50 μl of qPCR reaction mixture. The primers for rat OA were sense; 5'-CCAGAAGAATGACCG-GAACTCG-3' and antisense 5'-CAGGCTTCCGTGG-TAGTGG-3' and the primers for rat G3PDH were sense; 5'-ACCACAGTCCATGCCATCAC-3' and antisense 5'-TCCACCACCCTGTTGCTGTA-3'. Q-PCR was performed on ABI PRISM 7700 using the SYBER Green method. OA values were quantified using the equation ($-\Delta\Delta C_T$); C_T = Threshold cycle.

Fractionation of Cellular Compartments

Different cellular compartments were fractionated using membrane protein extraction reagent kit (Pierce, Rockford, IL). Briefly, cells were harvested from a 3 wks old cultures and centrifuged at 850 xg for 2 minutes; the cell pellet was then washed in PBS. Next, 150 μl of reagent A was added to the cell pellet with pipetting up and down to ensure a homogenous cell suspension. The mixture was then incubated for 10 minutes at R.T. with occasional vortexing. Next, 450 μl of diluted reagent C (diluted according to manufacture's protocol) was added to the cell lysate and left on ice for 30 minutes with vortexing every 5 minutes. The cell lysate was centrifuged at 10,000 xg for 3 minutes at 4°C. The supernatant was transferred to a new tube and incubated for 10 minutes at 37°C to separate out the membrane protein fraction.

For isolation of the nuclear and cytoplasmic fraction using Reagents Kit (Pierce, Rockford, IL), 20 μl of packed cell volume was isolated by centrifugation at 500 xg for 2 minutes. The supernatant was discarded, leaving the cell pellet as dry as possible. Two hundreds μl of ice-cold CER I was added to the cell pellet and vortexed vigorously on the highest setting for 15 seconds to fully re-suspend the cell pellet. The cell pellet was then incubated on ice for 10 minutes. Eleven μl of ice-cold CER II was added to the tube and vortexed for 5 seconds before incubation on ice for 1 minute. The tube was centrifuged at 16,000 xg for 5 minutes and the supernatant (cytoplasmic extract) fraction was transferred to a new tube on ice. The insoluble pellet fraction was re-suspended in 100 μl of ice-cold NER. The tube was incubated on ice and vortexed for every 10 minutes, for a total of 40 minutes. The tube was centrifuged at 16,000 xg for 10 minutes before transferring the supernatant (nuclear extract) fraction to a new tube on ice.

Metabolic Labeling and Pulse Chase of OA in Osteoblasts

Primary osteoblasts were cultured in 6-well plates at a density of 50,000 cells/well for 3 days. Cells were washed twice with PBS and incubated with methionine free EMEM medium containing 10% FBS for 1 hour. ^{35}S methionine (Amersham Biosciences,) was added to a final activity of 150 μCi/ml. Cells were incubated for 1 hour then washed twice with chase medium (EMEM with 10% FBS, 2 mM methionine) and incubated in the chase medium for 0, 5, 10, 30, 60 and 120 minutes. After the chase, cells were washed twice with ice cold PBS and lysed in RIPA buffer. OA protein was immunoprecipitated and electrophoresed on 10% SDS-PAGE gel. The gel was dried in a gel dryer at 80°C for 2 hours and exposed to Eastman Kodak Co. MR x-ray film for at least 24 hours.

Treatment with Retinoic Acid and Tunicamycin

Primary osteoblasts were cultured in 6-well plates at a density of 50,000 cells/well, rinsed with Hank's medium, and treated with 10^{-6} M all-trans-retinoic acid (RA) (Sigma-Aldrich, St. Louis, MO) in the presence or absence of 1 μg/ml of tunicamycin (TM) (A.G.Scientific, San Deigo, CA) or TM alone for 24 hours. Untreated cultures served as controls. Cultures were terminated on day 14 and 21, depending on the experimental protocol. OA protein expression was then assessed using Western blot analysis.

Incorporation of Radiolabeled Sugar Molecules into OA Protein

Primary osteoblasts were cultured in 6-well plates at a density of 50,000 cells/well for 5 days. Cells were treated with 10^{-6} M of RA in the presence or absence of 1 μg/ml of TM. Untreated cultures were served as controls. After 24 hours, cells were washed with PBS and incubated with serum free medium containing ^{14}C mannose (1 μCi/ml) for 12 hours at 37°C. Incorporation was determined by cooling the plates to 0°C, removing the medium, and washing twice with cold PBS. OA protein was immunoprecipitated and radioactivity incorporated was counted in a liquid scintillation counter. For deglycosylation experiments, the OA immunoprecipitated beads were treated with PNGase for 3 hours at 37°C and the release of ^{14}C mannose into the supernatant was determined in a liquid scintillation counter.

Protein Isolation

Total protein was isolated as described previously.[23] Briefly, osteoblast cultures terminated at different time points, based on the experimental strategies, were trypsinized with 0.25% trypsin and centrifuged for 10 minutes. Cells were lysed in RIPA buffer and protein concentration was measured using bicinchoninic acid (BCA) protein assay.

Protein de-glycosylation

Twenty μg of total protein isolated from 7, 14 and 21 day primary osteoblast cultures was treated with enzymatic carborelease kit (QA-bio, Rockford, IL) to free N- and O-linked sugar groups. Total protein sample was mixed with 10 μl reaction buffer in 35 μl distilled water. Denaturation buffer (2.5 μl) was added to the protein sample and mixed gently, boiled at 100°C for 5 minutes and chilled on ice. Two μl of each enzyme (PNGase F, Sialidase, b-galactosidase, Glucosaminidase, and O-Glycosidase) was added to the protein sample and incubated for 3 hours in water bath at 37°C.

Immunoprecipitation

Fifty μg of total proteins isolated from primary osteoblast cultures were immunoprecipitated using immunoprecipitation kit (Roche Diagnostic, Corp., IN) to isolate OA proteins. Twenty five μg of agarose A/G beads were added to each protein sample and incubated overnight at 4°C. Beads were sedimented by centrifugation at 12000 xg for 20 seconds then the supernatant was transferred to fresh tube fro immunoprecipitation according to the manufacturer's protocol. Twenty five μl of gel loading buffer was added to each sample; proteins were denatured by heating to 100°C for 5 minutes and analyzed by SDS gel electrophoresis.

Western Blot Analysis

Protein was isolated and subjected to SDS-PAGE as described previously.[23] Briefly, proteins isolated from primary cultures were mixed with denature buffer and heated at 100°C for 5 minutes. Samples were subjected to 10% SDS-PAGE in 1x TGS for one hour. Gel was then transferred to PVDF membrane by semi-dry transfer apparatus (Biorad, Hercules, CA) for one hour. The blot was incubated in blocking buffer (0.5% BSA and skim milk in PBS) for one hour then primary antibody was added to blocking buffer overnight at 4°C. The blot was washed 5 times in 1X TTBS 5 minutes each then incubated with HRP-conjugated secondary antibody, for one hour. The blot was washed again in TTBS for 5 times and the signals were developed using ECL kit and detected on XL-exposure films.

Staining of Sugar Molecules Within OA Protein

For the evaluation of sugar molecules incorporated within OA protein, immunoprecipitated OA protein was subjected to SDS PAGE. Gel was then stained using Pro-Q Emerald Glycoprotein Gel Stain kit (Molecular Probes, Eugene, OR). The gel was incubated in 100 ml of fix solution (50% methanol and 5% acetic acid in dH_2O) at R.T. for 45 minutes to wash out SDS. The gel was washed in 100 ml of wash solution (3% glacial acetic acid in dH_2O) with gentle agitation at R.T. for 20 minutes. The gel was then incubated in 25 ml of oxidizing solution (3% acetic acid and 1% periodic acid) with gentle agitation for 30 minutes. The gel was washed again in 100 ml of wash solution for 20 minutes then incubated with 25 ml of the pro-Q emerald solution diluted 1:50 in staining buffer with gentle agitation for 90 minutes. The signals were detected via Alpha Imager apparatus with ultraviolet light.

Alkaline Phosphatase (ALP) Activity Measurement

ALP activity was measured as described previously.[20] Briefly, cell layers of 14 day culture were treated with TZM buffer for 30 minutes. Aliquots were mixed with p-nitrophenol substrate in 10x methylating triazene temozolomide (TZM) buffer. ALP activity results were normalized to the total protein content.

Alkaline Phosphatase Histochemistry

Primary cultures were stained for Alkaline Phosphatase (ALP) as described previously.[23] Briefly, ALP staining was performed on cultures at day 14 using ALP staining kit (Sigma). Cells were counterstained with hematoxylin and allowed to air dry before evaluating with inverted microscope.

Osteocalcin Measurement

Osteocalcin concentration was measured using sandwich ELISA kits as described previously.[20] Briefly, cell layers and conditioned media of 21 day cultures and standards were incubated in ELISA plates. After incubation with peroxidase-conjugated secondary antibody for 1 hour, TMB substrate was added for 30 minutes and absorbance was read at 450 nm using ELISA reader. Osteocalcin values (ng/ml) were normalized to the total protein content.

Calcium Measurement

Calcium concentration was determined as described previously.[20] Briefly, cell layers of 21 day cultures were lyzed with 0.5 N HCl. Aliquots were mixed with calcium binding reagent and read at 575 nm using spectrophotometer. Calcium values were calculated from the standard curve.

von Kossa Staining of Mineralized Nodules

Primary cultures were stained for mineralization as described previously.[23] Briefly, von Kossa staining was used to stain osteoblast mineralized nodules on day 21. Cells were counterstained with fast green then rinsed with dH_2O and allowed to air dry. Cells were then evaluated with TE300 inverted microscope.

MTT-cell Viability Assay

Cell viability assay was performed as described previously.[23] Briefly, MTT substrate was added on cultured osteoblasts in 24-well plate (100 μl/well) and incubated for 4 hours. Solubilizer was added (250 μl/well) overnight. Samples were read in 96-well plate on ELISA reader at 570 nm.

Image Analysis

Pictures were analyzed as described previously.[23] Briefly, pictures were obtained from different fields and images were analyzed using BIOQUANT 98 software. The size of the nodules was computed using the area measurement option of the program. Nodule mineralization was computed using the videocount area array option. Percent area fractions of alkaline phosphatase or von Kossa staining were calculated by dividing the videocount area containing pixels at or above the threshold by the videocount area of total number of pixels in the entire field, and multiplying by 100. This determination was made at 4 different locations per well, 4 wells per group.

Statistical Analysis

For multiple group comparison, analysis of variance (ANOVA) was used to evaluate the effect of one variable on multiple independent groups. In the event of a significant group effect, individual pairs of means were compared using Newman-Keuls post hoc test. A p value ≤0.05 was considered statistically significant. Group means + standard error of the mean (SEM) were plotted in graphs.

Results

Characterization of OA Protein Sequence and Its Homology to Different Family Members

Osteoactivin (OA), also known as glycoprotein nmb (gpnmb), is a type I transmembrane glycoprotein that consists of at least three different domains; an N-terminal domain with a signal peptide, a polycystic kidney disease domain (PKD) domain, and a transmembrane domain (TRM) (Figure 1A). The protein also contains an Arg-Gly-Asp (RGD) cell attachment domain, for integrin-mediated cell attachment and spreading.[39] As shown in Figure 1B, the rat OA protein shares 88% homology with mouse osteoactivin, also known as dendritic cell heparan sulfate proteoglycan integrin dependent ligand (DC-HIL); 77% homology with human hematopoietic growth factor inducible neurokinin (HGFIN) and human nmb; and 65% and 60% homology, with quail neuroretina protein (QNR71) and human Pmel-17/gP100 melanocyte specific protein, respectively. All of these proteins contain all of the domains described for OA (Figure 1A). OA also contains a sorting signal sequence in close proximity to the C-terminal domain. This signal sequence contains dileucine amino acids with a consensus sequence of EXXPLL, and is located 7 amino acids away from the C-terminal end of the protein. There is another signal sequence located 29 amino acids upstream of the sorting sequence, and this sequence has been suggested to play a role in protein sorting through the rough endoplasmic reticulum and the Golgi complex.[40] This signal sequence contains one tyrosine with a consensus sequence of YXPI (Figure 1C).

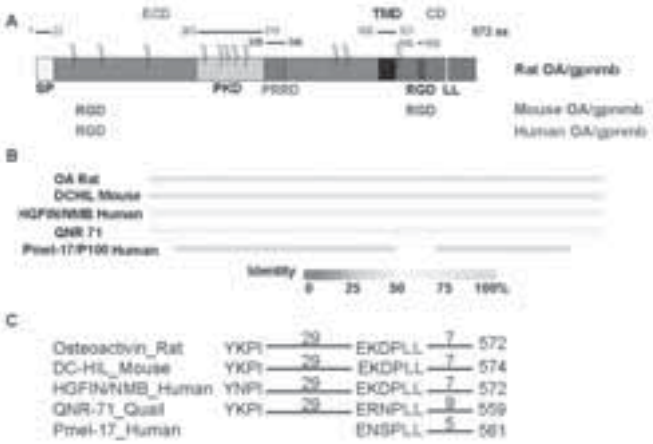


Figure 1. Primary structure of osteoactivin protein and its homology to other family members. (A) Schematic diagram of the primary structure of osteoactivin drawn to scale. The protein consists of three main parts, the extracellular domain (ECD), the transmembrane domain (TMD) and the cytoplasmic domain (CD). Numbers correspond to amino acid position. SP, signal peptide; PKD, polycystic kidney disease domain; PRRD, proline rich repeat domain; TMD, transmembrane domain; LL, dileucine sorting sequence; RGD, integrin binding domain. Note the presence of an RGD domain in the C-terminus of rat OA, while mouse OA has two RGD domains, one in the N-terminus and the other in the C-terminus, and human OA has only one RGD domain in the N-terminus. **(B)** High homology of rat OA to mouse DC-HIL, human HGFIN, human NMB, quail QNR-71 and human PMEL17. Percent of homology is represented by different colors in the identity bar. DC-HIL, denderitic cell heparan sulfate proteoglycan integrin dependent ligand; HGFIN, hematopoietic growth factor inducible neurokinin; NMB, non-melanoma B; QNR71, quail neuroretina; Pmel-17/gP100, melanocyte specific protein. **(C)** Sequence alignment of the cytoplasmic domain of integral membrane proteins targeted to vacuoles or melanosomes. Red labeled amino acids are the di-leucine- and tyrosine-based sorting signals in the indicated proteins. The indicated numbers reflect the number of amino acids between two signals.

Bioinformatic analysis of the amino acid sequence of the OA protein showed that the first 22 amino acids constitute a signal peptide.[1] Collectively, these data suggest that the OA protein is highly glycosylated and has two isoforms, secreted and transmembrane.

OA Expression During Osteoblast Differentiation in Culture

Expression of the endogenous OA protein isoforms was compared at the 3 stages of osteoblast development in culture (cell proliferation between days 3–7, matrix maturation between days 7–14, and matrix mineralization between days 14–21). Western blot analysis showed that OA was detected as two distinctly different molecular weight protein bands, one reflecting the native, immature protein at 65 kDa and the other reflecting a post-translationally modified isoform of the protein at 115 kDa (Figure 2A). The temporal pattern of OA expression during osteoblast differentiation demonstrated that both OA isoforms are expressed at all stages with increasing levels of expression as the osteoblasts terminally differentiate. Densitometric analysis of OA expression showed that both the mature and native isoforms increased by ~250%, in the third week of primary culture compared to the first week (Figure 2A). These data suggest an important role for the mature OA isoform in regulating the terminal differentiation of osteoblasts in culture.

We next examined the expression pattern of OA in different cellular compartments. Here we collected total primary osteoblast cell lysates that had been cultured for 3 weeks before termination. Fractionation of total cell lysates followed by Western blot analysis showed that the mature and native/immature OA isoforms were absent in the nuclear fraction, thereby confirming that OA protein has no nuclear localization sequence (Figure 2B). The mature OA isoform was highly expressed in the cytoplasmic fraction compared to the native/immature OA isoform (Figure 2B). The mature OA isoform was expressed in the membranous fraction while the native/immature OA isoform was absent from that fraction (Figure 2B). Next, we examined whether the mature isoform of OA is secreted by osteoblasts into the conditioned medium. Primary osteoblasts were cultured for three weeks, and 24 hours prior to harvesting; the cells were switched to serum-free medium. This conditioned medium and the corresponding cell layers were then analyzed for OA expression. Western blot analysis showed that the mature OA isoform of 115 kDa was highly expressed in the cell lysates and secreted into the conditioned medium (Figure 2C). Although the native/immature OA isoform of 65 kDa showed lower levels of expression in the osteoblast cell lysate, it was absent from the conditioned medium. These data suggest that the mature OA isoform is secreted; however, the native OA isoform is restricted to the cytoplasm, probably within different cellular compartments (see below).

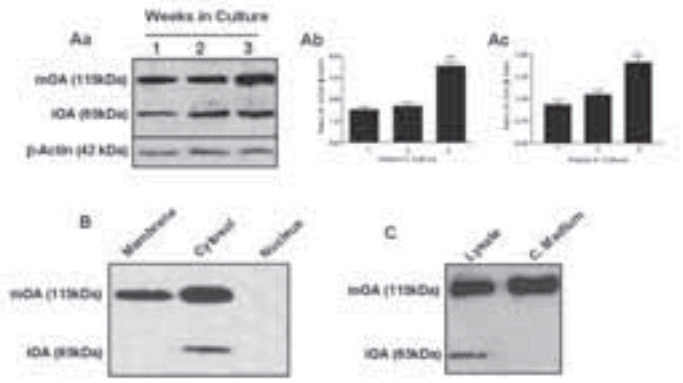


Figure 2. Osteoactivin expression during osteoblast differentiation. Primary rat osteoblasts were cultured and terminated after 1, 2 or 3 weeks of culture. (Aa) Immunoblot showed that the glycosylated, mature OA isoform (115 kDa) was expressed at higher levels than the immature OA isoform (65 kDa) after 3 weeks in culture. β actin was used as a loading control. (Ab and Ac) Densitometry of 3 immunoblots quantifying percent of the mature/glycosylated (115 kDa) (Ab), or the immature (65 kDa) isoforms (Ac) of OA protein as a ratio of β actin. Bars represent mean + SEM. *$p < 0.05$ when compared to first week of culture. (B and C) Localization of OA isoforms in osteoblasts. Primary osteoblasts were cultured for 3 weeks and cell lysates were fractionated. (B) Immunoblot showed that the cytoplasmic compartment (cytosol) contains both the glycosylated/mature (mOA) isoform of 115 kDa and the native (immature) (iOA) isoform of 65kDa. The membranous fraction (membrane) showed expression of the only glycosylated/mature OA isoform. There was no expression of either OA isoform in the nuclear fraction (nucleus). (C) Primary osteoblasts were cultured for 3 weeks, and then switched to serum free medium for 24 hours prior termination. Immunoblot showed that the mature highly glycosylated mOA isoform of 115 kDa is secreted into the conditioned medium (C. Medium). The osteoblast cell lysate contains both glycosylated/mature (mOA) and native/immature (iOA) isoforms of OA protein.

Localization and Trafficking of OA in Osteoblasts

From the data provided above, it is clear that OA is expressed and secreted by osteoblasts. In order to examine intracellular localization of OA within osteoblast cellular compartments, we performed immunofluorescent analysis. Primary osteoblasts were cultured for three days, then fixed and stained with anti-OA antibody (Ab-551) (red signal). In order to examine whether OA is co-localized with secretory organelles, a rough endoplasmic reticulum (rER) marker was used (green signal). OA was found to be co-localized with the rER marker, suggesting that the protein is processed through the secretory pathway (Figure 3A–C). These data are consistent with previous data on Pmel-17, another family member with similar pattern of localization.[35] To further visually confirm the intracellular localization of OA in osteoblasts, we transfected primary osteoblasts with a vector expressing an green fluorescent protein (GFP)-tagged-OA fusion protein under the control of the cytomegalovirus (CMV) promoter. Cells transfected with a GFP-only vector

served as non-specific controls (CMV-EV) (Figure 3D-G). At 24 hours following transfection, OA was localized in a punctuated, vesicle-like pattern in the peri-nuclear cytoplasm (Figure 3E). At 48 hours following transfection, the OA expression was localized towards the periphery of the osteoblasts (Figure 3G). In order to examine whether OA is localized to the plasma membrane, primary osteoblasts transfected with GFP-OA were labeled with DiD dye, a lipophilic membrane stain that is weakly fluorescent until incorporated into the plasma membrane.[41] Confocal microscopy revealed co-localization of OA signal with the plasma membrane signal (Figure 3H–J). Collectively, these data suggest that in osteoblasts, OA is synthesized and processed through the secretory pathway and anchored to the plasma membrane.

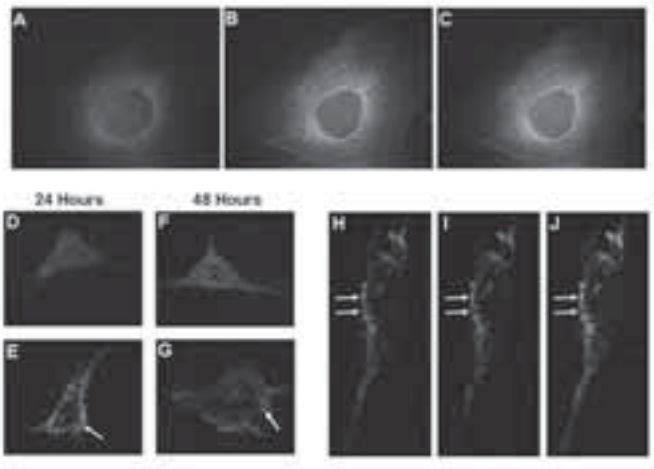


Figure 3. Localization of osteoactivin into osteoblasts. (A–C) Immunofluorescent localization of OA in osteoblasts. Primary rat osteoblasts were cultured for two days, fixed and dual stained with anti-OA antibody (A, red signal), or rough ER (rER) marker (B, green signal) and visualized using epifluorescent microscopy. OA is localized to the peri-nuclear area specifically in the rough ER as demonstrated by co-localization between OA and rER markers (C, yellow signal). **(D–G)** Transient overexpression/localization of OA in osteoblasts. Primary osteoblasts were transfected with CMV-GFP (D and F) or CMV-GFP-OA (E and G) constructs. Cells were visualized at 24 (D and E) and 48 (F and G) hours using confocal laser scanning microscopy (Magnification = 1500x). Note that CMV-GFP showed diffuse signal throughout the cell at both time points examined, while cells expressing CMVGFP-OA showed OA in vesicular-like structures localized to the perinuclear cytoplasm at 24 hours post-transfection (E) and toward the cell periphery at 48 hours pos-transfection (G). **(H–J)** Immunofluorescent dual staining in primary osteoblasts labeled with anti-OA antibody (H, green signal) and DiD plasma membrane dye (red signal). Photomicrographs were captured using confocal laser scanning microscope. Note the co-localization of OA signal with member dye (J, yellow signal).

Detection of OA Isoforms Intracellular with Pulse Chase

To track the intracellular processing of the OA protein in osteoblasts, we used a metabolic labeling approach. Primary osteoblasts were cultured for 3 days, and then incubated with EMEM medium containing [^{35}S]-methionine for 1 hour. Following pulse labeling, cells were then incubated with chase medium containing unlabeled L-methionine and terminated at different time points (0-60 minutes). Cell lysates were then immunoprecipitated using the OA-551 antibody (Figure 4A). The immature (iOA) isoform of 65 kDa appeared after 5 minutes and reached maximum expression after 30 minutes. The mature (mOA) isoform of 115 kDa appeared after 10 minutes (Figure 4A). After 60 minutes of chase, both isoforms of OA were reduced in intensity, with only the immature isoform being detectable (Figure 4A). Conditioned medium collected following [^{35}S]-methionine labeling and after 60 minutes of chase, showed that the mOA isoform is secreted and detectable after 60 minutes (Figure 4A). These data suggest that the half-life of the OA protein is short and although some of the mature protein is secreted, is the short half-life could be due to either degradation or recycling of the OA protein, possibilities which warrant further investigation.

From the above data, we propose that the mOA isoform is post-translationally modified. To further investigate this possibility, we immunoprecipitated OA protein from primary osteoblasts cultures isolated at 1-, 2- and 3-week. A gel on which cytoplasmic proteins from primary osteoblasts were separated was stained with the Pro-Q Emerald stain that detects glycoproteins by reacting with periodate-oxidized carbohydrate groups[42] (Figure 4B). Only the mOA isoform was detected, suggesting that this isoform is heavily glycosylated. Furthermore, its expression is increased as the osteoblasts differentiate, reaching maximum levels at 3 weeks in culture as described previously.[1, 23]

The above information clearly suggests that the mature, high molecular weight isoform of OA is glycosylated as part of its post-translation modification. Bioinformatic analysis of the OA protein sequence showed that OA is potentially glycosylated by O-linked (supplemental Figure 1C) and N-linked glycans.[20] To investigate this possibility, total protein isolated from three week primary osteoblast cultures was first treated with PNGase-F, an enzyme that cleaves all asparagine-linked complexes, hybrid or high mannose oligosaccharides. The treatment reduced the MW of the mOA isoform by approximately 20 kDa to a form migrating at 95 kDa. To analyze the O-glycan modification of the OA protein, we then treated these osteoblastic proteins with a combination of different enzymes. The combination of Sialidase and O-Glycosidase were used to remove all Ser/Thr-linked (O-linked) Gal-(b1-3)-GalNAc-(a1) and all sialic acid substituted Gal-(b1-3)-GalNAc-(a1), and the addition of β-Galactosidase and Glucosaminidase were used to assist in the deglycosylation of larger O-linked structures. Our data showed that the mOA isoform was reduced by only 15 kDa to a form migrating at approximately 100 kDa. A combination of the PNGase-F and the O-glycan de-glycosylation enzymes reduced the apparent molecular weight of the mOA isoform only slightly more than either did alone, to approximately 90 kDa (Figure 4C). As expected, in all cases, the migration of the immature isoform of OA (iOA) was not

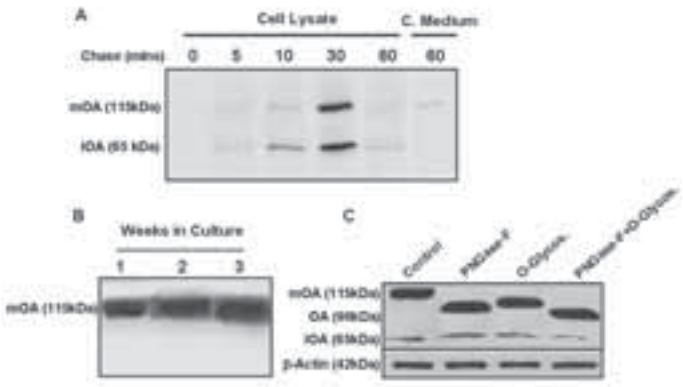


Figure 4. Processing and glycosylation of OA in osteoblasts. (A) Processing of OA protein isoforms in osteoblasts with pulse chase. Primary osteoblasts were cultured for 3 days, pulsed with 35S methionine (1μCi/ml) for 60 minutes, then chased for the time indicated in minutes. Fifty μg protein aliquots of cell lysates were immunoprecipitated with anti-OA antibody (OA 551), and immunoprecipitates were subjected to SDS-PAGE followed by autoradiography. The native/immature OA isoform of 65 kDa was observed after 5 minutes and gradually increased to maximum after 30 minutes. The upper/mature OA isoform of 115 kDa was observed after 10 minutes and reached maximum after 30 minutes. The conditioned medium (C. Medium) after 60 minutes of chased culture showed only the upper/mature OA isoform of 115 kDa was present. (B and C) Mature/secreted OA isoform is glycosylated. **(B)** Primary osteoblasts were cultured and terminated after 1, 2 and 3 weeks; 50 μg total protein from cell lysates were immunoprecipitated with OA antibody (OA-551), the immunoprecipitates were subjected to SDS-PAGE. The gel was then fixed and stained for glycoproteins with the Emerald 300 gel stain kit. The gel showed only the glycosylated OA isoform at 115 kDa. **(C)** Primary osteoblasts were cultured for 3 weeks and 20 g total protein from cell lysates were treated with enzymes to remove N-linked glycoconjugates using PNGase or O-linked glycoconjugates using O-glycosidase as described in the methods. Immunoblot showed a decrease in molecular weight (MW) of the glycosylated OA isoform to 90 kDa with PNGase treatment and to approximately 95 KDa with O-glycosidase treatment. Combined treatment of PNGase with O-glycosidase also decreased the MW of the glycosylated OA isoform to approximately 90 kDa. In all treatment conditions with the different enzymes, the MW of the native/immature OA isoform was not affected. β actin was used as a loading control.

affected. These results confirm that the OA protein is modified by a combination of N- and O- linked glycans.

Regulation of OA Glycosylation by Retinoic Acid and Tunicamycin

It has been reported that retinoic acid (RA) treatment alters the glycosylation of alkaline phosphatase in neuronal cell lines[43] and that the treatment with the antibiotic tunicamycin (TM) blocks the first step in glycoprotein synthesis, thus inhibiting the formation of N-glycans linked glycoproteins.[44] For our purpose, we were interested in examining whether RA treatment alters the nature of the mOA isoform in osteoblasts. Primary osteoblast cultures were treated with either 10^{-6} M RA, 0.25 μg/ml TM or the combination of both for 24 hours prior termination at day 14 (see below) or day 21 (data not shown). Western blots for alkaline phosphatase (ALP), a marker of differentiating osteoblasts used here as a positive control, and for OA were performed and analyzed (Figure 5A). RA treatment caused an increase in the amounts of both native (58 kDa; iALP) and glycosylated (67 kDa; mALP) isoforms of ALP, while treatment with TM caused a dramatic decrease in the glycosylated, but not the native isoform of ALP as compared to untreated controls. Treatment with both RA and TM was able to rescue the inhibitory effects of TM on ALP glycosylation (Figure 5A–C). It is interesting to note that treatment with RA increased only the glycosylated, mOA isoform, treatment with TM blocked the glycosylation of mOA. The combination of both factors rescued the glycosylation of mOA isoform similar to that observed for ALP. Unlike ALP, it is important to note that the iOA isoform was not altered in response to either RA or TM treatment (Figure 5A, D and E).

Densitometry showed increased expression of the glycosylated mOA isoform by 233% on day 14 (Figure 5D), and by 198% on day 21 (data not shown) in cultures, after RA treatment. Expression of the glycosylated OA isoform was inhibited by 89% on day 14 (Figure 5D), and by 85% on day 21 (data not shown) in culture, after TM treatment. The iOA isoform was not affected in response to treatment with RA or TM on day 14 (Figure 5E) or day 21 (data not shown) in culture. The results obtained from day 14 and 21 cultures suggested that the regulation of OA glycosylation, at least by RA and TM treatment, was not altered during osteoblast differentiation. These results confirm that OA is glycosylated by N-glycan modifications.

The effects of RA and TM on OA glycosylation was further determined by radiolabeling newly synthesized and modified OA protein using [^{35}S]-methionine and [^{14}C]-mannose incorporation. Primary osteoblast cultures were treated with RA, TM or both, and then radiolabeled as described in the methods section. OA was immunoprecipitated and the radioactivity incorporated into the newly synthesized OA protein was counted. Treatment with RA significantly increased OA protein synthesis and induced a 2-fold increase in mannosylation, as determined by the incorporation of [^{35}S]-methionine and [^{14}C]-mannose, respectively (Figure 5F and G). TM treatment inhibited ^{14}C mannose incorporation into OA protein by 45% compared to untreated controls. RA countered the effect of TM on OA protein mannosylation to levels similar to the control (Figure 5F and G). The ratio of [^{14}C]-mannose over [^{35}S]-methionine incorporation was increased in response to RA treatment (Figure 5H). To further confirm that RA treatment stimulates mannose incorporation into OA protein, immunoprecipitated OA protein-beads were treated with PNGase-F and free [^{14}C]-mannose released into the supernatant was increased by RA treatment compared to untreated controls (Figure 5I). Collectively, these data clearly suggest that OA protein is heavily glycosylated and its glycosylation can be modulated by RA. How-

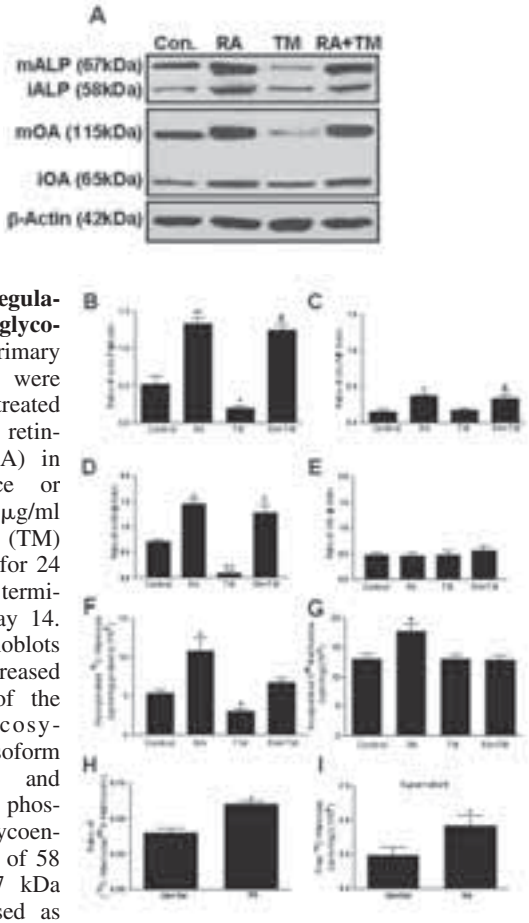


Figure 5. Regulation of OA glycosylation. Primary osteoblasts were cultured and treated with 10^{-6} M retinoic acid (RA) in the presence or absence of 1 μg/ml tunicamycin (TM) or TM only for 24 hours prior termination on day 14. **(A)** Immunoblots showed increased expression of the mature/glycosylated OA isoform of 115kDa and alkaline phosphatase glycoenzyme (ALP) of 58 kDa and 67 kDa isoforms (used as positive control) compared to untreated controls (Con.). Tunicamycin (TM) treatment inhibited glycosylation of both mature OA and ALP isoforms when compared to untreated controls. Treatment of osteoblast lysates with both RA and TM stimulates the glycosylation of the immature (58 kDa) and mature (67kDA) ALP isoforms, but only the mature OA (115 kDA) isoform. β actin was used as a loading control. **(B and C)** Densitometry of 3 immunoblots quantifying the ratio of the glycosylated/mature ALP (B) and native/immature ALP (C) isoforms over β actin. **(D and E)** Densitometry quantifying the ratio of the glycosylated/mature OA (D) and native/immature OA (E) isoforms over β actin. **(F–I)** Incorporation of radiolabeled ^{14}Cmannose and 35S-methionnine into OA. Primary osteoblasts were cultured for 3 days then treated with RA, TM, or RA and TM for 24 hours. Primary cultures were then switched to serum free medium that have either ^{14}C-mannose (1μCi/ml) or 35S-methionine (1μCi/ml) for 12 hours before termination. Fifty μg protein aliquots of cell lysates were immunoprecipitated with anti-OA antibody (OA-551). Incorporation of ^{14}C-mannose and ^{35}S-methionine in OA protein were determined via scintillation counting. RA treatment increased ^{14}C-mannose (F) and ^{35}Smethionine (G) incorporation into OA protein, while TM treatment reduced only ^{14}C-mannose incorporation into OA protein (F). Another 50 μg protein aliquot of cell lysates were immunoprecipitated with OA antibody and incubated with PNGase for 1 hour at 37°C and the free ^{14}C-mannose in the supernatant was counted. The ratio of ^{14}C-mannose over ^{35}Smethionine incorporation into OA protein and the free released ^{14}C-mannose from OA protein was calculated and showed that RA treatment increased OA protein synthesis and glycosylation (H and I). Bars represent mean + SEM. *$p < 0.05$; **$p < 0.01$ when compared to untreated controls; $^{\delta}p < 0.01$ when compared to TM treated cultures.

ever, the mechanism associated with the effect of RA on stimulation of glycosylation requires further investigations.

Blocking the Secreted/Mature Glycosylated OA Protein Inhibits Early Osteoblast Differentiation and Function

To examine whether the secreted, mature, glycosylated, isoform of OA has a role in early osteoblast differentiation, primary osteoblasts cultures were treated with different concentrations of anti-OA antibody (OA-551) (Figure 6, dose response not shown), every time the medium was changed. Cultures were terminated and stained for alkaline phosphatase (ALP), a marker of early osteoblast differentiation, on day 14 and for mineralized nodules assessed on day 17. Primary cultures treated with OA-551 showed less ALP staining (Figure 6Aa) as well as ALP activity (Figure 6B) when compared to non-immune IgY treated, control cultures.

The percent of ALP positive area fraction was quantified in each treated and untreated condition using computerized software (BioquantOsteo). Anti-OA antibody treated cultures showed a decrease of 67% in percent ALP area fraction compared to untreated controls (Figure 6Ab). Anti-OA antibody treated cultures showed a significant decrease in nodule formation (Figure 6Ca), total number of mineralized nodules (Figure 6Cb) and average nodule size (Figure 6Cc) when compared to control cultures. These data suggest an important functional role of the secreted/mature glycosylated OA isoform in the regulation of early osteoblast differentiation.

Blocking the Secreted/Mature Glycosylated OA Protein Inhibits Late Osteoblast Differentiation

To investigate whether the secreted, mature, glycosylated, isoform of OA has a role in terminal osteoblast differentiation and matrix mineralization, primary osteoblasts were cultured and treated with different concentrations of anti-OA antibody (OA-551) and terminated at day 21 for the measurement of late stage osteoblast differentiation makers (Figure 7). In order to determine whether the effect of OA-551 on late differentiation is due to a direct effect on cell proliferation or on later stages of differentiation, cultures were treated starting on day 3, when osteoblasts are actively proliferating, with different doses of OA-551, and parallel cultures were treated with the same doses of OA-551 starting on day 11, when the osteoblasts are at the matrix maturation stage. Both cultures were terminated at day 21 for the measurement of late stage osteoblast differentiation markers, such as nodule mineralization by von Kossa staining, calcium deposition, and osteocalcin production (Figure 7).

When mineralization (percent area fraction of von Kossa staining) was quantified in each treated and untreated condition, we found that anti-OA antibody treatment initiated at either day 3 or day 11 in culture showed a dramatic reduction in areas stained with von Kossa when compared to controls (Figure 7Aa and Ab for presentation of one dose treat-

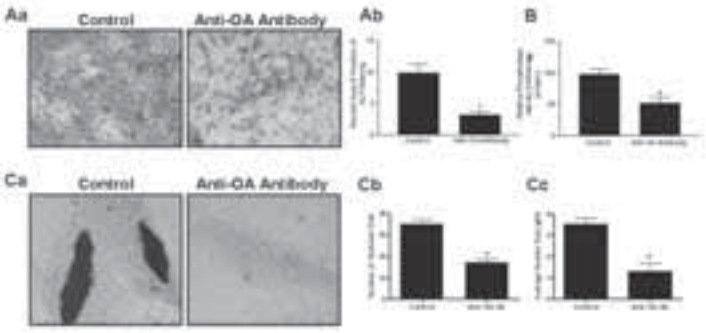


Figure 6. Blocking the secreted/mature glycosylated OA protein inhibits osteoblast differentiation. Primary osteoblasts were cultured and treated with anti-OA antibody (OA-551) (40 μg/ml) with every medium change, prior to alkaline phosphatase (ALP) staining, on day 14. **(Aa)** Photomicrographs showed diminished ALP staining in cultures treated with anti-OA antibody compared to non-immune IgY treated controls. **(Ab)** Bioquantification of 3 experiments determined that percent area fraction of the field occupied by ALP staining was significantly less with anti-OA antibody treatment. **(B)** Alkaline phosphatase activity in osteoblasts treated with anti-OA antibody for 14 days, was significantly decreased compared to non-immune IgY treated controls. Measurement of mineralized nodule formation in osteoblasts treated with anti-OA antibody on day 17 (Ca and Cb). **(Ca)** Phase contrast photomicrographs representative of three independent experiments. Nodules are smaller in size and lack minerals in cultures treated with anti-OA antibody when compared to non-immune IgY (control) cultures. **(Cb–c)** Quantification of three independent experiments for total number of nodules/ well and average nodule size. Anti-OA antibody treated cultures showed a significant decrease in total number of nodules (Cb) and average nodule size (Cc) when compared to non-immune IgY (control) cultures. Bars represent mean + SEM. *$p < 0.05$ when compared to non-immune IgY controls.

ment started at day 3 and terminated at day 21). Anti-OA antibody treated cultures showed a decrease of 70% in percent von Kossa area fraction staining (Figure 7Ac), as well as a significant decrease in total number of nodules as well as mineralized nodules and nodule size by 54% on day 21 (data not shown) compared to, non-immune IgY, control cultures. Calcium deposition, a marker also reflecting the matrix mineralization of late stage differentiated osteoblasts, increases in a temporal pattern with osteoblast culture differentiation (Figure 7B). Treatment with different doses of anti-OA antibody (OA-551), started at day 3 or day 11, significantly inhibited calcium deposition within the osteoblast cultures in a dose response manner (Figure 7Ca and Cb). In order to examine whether treatment with OA-551 had any effect on cell viability, cultures treated with different doses of anti-OA antibody starting at day 3 or day 11 were terminated at days 5 and 21, respectively, for measurement of cell viability using the MTT assay. OA-551 treatment did not have a significant effect on cell viability when compared to control (non-immune IgY) treated cultures (Figure 7Da and Db).

Osteocalcin, a secreted marker of terminally differentiated osteoblasts, was also measured in the cell-matrix layer and in the conditioned medium. OA-551 treatment caused a significant decreased in osteocalcin production within the cell matrix layer and the conditioned medium when compared to control cultures (Figure 7Ea and Eb). Collectively, these data demonstrate a crucial role for the secreted isoform of OA in the regulation of terminal osteoblast differentiation and matrix mineralization.

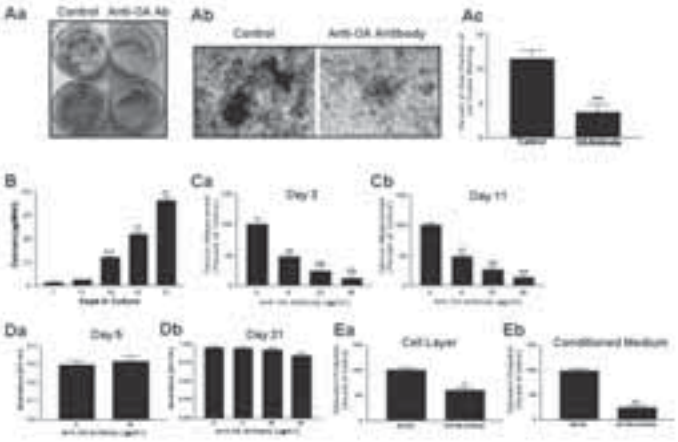


Figure 7. Blocking the secreted/mature glycosylated OA protein inhibits osteoblast matrix mineralization. Primary osteoblasts were cultured and treated with anti-OA antibody (OA-551) (40 μg/ml) with every medium change, prior to von Kossa staining for matrix mineralization and light green counterstaining on day 21. **(A)** Photomicrographs of culture wells (Aa) and phase contrast microscopy (Ab) of osteoblasts treated with either non-immune IgY (control) or anti-OA antibody. Von Kossa staining showed a decrease in matrix mineral deposition in cultures treated with anti-OA antibody compared to non-immune IgY treated controls. (Ac) Bioquantification of 3 experiments determined that percent area fraction of the field occupied by von Kossa staining was significantly less with anti-OA antibody treatment when compared to non-immune IgY treated control cultures. **(B)** Temporal pattern of calcium deposition in normal, untreated primary osteoblast culture matrix over time. Calcium deposition began around day 14 and increased during the period of terminal osteoblast differentiation. **(C)** Effect of different indicated doses of anti-OA antibody treatment on osteoblast matrix mineralization. Treatment started at different time points, day 3 (Ca) and day 11 (Cb), and terminated at day 21 in culture. **(D)** MTT cell viability assay of parallel cultures described in C. Primary osteoblasts were cultured as described in C and treated with anti-OA antibodies starting at day 3 (Da) or day 11 (Db). Both cultures were terminated at day 21 for the measurements of cell viability using the MTT assay as described on the method section. **(Ea and Eb)** Osteocalcin production in osteoblasts in cell lysates (Ea) and conditioned medium (Eb). Anti-OA antibody treatment significantly reduced osteocalcin production by osteoblasts when compared to non-immune IgY treated cultures. Bars represent mean + SEM of three independent experiments. **$p < 0.01$, ***$p < 0.001$ when compared to non-immune IgY controls or zero in graphs.

Over-expression of OA Enhances Osteoblast Differentiation and Function

We next examined gain-of-function of OA on osteoblast differentiation and function. For this experiment, we utilized

the retrovirus pBABE system to over-express OA in osteoblasts using the MC3T3-E1 osteoblast-like cell line. RetroMax® retrovirus vector system is based on the pCL vector system developed by Naviaux et al.[45] Cells were infected with either pBABE empty vector (pBABE-EV) used as control or pBABE vector over-expressing OA protein (pBABE-OA). pBABE-OA infected cells demonstrated over-expression of both OA transcript and protein by approximately 2.5-fold (Figure 8A and Ba). Densitometric analysis of Westerm blots of the OA protein showed that pBABE-OA infected cells over-expressed the mature isoform of OA by approximately 2-fold and the native isoform of OA by approximately 3-fold (Figure 8Bb and Bc) compared to control (pBABE-EV). We then first examined whether over-expression of OA alters osteoblast proliferation and viability. There was no significant difference between the pBABEOA and the pBABE-EV cells versus untreated control (Figure 8C). Next, we tested the effect of OA over-expression on early (alkaline phosphatase, ALP activity) and late (nodule mineralization, calcium deposition and osteocalcin production) osteoblast differentiation markers. pBABE-OA cells exhibited a significant increases in ALP activity when compared to pBABE-EV and untreated controls (Figure 8D). Nodule mineralization as measured by von Kossa staining showed that pBABE-OA cells formed a significantly greater number of mineralized nodules compared to the pBABE-EV control cells (Figure 8Ea and Eb). Over-expression of OA caused a significant increase in calcium deposition (Figure 8F) and osteocalcin production (Figure 8G). Collectively, these data suggest that over-expression of OA augments osteoblast differentiation and function.

The OA Mutant Mouse Displays Defective Osteoblast Differentiation Ex Vivo

A natural point mutation in the osteoactivin mouse gene in which a single nucleotide change introduced a stop codon leading to the generation of a truncated OA protein of only 150 amino acids was originally identified by our collaborators[8] (Figure 9A). The OA mutant mice develop pigmentary glaucoma[7] and demonstrate enhanced macrophage function.[25] Although the OA mutant mice are fertile and develop normally, we were interested in examining the ability of osteoblasts isolated from OA mutant mice to differentiate ex vivo. We first confirmed that the OA mutant mice have the point mutation (data not shown). We then evaluated the expression of the OA protein in primary cultures of osteoblasts established from OA mutant and wild-type mice, using Western blot analysis. Using an anti-OA antibody directed at the Nterminal end of the mature OA protein (OA-35), we could not unambiguously detect an OA protein in the mutant osteoblasts (data not shown). We next analyzed the localization of the OA protein in osteoblasts isolated from OA mutant and wild-type mice. Immunofluorescent analysis of OA protein in mutant osteoblasts using the OA-35 antibody

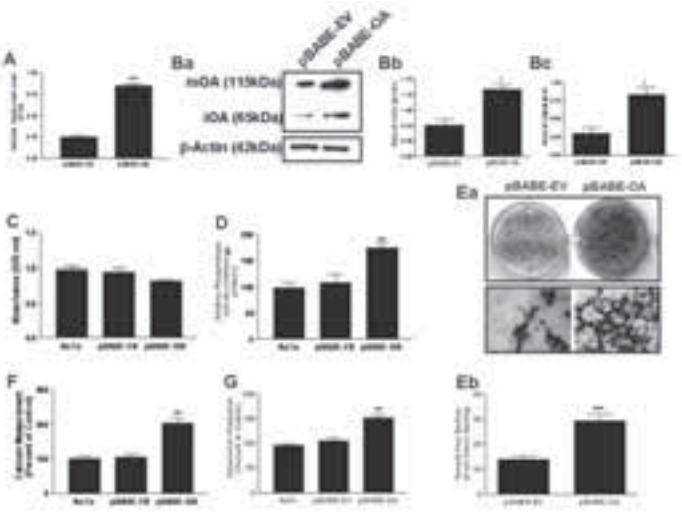


Figure 8. Over-expression of OA Enhances Osteoblast Differentiation and Function. MC3T3-E1 osteoblast cultures were stably infected with either pBABE-empty retroviral vector (pBABE-EV) or retroviral vector over-expressing osteoactivin (pBABE-OA). Parallel uninfected cultures (No Tx) were used as control. Cultures were terminated at day 5 for the evaluations of OA gene **(A)** and protein **(Ba)** expression using qPCR and Western blot analysis, respectively. There was ~2.5 fold increase in OA protein levels in cells over-expressing OA when compared to cells infected with empty vector alone. **(Bb and Bc)** Densitometry of 3 immunoblots quantifying percent of the mature/glycosylated (115 kDa) (Bb), or the immature (65 kDa) isoforms (Bc) of OA protein as a ratio of β actin. Bars represent mean + SEM. *$p < 0.05$ when compared to cells infected with empty vector. **(C)** Un-infected (NoTx), stably infected (either pBABE-EV or pBABE-OA) MC3T3-E1 cells were cultured and terminated at day 5 for measurement of cell viability. There was no significant difference among all culture conditions. **(D)** Un-infected (NoTx) or stably infected (either pBABE-EV or pBABE-OA) MC3T3-E1 cells were cultured and terminated at day 14 for ALP measurement. pBABE-OA infected cells showed significant increase in ALP activity when compared to either uninfected (NoTx) or pBABE-EV infected cells. **(E–G)** Parallel cultures were terminated at day 21 for the measurement of nodule formation and matrix mineralization. (E) Photomicrographs (40x magnification) of culture wells (upper panel) and phase contrast (lower panel) of osteoblasts infected with either pBABE-EV or pBABE-OA. Von Kossa staining showed dramatic increased in matrix mineral deposition in cultures over-expressing OA when compared to pBABE-EV infected control cultures. (F) Bioquantification of 3 independent experiments determined that percent area fraction of the field occupied by von Kossa staining was significantly increased in cells over-expressing OA (pBABE-OA) when compared control pBABE-EV infected cultures. (G) Calcium deposition was significantly increased in cells infected with pBABE-OA when compared to control cells infected with pBABE-EV or untreated. (H) Osteocalcin production in cell layer of osteoblasts was significantly increased in cultures infected with pBABE-OA when compared to control cultures infected with pBABE-EV or untreated control (NoTx). Bars represent mean + SEM of three independent experiments. **$p < 0.01$, when compared to either NoTx or pBABE-EV. ***$p < 0.001$ when compared to pBABE-EV.

showed that the OA protein was strictly localized to the perinuclear cytoplasmic regions, in contrast to wild type osteoblasts where OA is also found in punctuated vesicle-like structures localized toward the peripheral cytoplasmic compartment (Figure 9B). These data suggest that the OA protein is not processed normally and is retained within the ER/Golgi in OA mutant osteoblasts. We next examined OA mutant osteoblasts for their ability to differentiate ex vivo. Bone marrow stromal cells were isolated from OA mutant and wild-type new born mice and cultured for 14 and 21 days. ALP activity and calcium deposition were measured as markers of early and late osteoblast differentiation and function, respectively. Both ALP activity and calcium deposition were dramatically reduced in OA mutant compared to wild-type osteoblasts (Figure 9C and D). These data suggest that OA acts as positive regulator of osteoblastogenesis ex vivo and that absence of OA causes a cell autonomous defect in osteoblast differentiation and function.

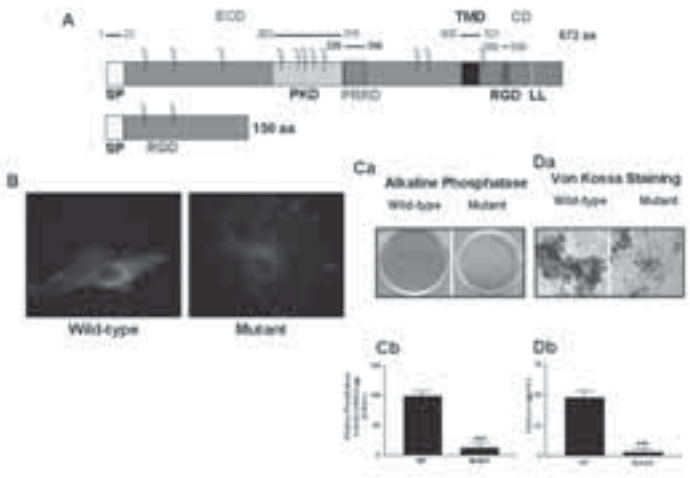


Figure 9. Defective differentiation in OA mutant osteoblasts. **(A)** Schematic representation of the wild type OA (top) and the naturally occurring mutant OA (bottom) proteins. The mutant OA is generated by a premature stop codon mutation. **(B)** Immunofluorescent localization of OA in normal (wild-type) and OA mutant osteoblasts. Primary osteoblasts were isolated from normal and OA mutant mice and cultured for three days and stained with anti-OA antibody (OA-35) (red signal). Note the vesicular localization of OA in wild type osteoblasts in both perinuclear and peripheral area of the cytoplasm, while in OA mutant osteoblasts, OA is only localized to the perinuclear areas. **(C)** Bone marrow stromal cells from normal and OA mutant mice were harvested as described in the method sections, cultured for 14 days and stained for alkaline phosphatase (ALP) activity. Photomicrographs of culture plate (Ca) or measurement of ALP activity (Cb). Mutant osteoblast cultures demonstrated a significant decrease in ALP staining and activity compared to wild-type cultures. **(D)** Bone marrow stromal cells from normal and OA mutant mice were cultured for 28 days and stained with von Kossa for mineral deposition. Photomicrographs of phase contrast pictures (upper panel) (Da) or calcium measurement (Db). Note lack of mineralization in cultures of mutant compared to wild-type osteoblasts.

Discussion

In the present study, we demonstrated that OA protein is expressed and secreted by osteoblasts in vitro. We also showed that osteoblasts expressed both the immature and mature/glycosylated isoforms of OA and that retinoic acid and tunicamycin can modulate the glycosylation of OA in osteoblasts and that osteoblasts secret the mature/glycosylated isoform of OA. This isoform of OA plays a role in osteoblast differentiation and function. Osteoblasts express a mutant isoform of OA are defective in their differentiation ex vivo suggesting that OA has a positive cell autonomous effect on osteoblastogenesis in vivo.

Osteoactivin (OA) was initially identified as a transmembrane type I glycoprotein nonmelanoma b (gpnmb) in low metastatic melanoma cell lines.[4] OA was identified by several investigators in different species, mouse OA was identified in dendritic cells, termed cell heparan sulfate proteoglycan integrin dependant ligand (DC-HIL). Human OA was identified in hematopoietic cells, termed growth factor inducible neurokinin (HGFIN). In bone, our group was the first to identify OA[1] in animal model of osteopetrosis. OA has not yet been designated to specific family of proteins; however, it has high homology to Pmel-17/gp100, a melanocytes specific protein[46] and quail neuroretina, QNR-71 protein, all of which are type I transmembrane glycoprotein with secreted isoforms.[40, 47]

In this study, we characterized OA protein processing in osteoblasts and examined its role in osteoblast differentiation and function using gain- and loss-of-function approaches. Data presented in this study showed that OA protein is expressed by primary osteoblasts in culture. The temporal pattern of OA expression during osteoblast differentiation in culture was examined and showed that OA expression was increased as osteoblast terminally differentiated. OA expression has been associated with differentiating cells of various types such as chondrocytes,[48] denderitic cells,[10] macrophages,[34] myocytes,[30] and osteoclasts (unpublished observations and personal communication with Dr. Mary Nakamura, University of California, San Francisco). Taken together, our data and others suggested that OA plays a role in cell differentiation.

Examination of OA protein sequence using different bioinformatic resources revealed that OA protein is a type I transmembrane glycoprotein with a signal peptide, and three main domains, a long extracellular (luminal) domain (amino acid 23–500), short transmembrane domain (amino acids 501–521) and the cytoplasmic domain (amino acids 522–572). Previous reports suggest that the signal peptide sequence of other OA homology proteins such as; Pmel-17, determine their entry into the secretory pathway.[49]

Within the extracellular domain, there are three subdomains; the RGD domain, the polycystic kidney disease-like domain (PKD) domain, and the proline rich repeat domain (PRRD). The RGD domain is only present in the

N-terminus of moue and human but not in the rat OA. This domain has been shown to mediate the attachment of smooth blood vessels endothelial cell line (SVEC) via heparan sulfate proteoglycan-dependent mechanism.[10] The PKD domain has an immunoglobulin-like folding structure.[50] This domain is suggested to mediate protein-protein interaction and protein-carbohydrate interaction.[51] The PRR domain has been linked to O-linked glycans of Pmel-17 and the formation of melanocyte organelle fibers.[37] To date, there is no studies been reported on the functions of different domains of OA in bone cells, however, recent studies using mutant OA lacking the PKD or the PRR domains and tagged to the IgG-Fc demonstrated that the PDK domain with lesser extent, the PRR domain, are required for the inhibitory effect of OA, on T cell activation.[9]

The transmembrane domain of OA again has no clear function and yet to be determined by our group in osteoblasts, however, it seems that it plays a role in anchoring OA protein within the membrane. It is interesting however; that the cytoplasmic domain of OA consists of RGD domain only in the mouse and rat sequence, and the C-terminal domain also contains di-leucine motif in all species examined. This sequence has been reported to be important for protein sorting of the rough endoplasmic reticulum, in two high homology proteins to OA, Pmel-17 and QNR-71 and several other proteins.[38, 40, 52, 53]

Studying the subcellular localization of OA and its processing will shed some light on its mechanism of action on bone cells. For this purpose, our cell fractionation results clearly showed that OA has two isoforms in bone cells. Both protein isoforms are made within the cytosol and only the mature isoform is localized to the membranous fraction. It is important to note that this fraction not only includes the plasma membrane but also all membrane proteins within different cellular compartments. We also presented immunofluorescent data where EGFP-tagged-OA in osteoblasts, these data suggested that the protein is made, and localized in vesicular-, endosomallike structures within the first 24 hours of expression, then; the protein moves toward the periphery and either anchored itself to the plasma membrane or become secreted. Similar to our results, Shikano et al., showed that in denderitic cells, OA is localized to vesicles-like structures perinuclear as well as small vesicles scattered toward the periphery and present at low levels on the cell surface.[10] Another study showed that subcellular localization of EGFP-tagged OA transfected into COS7 and HEK293 cells. OA was localized to vesicular, endosomal-like structures and this localization was dispersed into the ER when the Golgi network was disrupted with BFA treatment. Brefeldin A (BFA) is a fungal metabolite that blocks cytosolic coat protein complex (COP) function within Golgi compartment.[54, 55] Additional supporting evidence on OA subcellular localization came from the co-localization of OA with β-COP, cytosolic coat protein complex, a protein that is associated with membranous structure of the Golgi complex.[56–58] Subcellular localization of Pmel-17 in melanocytes is extensively studied by different groups.[38, 59–61] Pmel-17 accumulates in both multivesicular bodies (MVB) and in early endosomal like organelles involved in protein sorting to the endocytic and secretory pathways, respectively. Our group is in the process of characterizing in details the subcellular localization of OA and its relationship to osteoblast function.

OA protein synthesis and stability in osteoblasts were also examined in this study using the pulse chase approach and found that OA protein is synthesized within the first 5 minutes of chasing and both isoforms (immature and mature) are present after 30 minutes. Within an hour of chasing, most of the newly synthesized protein was decreased and only after 2 hours, some of the protein was secreted. These data suggested that the half life of OA protein in osteoblasts is short, thus, suggesting that the protein is unstable. Unlike OA, in melanocytes, pulse chase studies showed that Pmel-17 is more stable at least for the first 4 hours (see below for possible explanations).

In this study, we also found that OA protein is heavily glycosylated by N-linked and Olinked glycans and that the secreted isoform of OA is the glycosylated/mature isoform of the protein. The fact that treatment of osteoblastic proteins with different enzymes that modulate the N-and O- glycans of OA did not trim all of the sugar modifications of the protein, i.e. we were unable to reduce the MW of OA protein to its native (65kDa) size. This is could be due to the time and or the amount of enzymes used in this study. Different patterns of OA glycosylation were suggested based on the cell type examined. Shikano et al., showed discrepancies in the molecular weight of mouse OA between its native size in XS52 denderitic cells and its recombinant form expressed in COS-1 cells and suggested that this heterogeneity in OA proteins may be produced as a result of differential N- and/or O-glycosylation.[10] Similar observations are recently reported using the same de-glycosylation enzymes to modulate the sugar modifications of Pmel-17 in melanocytes.[35] The same group reported that Pmel-17 is glycosylated differently in the Golgi and sorted through the secretory pathway. Using glycosylation-deficient mutant cells revealed that Pmel-17 lacking the correct addition of sialic acid and galactose loses the ability to from fibrils, a critical component of melanin biosynthesis.[35]

We went further to examine the regulation of the N-glycan modification of OA protein in osteoblasts and found that retinoic acid (RA), and tunicamycin (TM), treatments stimulates Nmannose incorporation and inhibits N-glycans of OA, respectively. RA has been reported to affect protein glycosylation in vitro[62] and in vivo.[63, 64] It has also been reported that changes in cell surface sugar molecules as well as the activities of specific glycosyltransferases are altered during RA-mediated differentiation of F9 cells.[65–67] In this study, we showed that treatment of primary osteoblasts with RA increases the glycosylation of the mature isoform of OA and

this treatment was associated with increased osteoblast differentiation and function marked by increased ALP activity and matrix mineralization (data not shown). Tunicamycin on the other hand, inhibited the glycosylation of the mature OA isoform and this treatment was also correlated with decreased osteoblast differentiation and function, demonstrated by dramatic reduction of differentiation markers such as; ALP activity and calcium deposition (data not shown). Collectively, these results probably reflect an overall modulation of osteoblast differentiation and function due to modulation of OA glycosylation. However, we can not exclude the possibility that other glycoproteins in osteoblasts such as, ALP and bone morphogenetic proteins,[43, 68] may also be modified by the treatment with RA and TM.

The role of RA in mediating protein glycosylation and function has been previously reported, where oligosaccharide chains of fibronectin have decreased uptake of sugars from vitamin A deficient hepatocytes, was observed and this decrease was reversed by adding RA at physiological concentration.[63]

The role of the secreted, glycosylated isoform of OA in osteoblast differentiation was evident by the effect of anti-OA antibody treatment in osteoblast cultures. Treatment with anti-OA antibody (OA-551) neutralizes the constitutively produced OA by osteoblasts and showed a dramatic decrease in markers of osteoblast differentiation and function in a dose-dependent manner. Recent studies by our laboratory also showed that transfection of OA-551 into osteoblasts significantly reduced osteoblast differentiation and function.[20] It is important to note that OA-551 antibody was raised against a sequence that spans the sorting signal in the cterminal domain of OA. This suggests that the antibody blocks the sorting, processing and secretion of OA by osteoblasts and ultimately inhibits osteoblast differentiation and function.

Glycosylation of protein has major effect on its biological activity,[69] such as in case of BMP-1. BMP-1 is a glycosylated metalloproteinase that is important for the synthesis of a normal extracellular matrix because it cleaves type I procollagen as well as other precursor proteins. Recombinant BMP-1 molecules lacking all N-linked glycosylation sites were not secreted in the media suggesting that glycosylation of BMP-1 is important for secretion and stability of the protein.[68]

In addition, it has been shown that treatment of mammalian heart and skeletal muscle cells with RA causes time and concentration dependant increase of the specific activity of alkaline phosphatase through glycosylation of ALP protein which is important for its insertion into the plasma membrane and so its function.[70] When TM was used to inhibit protein Nglycosylation, ALP activity was declined.[43]

Carbohydrate chains of glycoprotein modulate a wide range of cellular events, including development and differentiation.[71] The strength of integrin binding that mediate cell adhesion, migration and differentiation to defined peptide sequence was dependant on the status of glycosylation of integrin proteins.[72] Also, Adhesion of NIH3T3 cells to fibronectin was increased in the presence of RA that cause alteration in the amounts and types of oligosaccharides of the glycoprotein on the cell surface.[73]

The effect of OA-551 treatment on osteoblast differentiation was supported by the effect of gain-of-function of OA in osteoblasts. Over-expression of OA stimulated markers of osteoblast-differentiation and function. These data suggest that OA has a crucial function in the regulation of osteoblast differentiation.

The role of OA in osteoblast differentiation and function in vivo was further investigated using a mouse model with a natural mutation in the OA gene causing a premature stop codon that results in the generation of a truncated OA protein.[7, 8, 32, 33] These mice develop an eye phenotype with iris pigmentary dispersion (IPD) and iris stromal atrophy (ISA) (see below for other phenotypes). They also have increased macrophage function.[34] In this study we examined the ability of bone marrow stromal cells isolated from OA mutant mice to differentiate into osteoblasts. We found that osteoblast differentiation was impaired in OA mutant compared to wild-type mice. These data suggest that OA acts as a positive regulator of osteoblastogenesis in vivo. Further characterization of the skeletal phenotype of these mice warrants further investigations. The fact that mutant OA mice produce truncated OA protein that is lacking most of the structural domains suggested that the truncated OA is retained within the endoplasmic reticulum (ER) resulting in defective protein processing, glycosylation, trafficking, and secretion in osteoblasts. Increased trafficking of OA to lysosomes and/or proteasomal degradation could also be occurring in OA mutant osteoblasts. However, these speculations require further investigation. Similar findings were demonstrated in the mouse *sliver* mutant where Pmel-17, a family member to OA, is truncated at the C-terminal domain, leading to protein retention in the ER and defective protein processing, glycosylation, trafficking and function in melanocytes resulting in a defective coat color and depletion of hair follicle melanocytes with age.[74, 75] Another example has been reported for the human Crouzon craniosynostosis syndrome involving aberrant development of the craniofacial skeleton,[76] is associated with an FGFR2 mutation that results in ER retention, diminished glycosylation and increased degradation in osteoblasts.[77]

OA protein has maximal expression during last stage of osteoblast differentiation (Figure 3) and using anti-OA antibody (Ab-551) *in vitro* showed inhibition of osteoblast differentiation and function.[20] This stage is important during normal bone growth and during fracture repair process where osteoblasts are responsible for the production of new bone matrix proteins during bone remodeling.[78]

The mechanism by which OA regulates osteoblast differentiation and function could be direct by regulating specific signaling pathways that stimulate the regulation of osteo-

blast differentiation and function. Another possibility of the effect of OA on osteoblasts could be explained by the recent study reported by our group where OA acts as a downstream mediator of BMP-2 effects in osteoblasts. Loss-of-function or gain-of-function of OA could either decrease or enhance the function of endogenous BMP-2 produced by osteoblasts, receptively.[23]

Collectively, in this study we showed that OA acts as anabolic factors where it regulates osteoblast differentiation and function in vitro. Further studies are warranted to determined the mechanism by which OA regulate osteoblast differentiation and bone formation.

Identification of such bone anabolic agents that have potential therapeutic applications would be beneficial for local (as in fracture repair or localized osteopenia) and/or systemic diseases (as in generalized osteoporosis).

Acknowledgement

This research work was supported by grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR48892), to F.F.S, National Institute of Health and Grant from the Department of Health, State of Pennsylvania to S.M.A. The authors will also like to thank Dr. Archana Sanjay for her comments and suggestions on some experimental design.

References

1. Safadi, F. F., Xu, J., Smock, S. L., Rico, M. C., Owen, T. A., and Popoff, S. N. (2001). Cloning and characterization of osteoactivin, a novel cDNA expressed in osteoblasts. *J Cell Biochem* 84, 12–26.
2. Kuan, C. T., Wakiya, K., Dowell, J. M., Herndon, J. E., 2nd, Reardon, D. A., Graner, M. W., Riggins, G. J., Wikstrand, C. J., and Bigner, D. D. (2006). Glycoprotein nonmetastatic melanoma protein B, a potential molecular therapeutic target in patients with glioblastoma multiforme. *Clin Cancer Res* 12, 1970–82.
3. Tse, K. F., Jeffers, M., Pollack, V. A., McCabe, D. A., Shadish, M. L., Khramtsov, N. V., Hackett, C. S., Shenoy, S. G., Kuang, B., Boldog, F. L., MacDougall, J. R., Rastelli, L., Herrmann, J., Gallo, M., Gazit-Bornstein, G., Senter, P. D., Meyer, D. L., Lichenstein, H. S., and LaRochelle, W. J. (2006). CR011, a fully human monoclonal antibody-auristatin E conjugate, for the treatment of melanoma. *Clin Cancer Res* 12, 1373–82.
4. Weterman, M. A., Ajubi, N., van Dinter, I. M., Degen, W. G., van Muijen, G. N., Ruitter, D. J., and Bloemers, H. P. (1995). nmb, a novel gene, is expressed in low-metastatic human melanoma cell lines and xenografts. *Int J Cancer* 60, 73–81.
5. Okamoto, I., Pirker, C., Bilban, M., Berger, W., Losert, D., Marosi, C., Haas, O. A., Wolff, K., and Pehamberger, H. (2005). Seven novel and stable translocations associated with oncogenic gene expression in malignant melanoma. *Neoplasia* 7, 303–11.
6. Pollack, V. A., Alvarez, E., Tse, K. F., Torgov, M. Y., Xie, S., Shenoy, S. G., MacDougall, J. R., Arrol, S., Zhong, H., Gerwien, R. W., Hahne, W. F., Senter, P. D., Jeffers, M. E., Lichenstein, H. S., and LaRochelle, W. J. (2007). Treatment parameters modulating regression of human melanoma xenografts by an antibody-drug conjugate (CR011-vcMMAE) targeting GPNMB. *Cancer Chemother Pharmacol* 60, 423–35.
7. Anderson, M. G., Libby, R. T., Mao, M., Cosma, I. M., Wilson, L. A., Smith, R. S., and John, S. W. (2006). Genetic context determines susceptibility to intraocular pressure elevation in a mouse pigmentary glaucoma. *BMC Biol* 4, 20.
8. Anderson, M. G., Smith, R. S., Hawes, N. L., Zabaleta, A., Chang, B., Wiggs, J. L., and John, S. W. (2002). Mutations in genes encoding melanosomal proteins cause pigmentary glaucoma in DBA/2J mice. *Nat Genet* 30, 81–5.
9. Chung, J. S., Sato, K., Dougherty, II, Cruz, P. D., Jr., and Ariizumi, K. (2007). DC-HIL is a negative regulator of T lymphocyte activation. *Blood* 109, 4320–7.
10. Shikano, S., Bonkobara, M., Zukas, P. K., and Ariizumi, K. (2001). Molecular cloning of a dendritic cell-associated transmembrane protein, DCHIL, that promotes RGD-dependent adhesion of endothelial cells through recognition of heparan sulfate proteoglycans. *J Biol Chem* 276, 8125–34.
11. Bandari, P. S., Qian, J., Yehia, G., Joshi, D. D., Maloof, P. B., Potian, J., Oh, H. S., Gascon, P., Harrison, J. S., and Rameshwar, P. (2003). Hematopoietic growth factor inducible neurokinin-1 type: a transmembrane protein that is similar to neurokinin 1 interacts with substance P. *Regul Pept* 111, 169–78.
12. Adema, G. J., de Boer, A. J., Vogel, A. M., Loenen, W. A., and Figdor, C. G. (1994). Molecular characterization of the melanocyte lineage-specific antigen gp100. *J Biol Chem* 269, 20126–33.
13. Boissy, R. E., Richmond, B., Huizing, M., Helip-Wooley, A., Zhao, Y., Koshoffer, A., and Gahl, W. A. (2005). Melanocyte-specific proteins are aberrantly trafficked in melanocytes of Hermansky-Pudlak syndrome-type 3. *Am J Pathol* 166, 231–40.
14. Jager, E., Maeurer, M., Hohn, H., Karbach, J., Jager, D., Zidianakis, Z., Bakhshandeh-Bath, A., Orth, J., Neukirch, C., Necker, A., Reichert, T. E., and Knuth, A. (2000). Clonal expansion of Melan A-specific cytotoxic T lymphocytes in a melanoma patient responding to continued immunization with melanoma-associated peptides. *Int J Cancer* 86, 538–47.
15. Kierstead, L. S., Ranieri, E., Olson, W., Brusic, V., Sidney, J., Sette, A., Kasamon, Y. L., Slingluff, C. L., Jr., Kirkwood, J. M., and Storkus, W. J. (2001). gp100/pmel17 and tyrosinase encode multiple epitopes recognized by Th1-type CD4+T cells. *Br J Cancer* 85, 1738–45.
16. Sensi, M., Pellegatta, S., Vegetti, C., Nicolini, G., Parmiani, G., and Anichini, A. (2002). Identification of a novel gp100/pMel17 peptide presented by HLAA* 6801 and recognized on human melanoma by cytolytic T cell clones. *Tissue Antigens* 59, 273–9.
17. Valencia, J. C., Hoashi, T., Pawelek, J. M., Solano, F., and Hearing, V. J. (2006). Pmel17: controversial indeed but critical to melanocyte function. *Pigment Cell Res* 19, 250–2; author reply 253–7.
18. Wagner, S. N., Wagner, C., Schultewolter, T., and Goos, M. (1997). Analysis of Pmel17/gp100 expression in primary human tissue specimens: implications for melanoma immuno- and gene-therapy. *Cancer Immunol Immunother* 44, 239–47.
19. Berson, J. F., Harper, D. C., Tenza, D., Raposo, G., and Marks, M. S. (2001). Pmel17 initiates premelanosome morphogenesis within multivesicular bodies. *Mol Biol Cell* 12, 3451–64.
20. Selim, A. A., Abdelmagid, S. M., Kanaan, R. A., Smock, S. L., Owen, T. A., Popoff, S. N., and Safadi, F. F. (2003). Anti-osteoactivin antibody inhibits osteoblast differentiation and function in vitro. *Crit Rev Eukaryot Gene Expr* 13, 265–75.
21. Rich, J. N., Shi, Q., Hjelmeland, M., Cummings, T. J., Kuan, C. T., Bigner, D. D., Counter, C. M., and Wang, X. F. (2003). Bone-related genes expressed in advanced malignancies induce invasion and metastasis in a genetically defined human cancer model. *J Biol Chem* 278, 15951–7.
22. Owen, T. A., Smock, S. L., Prakash, S., Pinder, L., Brees, D., Krull, D., Castleberry, T. A., Clancy, Y. C., Marks, S. C., Jr., Safadi, F. F., and Popoff, S. N. (2003). Identification and characterization of the genes encoding human and mouse osteoactivin. *Crit Rev Eukaryot Gene Expr* 13, 205–20.
23. Abdelmagid, S. M., Barbe, M. F., Arango-Hisijara, I., Owen, T. A., Popoff, S. N., and Safadi, F. F. (2007). Osteoactivin acts as downstream mediator of BMP-2 effects on osteoblast function. *J Cell Physiol* 210, 26–37.
24. Lennerz, V., Fatho, M., Gentilini, C., Frye, R. A., Lifke, A., Ferel, D., Wolfel, C., Huber, C., and Wolfel, T. (2005). The response of autologous T cells to a human melanoma is dominated by mutated neoantigens. *Proc Natl Acad Sci USA* 102, 16013–8.

25. Mo, J. S., Anderson, M. G., Gregory, M., Smith, R. S., Savinova, O. V., Serreze, D. V., Ksander, B. R., Streilein, J. W., and John, S. W. (2003). By altering ocular immune privilege, bone marrow-derived cells pathogenically contribute to DBA/2J pigmentary glaucoma. *J Exp Med* 197, 1335–44.
26. Ahn, J. H., Lee, Y., Jeon, C., Lee, S. J., Lee, B. H., Choi, K. D., and Bae, Y. S. (2002). Identification of the genes differentially expressed in human dendritic cell subsets by cDNA subtraction and microarray analysis. *Blood* 100, 1742–54.
27. Haralanova-Ilieva, B., Ramadori, G., and Armbrust, T. (2005). Expression of osteoactivin in rat and human liver and isolated rat liver cells. *J Hepatol* 42, 565–72.
28. Onaga, M., Ido, A., Hasuike, S., Uto, H., Moriuchi, A., Nagata, K., Hori, T., Hayash, K., and Tsubouchi, H. (2003). Osteoactivin expressed during cirrhosis development in rats fed a choline-deficient, L-amino acid-defined diet, accelerates motility of hepatoma cells. *J Hepatol* 39, 779–85.
29. Abe, H., Uto, H., Takami, Y., Takahama, Y., Hasuike, S., Kodama, M., Nagata, K., Moriuchi, A., Numata, M., Ido, A., and Tsubouchi, H. (2007). Transgenic expression of osteoactivin in the liver attenuates hepatic fibrosis in rats. *Biochem Biophys Res Commun* 356, 610–5.
30. Ogawa, T., Nikawa, T., Furochi, H., Kosyoji, M., Hirasaka, K., Suzue, N., Sairyo, K., Nakano, S., Yamaoka, T., Itakura, M., Kishi, K., and Yasui, N. (2005). Osteoactivin upregulates expression of MMP-3 and MMP-9 in fibroblasts infiltrated into denervated skeletal muscle in mice. *Am J Physiol Cell Physiol* 289, C697–707.
31. Nakamura, A., Ishii, A., Ohata, C., and Komurasaki, T. (2007). Early induction of osteoactivin expression in rat renal tubular epithelial cells after unilateral ureteral obstruction. *Exp Toxicol Pathol* 59, 53–9.
32. Anderson, M. G., Smith, R. S., Savinova, O. V., Hawes, N. L., Chang, B., Zabaleta, A., Wilpan, R., Heckenlively, J. R., Davisson, M., and John, S. W. (2001). Genetic modification of glaucoma associated phenotypes between AKXD-28/Ty and DBA/2J mice. *BMC Genet* 2, 1.
33. Ott, C., Iwanciw, D., Graness, A., Giehl, K., and Goppelt-Struebe, M. (2003). Modulation of the expression of connective tissue growth factor by alterations of the cytoskeleton. *J Biol Chem* 278, 44305–11.
34. Ripoll, V. M., Irvine, K. M., Ravasi, T., Sweet, M. J., and Hume, D. A. (2007). Gpnmb is induced in macrophages by IFN-gamma and lipopolysaccharide and acts as a feedback regulator of proinflammatory responses. *J Immunol* 178, 6557–66.
35. Valencia, J. C., Rouzaud, F., Julien, S., Chen, K. G., Passeron, T., Yamaguchi, Y., Abu-Asab, M., Tsokos, M., Costin, G. E., Yamaguchi, H., Jenkins, L. M., Nagashima, K., Appella, E., and Hearing, V. J. (2007). Sialylated core 1 O-glycans influence the sorting of Pmel17/gp100 and determine its capacity to form fibrils. *J Biol Chem* 282, 11266–80.
36. Lau, K. S., Partridge, E. A., Grigorian, A., Silvescu, C. I., Reinhold, V. N., Demetriou, M., and Dennis, J. W. (2007). Complex N-glycan number and degree of branching cooperate to regulate cell proliferation and differentiation. *Cell* 129, 123–34.
37. Hoashi, T., Muller, J., Vieira, W. D., Rouzaud, F., Kikuchi, K., Tamaki, K., and Hearing, V. J. (2006). The repeat domain of the melanosomal matrix protein PMEL17/GP100 is required for the formation of organellar fibers. *J Biol Chem* 281, 21198–208.
38. Theos, A. C., Truschel, S. T., Tenza, D., Hurbain, I., Harper, D. C., Berson, J. F., Thomas, P. C., Raposo, G., and Marks, M. S. (2006). A lumenal domain-dependent pathway for sorting to intralumenal vesicles of multivesicular endosomes involved in organelle morphogenesis. *Dev Cell* 10, 343–54.
39. Rezania, A., and Healy, K. E. (1999). Integrin subunits responsible for adhesion of human osteoblast-like cells to biomimetic peptide surfaces. *J Orthop Res* 17, 615–23.
40. Le Borgne, R., Planque, N., Martin, P., Dewitte, F., Saule, S., and Hoflack, B. (2001). The AP-3-dependent targeting of the melanosomal glycoprotein QNR-71 requires a di-leucine-based sorting signal. *J Cell Sci* 114, 2831–41.
41. Khoobehi, B., and Peyman, G. A. (1999). Fluorescent labeling of blood cells for evaluation of retinal and choroidal circulation. *Ophthalmic Surg Lasers* 30, 140–5.
42. Schulenberg, B., Beechem, J. M., and Patton, W. F. (2003). Mapping glycosylation changes related to cancer using the Multiplexed Proteomics technology: a protein differential display approach. *J Chromatogr B Analyt Technol Biomed Life Sci* 793, 127–39.
43. Mueller, W. H., Kleefeld, D., Khattab, B., Meissner, J. D., and Scheibe, R. J. (2000). Effects of retinoic acid on N-glycosylation and mRNA stability of the liver/bone/kidney alkaline phosphatase in neuronal cells. *J Cell Physiol* 182, 50–61.
44. Takahashi, N., Iwahori, A., Breitman, T. R., and Fukui, T. (1997). Tunicamycin in combination with retinoic acid synergistically inhibits cell growth while decreasing palmitoylation and enhancing retinoylation of proteins in the human breast cancer cell line MCF-7. *Oncol Res* 9, 527–33.
45. Naviaux, R. K., Costanzi, E., Haas, M., and Verma, I. M. (1996). The pCL vector system: rapid production of helper-free, high-titer, recombinant retroviruses. *J Virol* 70, 5701–5.
46. Kobayashi, T., Urabe, K., Orlow, S. J., Higashi, K., Imokawa, G., Kwon, B. S., Potterf, B., and Hearing, V. J. (1994). The Pmel 17/silver locus protein. Characterization and investigation of its melanogenic function. *J Biol Chem* 269, 29198–205.
47. Turque, N., Denhez, F., Martin, P., Planque, N., Bailly, M., Begue, A., Stehelin, D., and Saule, S. (1996). Characterization of a new melanocytespecific gene (QNR-71) expressed in v-myc-transformed quail neuroretina. *Embo J* 15, 3338–50.
48. James, C. G., Appleton, C. T., Ulici, V., Underhill, T. M., and Beier, F. (2005). Microarray analyses of gene expression during chondrocyte differentiation identifies novel regulators of hypertrophy. *Mol Biol Cell* 16, 5316–33.
49. Maresh, G. A., Marken, J. S., Neubauer, M., Aruffo, A., Hellstrom, I., Hellstrom, K. E., and Marquardt, H. (1994). Cloning and expression of the gene for the melanoma-associated ME20 antigen. *DNA Cell Biol* 13, 87–95.
50. Scanu, A. M., and Edelstein, C. (1994). Apolipoprotein(a): structural and functional consequences of mutations in kringle type 10 (or kringle 4-37). *Clin Genet* 46, 42–5.
51. Scheffers, M. S., Le, H., van der Bent, P., Leonhard, W., Prins, F., Spruit, L., Breuning, M. H., de Heer, E., and Peters, D. J. (2002). Distinct subcellular expression of endogenous polycystin-2 in the plasma membrane and Golgi apparatus of MDCK cells. *Hum Mol Genet* 11, 59–67.
52. Piccirillo, R., Palmisano, I., Innamorati, G., Bagnato, P., Altimare, D., and Schiaffino, M. V. (2006). An unconventional dileucine-based motif and a novel cytosolic motif are required for the lysosomal and melanosomal targeting of OA1. *J Cell Sci* 119, 2003–14.
53. Setaluri, V. (2000). Sorting and targeting of melanosomal membrane proteins: signals, pathways, and mechanisms. *Pigment Cell Res* 13, 128–34.
54. Bachner, D., Schroder, D., and Gross, G. (2002). mRNA expression of the murine glycoprotein (transmembrane) nmb (Gpnmb) gene is linked to the developing retinal pigment epithelium and iris. *Brain Res Gene Expr Patterns* 1, 159–65.
55. Bednarek, S. Y., Ravazzola, M., Hosobuchi, M., Amherdt, M., Perrelet, A., Schekman, R., and Orci, L. (1995). COPI- and COPII-coated vesicles bud directly from the endoplasmic reticulum in yeast. *Cell* 83, 1183–96.
56. Griffiths, G., Pepperkok, R., Locker, J. K., and Kreis, T. E. (1995). Immunocytochemical localization of beta-COP to the ER-Golgi boundary and the TGN. *J Cell Sci* 108 (Pt 8), 2839–56.
57. Scheel, J., Pepperkok, R., Lowe, M., Griffiths, G., and Kreis, T. E. (1997). Dissociation of coatomer from membranes is required for brefeldin Ainduced transfer of Golgi enzymes to the endoplasmic reticulum. *J Cell Biol* 137, 319–33.
58. Hendricks, L. C., McCaffery, M., Palade, G. E., and Farquhar, M. G. (1993). Disruption of endoplasmic reticulum to Golgi transport leads to the accumulation of large aggregates containing beta-COP in pancreatic acinar cells. *Mol Biol Cell* 4, 413–24.
59. Valencia, J. C., Watabe, H., Chi, A., Rouzaud, F., Chen, K. G., Vieira, W. D., Takahashi, K., Yamaguchi, Y., Berens, W., Nagashima, K., Shabanowitz, J., Hunt, D. F., Appella, E., and Hearing, V. J. (2006). Sorting of Pmel17 to melanosomes through the plasma membrane by AP1 and AP2: evidence for the polarized nature of melanocytes. *J Cell Sci* 119, 1080–91.
60. Raposo, G., Tenza, D., Murphy, D. M., Berson, J. F., and Marks, M. S. (2001). Distinct protein sorting and localization to premelanosomes, melanosomes, and lysosomes in pigmented melanocytic cells. *J Cell Biol* 152, 809–24.

61. Setty, S. R., Tenza, D., Truschel, S. T., Chou, E., Sviderskaya, E. V., Theos, A. C., Lamoreux, M. L., Di Pietro, S. M., Starcevic, M., Bennett, D. C., Dell'Angelica, E. C., Raposo, G., and Marks, M. S. (2007). BLOC-1 is required for cargo-specific sorting from vacuolar early endosomes toward lysosome-related organelles. *Mol Biol Cell* 18, 768–80.
62. De Luca, L., and Wolf, G. (1970). Vitamin A and mucus secretion. A brief review of the effect of vitamin A on the biosynthesis of glycoproteins. *Int Z Vitaminforsch* 40, 284–90.
63. Kirven, M. J., and Wolf, G. (1991). Synthesis and glycosylation of fibronectin in hepatocytes from vitamin A-deficient rats. *Mol Cell Biochem* 101, 101–14.
64. Rimoldi, D., Creek, K. E., and De Luca, L. M. (1990). Reduced mannose incorporation into GDP-mannose and dolichol-linked intermediates of Nglycosylation in hamster liver during vitamin A deficiency. *Mol Cell Biochem* 93, 129–40.
65. Heffernan, M., Lotan, R., Amos, B., Palcic, M., Takano, R., and Dennis, J. W. (1993). Branching beta 1-6N-acetylglucosaminetransferases and polylactosamine expression in mouse F9 teratocarcinoma cells and differentiated counterparts. *J Biol Chem* 268, 1242–51.
66. Amos, B., and Lotan, R. (1990). Modulation of lysosomal-associated membrane glycoproteins during retinoic acid-induced embryonal carcinoma cell differentiation. *J Biol Chem* 265, 19192–8.
67. Linder, S., Krondahl, U., Sennerstam, R., and Ringertz, N. R. (1981). Retinoic acid-induced differentiation of F9 embryonal carcinoma cells. *Exp Cell Res* 132, 453–60.
68. Garrigue-Antar, L., Hartigan, N., and Kadler, K. E. (2002). Posttranslational modification of bone morphogenetic protein-1 is required for secretion and stability of the protein. *J Biol Chem* 277, 43327–34.
69. Chamorey, A. L., Magne, N., Pivot, X., and Milano, G. (2002). Impact of glycosylation on the effect of cytokines. A special focus on oncology. *Eur Cytokine Netw* 13, 154–60.
70. Freimuller-Kreutzer, B., Nasheuer, H. P., and Muller, W. H. (1985). [Induction of alkaline phosphatase by retinoic acid]. *Biol Chem Hoppe Seyler* 366, 317–21.
71. Varki, A. (1993). Biological roles of oligosaccharides: all of the theories are correct. *Glycobiology* 3, 97–130.
72. Gu, J., and Taniguchi, N. (2004). Regulation of integrin functions by Nglycans. *Glycoconj J* 21, 9–15.
73. He, J. Y., Cao, L. H., Li, Y. B., and Zha, X. L. (1998). Study on the Mechanism of Fibronectin Adhesion to NIH3T3 cell Stimulated by Retinoic Acid. *Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao (Shanghai)* 30, 59–62.
74. Theos, A. C., Berson, J. F., Theos, S. C., Herman, K. E., Harper, D. C., Tenza, D., Sviderskaya, E. V., Lamoreux, M. L., Bennett, D. C., Raposo, G., and Marks, M. S. (2006). Dual loss of ER export and endocytic signals with altered melanosome morphology in the silver mutation of Pmel17. *Mol Biol Cell* 17, 3598–612.
75. Theos, A. C., Truschel, S. T., Raposo, G., and Marks, M. S. (2005). The Silver locus product Pmel17/gp100/Silv/ME20: controversial in name and in function. *Pigment Cell Res* 18, 322–36.
76. Mangasarian, K., Li, Y., Mansukhani, A., and Basilico, C. (1997). Mutation associated with Crouzon syndrome causes ligand-independent dimerization and activation of FGF receptor-2. *J Cell Physiol* 172, 117–25.
77. Hatch, N. E., Hudson, M., Seto, M. L., Cunningham, M. L., and Bothwell, M. (2006). Intracellular retention, degradation, and signaling of glycosylationdeficient FGFR2 and craniosynostosis syndrome-associated FGFR2C278F. *J Biol Chem* 281, 27292–305.
78. Franceschi, R. T., Yang, S., Rutherford, R. B., Krebsbach, P. H., Zhao, M., and Wang, D. (2004). Gene therapy approaches for bone regeneration. *Cells Tissues Organs* 176, 95–108.

Basic Science Research

The Relationship Between Concussion History and Post-Concussion on Neurocognitive Performance and Symptoms in Collegiate Athletes

Tracey Covassin, PhD, ATC,[1] David Stearne, PhD, ATC,[2] Robert Elbin, III, MA[1]

[1]*Department of Kinesiology, Michigan State University, East Lansing, MI,*
[2]*Department of Kinesiology, Temple University, Philadelphia, PA*

Abstract

Context: Athletes who participate in sports are at an inherent risk for sustaining concussions. Research examining the long-term consequences of sport-related concussion has been inconsistent in demonstrating lingering neurocognitive decrements that may be associated with a previous history of concussion.

Objective: To determine the relationship between concussion history and post-concussion neurocognitive performance and symptoms in collegiate athletes.

Design: A repeated measures design.

Setting: Multicenter analysis of collegiate athletes.

Patients or Other Participants: Fifty-seven concussed collegiate athletes (36 no history of concussion, 21 history of two or more concussions).

Interventions: The intervention consisted of a baseline neurocognitive test. Subjects who sustained a concussion were administered two follow-up tests at Day 1 and Day 5 post-injury. The independent variables were history of concussion (no history of concussion, two or more concussions) and time (baseline, Day 1 post-concussion, Day 5 post-concussion).

Main Outcome Measure(s): All subjects were administer an Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) neurocognitive test battery which measured verbal memory, visual memory, reaction time, visual processing speed, and 22 concussion symptom inventory.

Results: Results revealed a significant within-subjects effect (time) on ImPACT performance ($p < .001$), a between-subjects multivariate effect of group ($p < .001$), and a significant group-by-time interaction ($p = .034$). Athletes with a previous history of concussion performed significantly worse on verbal memory ($p = .01$) and reaction time ($p = .023$) when compared to athletes who did not report a previous concussion at Day 5 post-concussion. There were no significant group differences at Day 5 post-injury on visual memory ($p = .167$), processing speed ($p = .179$), and total concussion symptoms ($p = .87$).

Conclusion: The results of neurocognitive testing indicate that concussed collegiate athletes with a previous history of two or more concussions took longer to recover on verbal memory and reaction time than athletes without a previous history of concussion.

Key Words: multiple concussions, ImPACT, memory, reaction time.

Introduction

Sports-related concussion continues to warrant attention from sports medicine professionals. There are approximately 300,000 sport-related concussions reported each year.[1] An athlete who has suffered a concussion is at a three to six times greater risk for suffering a second concussion.[2–5] Long-term neurocognitive impairments are rarely associated with a single concussion, however multiple concussions have shown detrimental effects on athletes participating in boxing,[6] men's ice hockey,[7] and men's soccer.[8] Research findings on the cumulative effect of multiple concussions are equivocal with respect to significant lingering effects after injury. Furthermore, the majority of research on multiple concussions has been retrospective, using post-test only designs.

Several researchers have suggested that the cumulative effects of repeated concussions can have long-term consequences.[5, 9–13] Specifically, Guskiewicz et al.[9] found that an onset of dementia related symptoms may be a result of repetitive concussions in professional football players. In another study by Guskiewicz et al.,[5] collegiate football players with a history of three or more concussions were at a three times greater risk for suffering another concussion compared to athletes with no prior history of concussion. The proposed lingering or lasting effects from concussion have also been found in high school populations.[13] Iverson et al.[13] reported that high school athletes with a history of three or more concussions presented more symptoms and a significantly lower memory performance on neurocognitive testing at baseline than athletes with no previous history of concussion. In addition, Moser et al.[12] found that high school athletes with a history of two or more concussions demonstrated similar

cognitive performance when compared to high school athletes who had sustained a concussion in the past week. These results suggest that prior history of concussion may be associated with a prolonged recovery following subsequent concussions. Furthermore, these findings are consistent with previous research that suggest athletes with a history of three or more concussions showed decreased memory performance,[2] a greater number of post-concussion symptoms during baseline testing,[14] and three or four on-field markers.[15]

Several research efforts have examined the possible lingering effects of multiple concussions using subjects of different ages (i.e., high school and college) and the number of previous head injuries that have included one, two, or three concussions.[5, 12, 13] Wall et al.[16] examined cognitive performance in jockeys with a previous history of concussion compared to those with no previous history of concussion. After a three-month recovery period, jockeys with a history of sustaining concussions performed worse than their counterparts with no history of previous concussion on neurocognitive testing. In addition, younger jockeys with a history of concussion exhibited lower neurocognitive performance compared to older jockeys. This suggests that having a history of concussion may place an athlete at risk for developing long-term sequelae associated with post-concussion syndrome, and that younger athletes may be more vulnerable to long-term effects.

While the majority of current research demonstrates detrimental outcomes in athletes who have a prior history of concussion, there have also been studies that have demonstrated opposite findings. Iverson et al.[17] found that high school athletes with a history of two or more concussions demonstrated similar performance on processing speed and attention when compared to recently concussed athletes (i.e., within one week of injury). The researchers reported there were no significant effects for either of the groups across verbal memory, visual memory, reaction time, processing speed, and post-concussion symptom totals. Brogilo et al.[18] examined baseline computerized neurocognitive performance of collegiate athletes with a history of zero, one, two, or three previous concussions. This study reported no between-group differences on computerized neurocognitive test performance, which contrasts with previous research that suggests there may be lingering cognitive deficits from previous concussion.[5, 9–13, 19] However, Broglio et al.[18] did not examine the influence of concussion history on neurocognitive performance immediately following a concussion.

There is considerable debate among sports medicine professionals regarding diagnosis of and safe return-to-play guidelines following a concussion. To support the on-field diagnoses, computerized neurocognitive testing has become widely utilized as an objective method for determining subtle cognitive changes associated with post-concussion athletes.[20, 21] Although normative data exists for using neurocognitive testing without a baseline, it is highly recommended that baseline testing is administered in order for athletes to serve as their own control to be used for comparing baseline and post-concussion data.[20]

The majority of researchers examining the effect of history on concussion have limited their scope to football players[2, 3] and/or high school athletes.[2, 13] Furthermore, few studies have been conducted that examine neurocognitive deficits in athletes with a history of two or more concussions, or in collegiate athletes from a variety of sports. Therefore, the purpose of the present study was to investigate whether concussed collegiate athletes with a history of two or more concussions demonstrate neurocognitive impairments when compared to concussed athletes with no previous history of concussion.

Methods

A repeated measures design was used to compare baseline and post-concussion neurocognitive scores and post-concussion symptoms. The independent variables were history of concussion (no history of concussion, two or more concussions) and time (baseline, Day 1 post-concussion, Day 5 post-concussion). The dependent variables were verbal memory, visual memory, reaction time, visual processing speed, and individual and total concussion related symptoms.

Subjects

Participants comprising the sample were collegiate athletes from five northeastern universities participating in men's and women's basketball, soccer, lacrosse, and men's baseball, football, wrestling, and women's gymnastics, softball, volleyball, and cheerleading. The athletes selected for this study were practicing and competing during the 2002–2003 and 2003–2004 academic season. A total of 57 athletes sustained a concussion during the 2-year study (see Table 1). There were 36 athletes in the control group (20.55 ± 1.54 years, 167.41 ± 7.49 cm, 76.8 ± 16.17 kg.) and 21 who had a history of two or more concussions (21.10 ± 1.69 years, 169.19 ± 8.10 cm, 75.43 ± 11.02 kg.). Athletes with a history of one concussion were excluded from this study due to a small sample size of adequate data.

Table 1. Sport by Sex Information on Previous History of Concussions (N = 57)

Sport	No Previous Concussion	Two or More Previous Concussions
Women's Soccer	4	2
Men's Soccer	3	3
Women's Basketball	4	2
Men's Basketball	2	2
Women's Gymnastics	3	2
Women's Lacrosse	2	0
Men's Lacrosse	3	2
Football	5	4
Wrestling	3	2
Women's Volleyball	1	1
Baseball	1	1
Cheerleading	3	0
Softball	2	0

Instrumentation

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) describes a cerebral concussion as an altered mental state that may or may not include loss of consciousness.[22] In this study, the AAN Grading scale criterion was used by physicians and certified athletic trainers to assess athletes who suffered a concussion.

The Immediate Post-Concussion Assessment Cognitive Testing (ImPACT) version 2.0 (NeuroHealth System, LLC, Pittsburgh, PA) computer software program was used to assess neurocognitive function and concussion symptoms in this study. This program consists of six neurocognitive tests that evaluate attention, verbal recognition memory, visual working memory, visual processing speed, reaction time, numerical sequencing ability, and learning. These six neurocognitive tests yield four "composite" scores in the areas of verbal memory, visual memory, reaction time, and processing speed. Using reliable change indices, repeated administrations over a 2-week period revealed no practice effects.[23] In another study, Iverson et al.[24] reported one-week test-retest reliability coefficients as follows: 0.70 for verbal memory, 0.67 for visual memory, 0.79 for reaction time, and 0.86 for processing speed; within-subject comparisons revealed significant test-retest differences for only the processing speed composite scores. Schatz and colleagues[25] documented a combined sensitivity of 81.9% for ImPACT indices and total symptom score, and a specificity of 89.4%; positive likelihood ratio was approximately 8:1 and negative likelihood ratio was 2:1.[25]

Testing Procedures

Approval for the study and use of human subjects was granted from each participating university's Institutional Review Board. Likewise, permission was obtained from all team physicians, athletic directors, athletes, and certified athletic trainers at each participating institution. Each athlete was explained all test procedures and then completed the ImPACT neurocognitive test battery in a computer laboratory at their own university during preseason for baseline, Day 1 post-concussion, and Days 5 post-concussion.

Data Analysis

The ImPACT yields composite scores for verbal memory, visual memory, visual processing speed, and reaction time. A higher score by the athlete on verbal and visual memory, and processing speed indicates better performance. Verbal and visual memory scores are presented as a percentage of 100 and processing speed as a number composite score. A lower score on reaction time indicates better performance. The ImPACT also yields individual scores for concussion symptoms. Athletes were required to indicate if they were experiencing any of the 22 concussion symptoms at the times of their post-concussion testing. Concussion symptoms were rated on a 6-point Likert scale, with zero indicating not experiencing and five indicating severe. The scores are also summed to reflect a total symptom score.

A Chi-Square using Fisher's Exact Test was performed on concussion severity by history of concussion. A 3x2 mixed-factoral design MANOVA was conducted with time (baseline, one day, five days) and group (no history of concussion, two or more concussions) as the factors and the ImPACT indices as the dependent variables. A MANOVA was conducted on all concussion symptoms across days and groups. The statistical significance level was set at $P \leq .05$ for ImPACT indices and concussion symptoms. All analyses were conducted using SPSS version 15.1 (SPSS Inc, Chicago, IL).

Results

A total of 57 athletes sustained a concussion during the two-year study. On average all athletes were post-tested 1.2 days and 5.1 days after sustaining a concussion. Of the 36 concussed athletes who reported no previous history of concussion, 29 suffered a Grade I, four had a Grade II, and three sustained a Grade III concussion. The group of previously concussed athletes (i.e., history of concussion) included 15 athletes who sustained a Grade I, one athlete sustained a Grade II, and five athletes that sustained a Grade III concussion. A Chi-Square using Fisher's Exact Test revealed that athletes with a history of concussion did not have a greater likelihood of sustaining a more severe concussion (i.e., Grade II or III concussion) compared to a Grade I concussion ($X^2_{(2)} = 5.02$; $p = 1.0$). In terms of on-field markers, five athletes with a history of two or more concussions (23.8%) and three athletes with no prior history of concussion (8.3%) suffered loss of consciousness. Six athletes with a history of two or more concussions (28.6%) and four athletes with no prior history of concussion (11.1%) reported both retrograde and anterograde amnesia following injury.

There was no violation to the assumption of covariance matrix homogeneity in the data ($M = 96.47$, $F_{(78,5675.08)} = .911$, $p = .698$). Wilks' Lambda revealed a multivariate within-subjects effect (time) on ImPACT performance ($\Lambda = .559$, $F_{(2,54)} = 4.73$; $p < .001$). Wilks' Lambda indicated a between-subjects multivariate effect of group ($\Lambda = .709$, $F_{(1,55)} = 5.35$; $p < .001$), and a significant group-by-time interaction ($\Lambda = .720$, $F_{(2,54)} = 2.33$; $p = .034$).

Univariate post-hoc analyses were conducted at Day 1 and Day 5 post-concussion to determine between group differences on neurocognitive function. Results revealed no significant differences between the two concussion groups one day after incurring a concussion ($p = .34$). However, there were significant differences at Day 5 post-concussion between the two groups. More specifically, athletes with a history of two or more concussions demonstrated a significantly lower verbal memory score ($p = .01$) and slower reaction time ($p = .023$) when compared to athletes who did not have a history of concussion (see Table 2). Results did not indicate any significant group differences at Day 5 post-

injury on visual memory (p = .167) and processing speed (p = .179).

Table 2. ImPACT Scores Comparing Baseline to Five Days Post-Concussion for Athletes with No Previous History of Concussion and Athletes with Two or More Previous Concussions (n = 57)

ImPACT Index	No Previous Concussion	2 or More Previous Concussions	P
Verbal Memory			
Baseline	.87 (.10)	.89 (.10)	
Day 1	.80 (.11)	.81 (.09)	
Day 5	.88 (.08)	.81 (.09)	.01*
Reaction Time			
Baseline	.53 (.06)	.53 (.07)	
Day 1	.60 (.05)	.63 (.08)	
Day 5	.52 (.06)	.60 (.07)	.023*
Visual Memory			
Baseline	.78 (.12)	.74 (.13)	
Day 1	.64 (.11)	.71 (.12)	
Day 5	.74 (.13)	.72 (.11)	.167
Processing Speed			
Baseline	39.86 (5.82)	39.50 (6.97)	
Day 1	32.37 (7.96)	33.29 (6.32)	
Day 5	37.64 (7.03)	37.26 (7.00)	.179

*Significant at the .05 level for between groups at five days post-concussion.

Within group comparisons for athletes with a history of two or more concussions revealed significantly worse verbal memory (p = .002), visual memory (p < .001), processing speed (p = .001), and reaction time (p < .001) one day post-injury compared to their baseline scores. Similarly, within group comparisons for athletes who did not report a previous history of concussion revealed significantly lower scores for verbal memory (p = .01), visual memory (p < .001), processing speed (p < .001), and reaction time (p < .001) at Day 1 following a concussion compared to their baseline scores. All athletes with a previous history of concussion significantly improved by Day 5 post-injury compared to Day 1 post-injury on verbal memory (p = .001), visual memory (p < .001), processing speed (p < .001), and reaction time (p < .001). All athletes with no previous history of concussion significantly improved at Day 5 post-injury compared to Day 1 post injury for verbal memory (p = .002), visual memory (p < .001), processing speed (p < .001), and reaction time (p < .001). In addition, all athletes in both groups significantly improved back to their baseline scores at Day 5 post-concussion in all ImPACT measures and total concussion symptoms.

Table 3 contains the means and standard deviations of all 22 concussion symptoms at baseline, Day 1 post-test, and Day 5 post-test. Multivariate assessment of symptoms across days and groups revealed no significant differences between the groups (Λ = .636, $F_{(1,55)}$ = .886; p = .622), within-subjects effect (time) (Λ = .157, $F_{(2,54)}$ = 1.63; p = .171), or group-by-time interaction (Λ = .224, $F_{(2,54)}$ = 1.046; p = .493).

Reliable Change Indices (RCI) were calculated to determine clinically significant decreases at Day 1 and Day 5. The use of RCI's are well documented and a discussion of application and implementation of RCI's using ImPACT was recently published by Iverson and colleagues.[23] At Day 1 post-injury, 81% of athletes with a history of concussion had at least one reliable decline in reaction time (n = 17), 57% in processing speed (n = 12), 52% in verbal memory (n = 11), and 48% in visual memory (n = 10). At Day 1 post-injury, 56% of athletes with no history of concussion had at least one reliable decline in processing speed (n = 20), 50% in reaction time (n = 18), 44% in visual memory (n = 16), and 39% in verbal memory (n = 14). At Day 5, 57% of athletes with a history of concussion had at least one reliable decline in both reaction time (n = 12) and verbal memory (n = 12), 48% in processing speed (n = 10), and 29% in visual memory (n = 6). At Day 5, 31% of athletes with no history of concussion had at least one reliable decline in processing speed (n = 11), 22% in visual memory (n = 8), 14% in reaction time (n = 5), and 11% in verbal memory (n = 4).

Discussion

While research continues to examine how history of concussion relates to lasting neurocognitive effects, the current study adds evidence that indicates there may be areas of concern regarding recovery and neurocognitive performance. The purpose of this study was to examine the potential effects that history of concussion may have on recovery in concussed collegiate athletes. The overall findings of this study suggest that collegiate athletes who report a history of concussion may take longer to recover following concussion on neurocognitive measures of verbal memory and reaction time when compared to athletes with no history of concussion. More specifically, athletes with a history of concussion were significantly impaired in verbal memory and reaction time at Day 5 post-concussion when compared to their baseline. In addition, RCI's were calculated to determine clinical interpretation of change in neurocognitive performance. A larger percentage of athletes with a history of concussion were found to have at least one reliable decline in reaction time and verbal memory compared to athletes with no previous history of concussion at Day 5 post-injury.

These findings add to the literature that suggests that there may be neurocognitive deficits in athletes who report a history of concussion.[13] In a study examining collegiate football players, Guskiewicz et al.[5] indicated that a history of three of more concussions may place an athlete at a higher risk of incurring a concussion in the same season. Furthermore, Guskiewicz et al.[5] suggest that athletes with multiple concussions may take longer to recover from subsequent concussions. Iverson et al.[13] found that athletes with a history of concussion exhibited a significant decrease in memory, and

Table 3. All Concussion Symptoms by History of Concussion (n = 57)

Symptom	History of Concussion	Mean (SD) Baseline	Mean (SD) Day 1	Mean (SD) Day 5
Headache	No Previous	.67 (1.06)	1.86 (1.6)	1.25 (.72)
	2 or More	.62 (.87)	2.56 (1.4)	1.73 (1.01)
Nausea	No Previous	.31 (.82)	.71(.85)	.03 (.67)
	2 or More	0 (0)	1.11(1.2)	.05 (.78)
Vomit	No Previous	0 (0)	.05 (.21)	.25 (.84)
	2 or More	0 (0)	.28(.66)	.83 (1.04)
Balance Problems	No Previous	0 (0)	.85 (1.25)	.25 (.55)
	2 or More	.11 (.40)	1.28 (1.5)	.10 (.43)
Dizziness	No Previous	.14 (.35)	1.19 (1.40)	.29 (.72)
	2 or More	.25 (.64)	1.75 (1.46)	.39 (.80)
Fatigue	No Previous	1.14 (1.5)	1.75 (1.79)	.65 (.90)
	2 or More	.81 (1.25)	2.19 (1.78)	.95 (.71)
Trouble Falling Asleep	No Previous	.72 (1.1)	.97 (1.6)	.15 (.62)
	2 or More	.43 (1.03)	.57 (1.3)	.56 (.74)
Sleeping More than Usual	No Previous	.28 (.74)	.91 (1.6)	.61 (.59)
	2 or More	.38 (.86)	.57 (1.03)	.47 (.32)
Sleeping Less than Usual	No Previous	.05 (.21)	.81 (1.6)	.10 (.41)
	2 or More	.56 (.97)	.57 (1.39)	.16 (.32)
Drowsiness	No Previous	.69 (1.14)	1.94 (1.7)	.63 (81)
	2 or More	.71 (1.10)	2.19 (2.1)	.93 (.67)
Sensitive to Light	No Previous	.44 (.87)	.67 (.85)	.25 (.54)
	2 or More	.33 (.97)	1.78 (1.8)	.10 (42)
Sensitive to Noise	No Previous	.19 (.75)	.86 (1.4)	.52 (.76)
	2 or More	.10 (.31)	1.31 (1.83)	.78 (.65)
Irritability	No Previous	.44 (.88)	1.08 (1.66)	.68 (.64)
	2 or More	.71 (1.3)	1.05 (1.68)	.85 (.50)
Sadness	No Previous	.14 (1.02)	.50 (.87)	.15 (.60)
	2 or More	.39 (1.05)	.43 (1.16)	.33 (.69)
Nervousness	No Previous	.14 (.35)	.75 (1.2)	.09 (91)
	2 or More	.72 (1.34	.33 (.79)	.12 (1.04)
Feeling More Emotional	No Previous	.53 (.97)	.56 (1.13)	.51 (.84)
	2 or More	.19 (.60)	.52 (1.12)	.72 (.75)
Numbness	No Previous	.25 (.94)	.44 (1.05)	.05 (.15)
	2 or More	0 (0)	.10 (.30)	.07 (21)
Feeling Slowed Down	No Previous	.53 (.88)	2.03 (1.89)	.41 (.34)
	2 or More	.38 (.97)	1.95 (1.94)	.45 (.41)
Feeling Mentally Foggy	No Previous	.56 (.97)	2.06 (1.85)	.39 (.80)
	2 or More	.29 (.90)	1.95 (1.66)	.29 (.72)
Difficulty Concentrating	No Previous	.24 (.70)	1.67 (1.56)	.44 (.82)
	2 or More	.83 (1.2)	1.97 (1.89)	.51 (1.03)
Difficulty Remembering	No Previous	.50 (1.02)	1.29 (1.48)	.35 (.59)
	2 or More	.24 (.77)	1.08 (1.42)	.48 (.66)
Visual Problems	No Previous	.25 (.65)	1.11 (1.58)	.09 (.26)
	2 or More	0 (0)	.67 (.97)	.18 (.35)
Total Symptoms	No Previous	10.38 (9.49)	22.08 (17.8)	6.40 (6.8)
	2 or More	5.9 (7.67)	25.91 (21.05)	5.30 (7.0)

were more likely to demonstrate a major drop in memory performance than athletes with no previous concussion two days following injury. However, at five-days post-injury, Iverson et al.[13] found no differences in neurocognitive function between the two groups of athletes. These findings differ from the current study's results that report a difference in verbal memory and reaction time at Day 5 post-concussion between athletes who had a previous history of concussion and athletes with no previous history of concussion.

Recent research has identified an emerging pattern of neurocognitive decrements that commonly occur in the days following a concussion. These impairments include visual-motor reaction time, memory, and attention.[26–28] The current study's findings of verbal memory and reaction time impairments in athletes with a history of concussion at Day 5 post-injury add to this emerging pattern. A possible explanation for these verbal memory and reaction time impairments in athletes with a history of concussion may be due to increased

glycolysis which leads to increased lactate production following a subsequent head injury.[29] This increase in lactate production following brain injury may lead to secondary ischemic injury which may predispose the brain to repeat injury.[30] Furthermore, animal studies have shown decreased cerebral blood flow up to 10 days following a concussion.[31] Although only shown in animal models, this decreased cerebral blood flow that results from incurring a concussion, may be a mechanism that predisposes athletes with a history of concussion to take longer to recovery and/or further injury. However, these results have not yet been tested in human models and need further investigation.

In contrast to findings in the present study, Macciocchi et al.[27] found no cumulative effects in athletes who sustained two Grade I concussions greater than two weeks apart. However, a low sample size (n = 24) may have limited their ability to obtain statistical significance in their study. Collie et al.[32] examined baseline neurocognitive performance in professional athletes with a previous history of concussion. No differences were found in cognitive function on measures of memory, motor function, decision making, attention, and learning. A similar study by Broglio and colleagues[18] also reported no difference in baseline neurocognitive function in athletes with a previous history of concussion. However, these studies did not examine neurocognitive performance in athletes recovering from a concussion.

Sports medicine professionals often rely on symptom reporting of the concussed athlete. A study by Gaetz et al.[14] reported that junior ice hockey players who had a history of three or more concussions demonstrate a greater number of post-concussion symptoms than those without a history of concussion. However, in this study, concussed athletes did not demonstrate differences between groups on concussion symptoms even though they were still exhibiting neurocognitive impairments on reaction time and verbal memory. In a study by Kampen et al.,[33] 19% of athletes did not report concussion symptoms, however, these concussed athletes did exhibit neurocognitive impairments two days post-injury. A possible explanation may be due to athletes trying to minimize their symptoms so they can continue to participate in practice or competition. Another explanation may be due to athletes not being fully aware of their concussion symptoms, thus not reporting them to the certified athletic trainer or team physician. Therefore, it is important that a concussed athlete not be returned to practice or competition until he or she is symptom free and returns to their baseline neurocognitive test scores. Furthermore, these findings concur with Kampen et al.[33] that suggest neurocognitive testing is a valuable tool to use in conjunction with reported symptoms increasing the accuracy in making safe return-to-play decisions.

The existing research that has examined the history of concussion and its influence on concussion outcomes have largely focused on football, soccer, and ice hockey. Our study examined athletes who incurred multiple concussions across a variety of collegiate sports including both male and female collegiate athletes. The majority of the sports played by both males and females had a fairly equal distribution of concussions between sexes. Unfortunately, statistical analyses could not be conducted on sex due to insufficient sample size. Considering sex differences and concussion history may warrant future attention as females have been found to demonstrate more severe declines in measures of reaction time and more total symptoms following a concussion when compared to males.[34] Therefore, future studies should compare neurocognitive effects of multiple concussions between sports and between sexes. Further research is also needed on time of year of previous concussion and how sports medicine professionals manage concussions in relation to the time the athlete suffered a concussion.

There are certain limitations of the current study that should be addressed. First, concussion history data were self-reported. It was impossible to verify medical records to establish if a concussion was diagnosed by a physician. Second, many concussions go unreported and unrecognized by certified athletic trainers and physicians. Third, athletes self-reported their concussion symptoms and may have been motivated to minimize or under-report their symptoms to continue sport participation. Therefore, sports medicine professionals should continue with follow-up testing, and closely monitor those athletes still displaying neurocognitive impairments before returning them to the playing field.[35]

References

1. Thurman D, Guerrero J. Trends in hospitalization associated with traumatic brain injury. *JAMA.* 1999;282:954–957.
2. Guskiewicz KM, Weaver NL, Padua DA, Garrett WE, Jr. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med.* 2000;28:643–650.
3. Gerberich SG, Priest JD, Boen JR, Straub CP, Maxwell RE. Concussion incidences and severity in secondary school varsity football players. *Am J Public Health.* 1983;73:1370–1375.
4. Zemper ED. Two-year prospective study of relative risk of a second cerebral concussion. *Am J Phys Med Rehabil.* 2003;82:653–659.
5. Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA.* 2003;290:2549–2555.
6. Thomassen A, Juul-Jensen P, de Fine Olivarius B, Braemer J, Christensen A. Neurological, electroencephalographic and neurocognitive examination of 53 former amateur boxers. *Acta Neurol Scand.* 1979;60:352–362.
7. Tegner Y, Lorentzon R. Concussion among Swedish elite ice hockey players. *Br J Sports Med.* 1996;30:251–255.
8. Autti T, Spila L, Autti H, Salonen O. Brain lesions in players of contact sports. *Lancet.* 1997;349:1144.
9. Guskiewicz KM, Marshall SW, Bailes J, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery.* 2005;57:719–726.
10. Killam C, Cautin RL, Santucci AC. Assessing the enduring residual neuropsychological effects of head trauma in college athletes who participate in contact sports. *Arch Clin Neuropsychol.* 2005;20:599–611.
11. Moser RS, Schatz P. Enduring effects of concussion in youth athletes. *Arch Clin Neuropsychol.* 2002;17:91–100.
12. Moser RS, Schatz P, Jordan BD. Prolonged effects of concussion in high school athletes. *Neurosurgery.* 2005;57:300–306.
13. Iverson GL, Gaetz M, Lovell MR, Collins MW. Cumulative effects of concussion in amateur athletes. *Brain Inj.* 2004;18:433–443.

14. Gaetz M, Goodman D, Weinberg H. Electrophysiological evidence for the cumulative effects of concussion. *Brain Inj.* 2000;14:1077–1088.
15. Collins MW, Lovell MR, Iverson GL, Cantu RC, Maroon JC, Field M. Cumulative effects of concussion in high school athletes. *Neurosurgery.* 2002;51:1175–1179.
16. Wall SE, Williams WH, Cartwright-Hatton S, et al. Neuropsychological dysfunction following repeat concussions in jockeys. *J Neurol Neurosurg Psychiatry.* 2006;77:518–520.
17. Iverson GL, Brooks BL, Lovell MR, Collins MW. No cumulative effects for one or two previous concussions. *Br J Sports Med.* 2006; 40:72–75.
18. Broglio SP, Ferrara MS, Piland SG, Anderson RB, Collie A. Concussion history is not a predictor of computerised neurocognitive performance. *Br J Sports Med.* 2006;40:802–805.
19. Gronwall D, Wrightson P. Delayed recovery of intellectual function following minor head injury. *Lancet,* ii. 1974:605–609.
20. Guskiewicz KM, Bruce SL, Cantu R, et al. Recommendations on management of sport-related concussion: summary of the National Athletic Trainers' Association position statement. *Neurosurgery.* 2004; 55:891–895.
21. Notebaert AJ, Guskiewicz KM. Current trends in athletic training practice for concussion assessment and management. *J Athl Train.* 2005;40:320–325.
22. Practice Parameter: The management of concussion in sport (summary statement). Report of the Quality Standards Subcommittee. *Neurology.* 1997;48:581–585.
23. Iverson GL, Brooks BL, Collins MW, Lovell MR. Tracking neuropsychological recovery following concussion in sport. *Brain Inj.* 2006; 20:245–252.
24. Iverson GL, Lovell MR, Collins MW. Validity of ImPACT for measuring attention, processing speed following sports-related concussion. *J Clin Exp Neuropsychol.* 2005;27:683–689.
25. Schatz P, Pardini J, Lovell MR, Collins MW, Podell K. Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes. *Arch Clin Neuropsychol.* 2006;21:91–99.
26. Collie A, Makdissi M, Maruff P, Bennell K, McCrory P. Cognition in the days following concussion: comparison of symptomatic versus asymptomatic athletes. *J Neurol Neurosurg Psychiatry.* 2006;77: 241–245.
27. Macciocchi SN, Barth JT, Alves W, Rimel RW, Jane JA. Neuropsychological functioning and recovery after mild head injury in collegiate athletes. *Neurosurgery.* 1996;39:510–514.
28. Collins MW, Grindel SH, Lovell MR, et al. Relationship between concussion and neuropsychological performance in college football players. *JAMA.* 1999;282:964–970.
29. Giza C, Hovda D. The neurometabolic cascade of concussion. *J Athl Train.* 2001;36:228–235.
30. Becker D, Jenkins L. The pathophysiology of head trauma. In: Miller TA, Rowlands B, eds. *The Physiological Basis of Modern Surgical Care.* St. Louis, MO: Mosby; 1987:763–788.
31. Giza C, Hovda D. Ionic and metabolic consequences of concussion. In: Cantu RC, Cantu RJ, eds. *Neurologic Athletic and Spine Injuries.* Philadelphia, PA: WB Saunders Co; 2000:80–100.
32. Collie A, McCrory P, Makdissi M. Does history of concussion affect current cognitive status? *Br J Sports Med.* 2006;40:550–551.
33. Kampen D, Lovell MR, Pardini J, Collins MW, Freddie F. The "value added" of neurocognitive testing after sports-related concussion. *Am J Sports Med.* 2006;34:1630–1635.
34. Broshek DK, Kaushik T, Freeman JR, Erlanger D, Webbe F, Barth JT. Sex differences in outcome following sports-related concussion. *J Neurosurg.* 2005;102:856–863.
35. McCrea M, Hammeke T, Olsen G, Leo P, Guskiewicz KM. Unreported concussion in high school football players: implications for prevention. *Clin J Sport Med.* 2004;14:13–17.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

Arthroscopic Repair of Subscapularis Tendon: Clinical Results

PRADEEP SETTY, BA,[1] JOHN D. KELLY, IV, MD,[2] JOSEPH J. THODER, MD[2]

[1]*Touro University Nevada, College of Osteopathic Medicine, Henderson, NV,*
[2]*Department of Orthopaedic Surgery, Temple University, Philadelphia, PA*

Abstract

Purpose: To study the results of arthroscopic repair of the subscapularis tendon.

Methods: A retrospective study was performed on patients who had undergone arthroscopic repair of the subscapularis tendon. Patients were evaluated with the UCLA Shoulder Assessment Score and American Shoulder & Elbow Surgeons (ASES) Shoulder Scale questionnaires. Bear-Hug, Lift-Off and Napoleon (belly-press) tests were also used in evaluation. Data was all used to determine clinical results of arthroscopic subscapularis tendon repair. Patients were evaluated at a minimum of one year post-op.

Results: Senior author performed thirty-six arthroscopic subscapularis tendon repairs between January 2004 and July 2006. Twenty-two patients were available for follow-up. The pre-operative mean UCLA and ASES scores were 9.0 and 7.9 respectively. The post-operative mean UCLA and ASES scores were 29.8 and 26.0 respectively. Fifteen of the twenty-two patients recorded post-operative UCLA scores that fell into the "good" or "excellent" range. All twenty-two patients recorded that they felt "satisfied and better" after the surgery. Ten of the twenty-two patients had perfect scores of 30 for the ASES scale.

Conclusions: All patients recorded improvements in both the UCLA and ASES scales. Patients that undergo arthroscopic subscapularis tendon repair can have successful outcomes at a minimum one year post-op.

Introduction

Arthroscopic repair of rotator cuff tears has been increasing in popularity in recent years among Orthopaedic Surgeons. Among the reasons that this trend is occurring is due to several benefits involved with the minimal invasiveness of arthroscopy, including same day surgery and decreased recovery time. Arthroscopic rotator cuff repair also provides better pain relief, better post-operative mobility and higher patient satisfaction when compared to the previously used open shoulder surgery.[3] Additionally, a majority of patients needing shoulder surgery would prefer to undergo arthroscopic repair as opposed to open shoulder repair.[12] As a result, over the past two decades arthroscopy has been replacing open shoulder surgery in the repair of rotator cuff tears.

Prior to the common usage of arthroscopic repair on rotator cuff tears, subscapularis tendon tears were not frequently found. The growing use of this procedure, however, has made these tears much more easily recognized by Orthopaedic Surgeons. Kim and McFarland found that 19% of their patients who underwent arthroscopic repair of the rotator cuff had at least partial tears of the subscapularis tendon.[8] Another study by Bennett found that 27% of their patients had subscapularis tendon tears that were found through arthroscopy.[2] As arthroscopy continues to increase the discovery of subscapularis tendon tears, it is important to further study these tears.

The subscapularis tendon can present with a wide variety of pathologies. Among these are isolated tears, partial-thickness tears, anterosuperior tears with or without the involvement a supraspinatus tear, complete rotator cuff alvusion and rotator interval lesions involving instability of the long head of the triceps.[9] While non-surgical treatment can provide improvement, often times surgical intervention is needed. Open shoulder surgery has shown to have the potential of leading to atrophy and fatty infiltration of the subscapularis, thus leading to increased subscapularis dysfunction.[11] It has also been found that arthroscopy does not violate the subscapularis musculotendinous unit and as a result does not compromise the muscle's function or integrity.[11] As a result, arthroscopy has shown to be a superior technique in repairing general rotator cuff repairs, as well as locating and repairing subscapularis tendon tears specifically. The goal of this study is to confirm the overall clinical benefits of arthroscopic repair of the subscapularis tendon.

Materials and Methods

Demographics

Approval from the Institutional Review Board for a retrospective, prospective study was first obtained. Between January 2004 and July 2006, the senior author (JDK IV) performed 36 arthroscopic rotator cuff repairs that involved subscapularis tendon repairs. These patients had their charts, operative reports and arthroscopic pictures reviewed retrospectively. The data collected from these sources, which included the patient's age, date of surgery, size of tear and other rotator cuff tears also found during surgery, was entered

into a database for analysis. The size of the tear was recorded as either fraying, half torn, largely torn or massively torn. This was based upon the discretionary recordings of the senior author (JDK IV) during the surgeries. Ages were recorded as at the time of the surgery. Patients were asked during the physical examination about the method and timing of their injury as well as which their dominant arm was. Injury methods that occurred slowly over time were recorded as "degenerative." Post-operative times were calculated as the time between surgery and the physical examination. Of the 36 patients that had undergone arthroscopic rotator cuff repair, 22 were available for a follow up evaluation at a minimum one year post-op.

Questionnaires

Patients were first asked to fill out the UCLA Shoulder Form (Table 1) and American Shoulder and Elbow Surgeons (ASES) Shoulder Score (Table 2). In the case of the ASES Shoulder Score, only the "ASES Patient Self-Evaluation: Activity of Daily Living Questionnaire" section was used. These scores underwent a data analysis to compare them to their corresponding pre-operative scores. The pre-operative scores for the UCLA Shoulder Form and ASES Shoulder Score were then compared to their respective post-operative scores.

Table 1. UCLA Shoulder Assessment Score

Pain
__1__Present all of the time and unbearable; strong medication frequently
__2__Present all of the time but bearable: strong medication occasionally
__4__None or little at rest, present during light activities; salicylates frequently
__6__Present during heavy or particular activities only; salicylates occasionally
__8__Occasional and slight
__10_None

Function
__1__Unable to use limb
__2__Only light activities possible
__4__Able to do light housework or most activities of daily living
__6__Most housework, shopping, and driving possible; able to do hair and dress and undress, including fastening brassiere
__8__Slight restrictions only; able to work above shoulder level
__10_Normal activities

Active Forward Flexion
__5__150° or more
__4__120° to 149°
__3__90° to 119°
__2__45° to 89°
__1__30° to 44°
__0__Less than 30°

Strength of Forward Flexion
__5__Grade 5 (normal)
__4__Grade 4 (good)
__3__Grade 3 (fair)
__2__Grade 2 (poor)
__1__Grade 1 (muscle contraction)
__0__Grade 0 (nothing)

Satisfaction of the patient (post-op only)
__5__Satisfied and better
__0__Not satisfied and worse

Excellent: 34–35 Good: 29–33 Poor: <29

Table 2. American Shoulder & Elbow Surgeons Scoring System

ASES Patient Self-Evaluation of Daily Living Questionnaire

0 = unable to do
1 = very difficult to do
2 = somewhat difficult
3 = not difficult

Activity				
1. Put on a coat	0	1	2	3
2. Sleep on your painful or affected side	0	1	2	3
3. Wash back or do up bra in back	0	1	2	3
4. Manage toileting	0	1	2	3
5. Comb hair	0	1	2	3
6. Reach a high shelf	0	1	2	3
7. Lift 10 lbs above the shoulder	0	1	2	3
8. Throw a ball overhand	0	1	2	3
9. Do usual work	0	1	2	3
10. Do usual sport	0	1	2	3

Physical Examination

Patients then underwent a three point physical examination to determine the overall strength of the surgically repaired subscapularis muscle. The examinations were conducted by the senior author (JDK IV). The first part of this exam, the Bear-Hug Test, checks for small tears of the subscapularis tendon. It consists of the patient putting their surgically repaired extremity at 45 degrees of forward flexion while placing their palm on the opposite shoulder. The physician then applies an external rotational force the patient's wrist while the patient attempts to keep their initial position via resisted internal rotation. If the patient is unable to do this or shows weakness while attempting to do this, the test is then deemed as positive.[1, 4] The second portion of the physical exam is the Napoleon Test (a.k.a. Belly-Press Test). In this test, the patient places the palm of the affected extremity immediately below the xiphoid process. The patient then presses their palm in against their abdomen while keeping their elbow in the coronal plane. The test is deemed positive if the patient shows the inability to keep their elbow in the coronal plane or if the patient shows compensatory wrist-flexion.[6] The third and final portion of the exam is the Lift-Off Test. This test consists of the patient placing the dorsum of their surgically repaired extremity on the lower lumbar section of the back. The patient then attempts to actively life their hand off of their back. If the patient is unable to do this, the test is deemed positive.[7]

Results

UCLA shoulder scores improved from a pre-operative mean of 9.0 to a post-operative mean of 29.8. All 22 patients had a pre-operative score that fell into the "poor" category. Post-operatively, however, 14% of patients recorded "excellent" scores, 55% recorded "good scores" and 32% recorded "poor" scores. 86% of patients recorded either occasional or no pain post-operatively. 73% recorded that they were able to resume normal function with slight or no restrictions. All patients could actively forward flex their surgically repaired

shoulder to at least 90°, with 86% able to actively flex to 120° or more and 59% able to actively flex to 150° or more. 23% reported poor or worse strength of forward flexion, while 77% reported good or normal strength of forward flexion. 14% of patients had perfect UCLA scores of 35. All 22 patients had improvements in their UCLA scores and recorded that they were satisfied with the treatment and that their shoulder has improved.

ASES Scoring System scores improved from a pre-operative average of 7.9 to a post-operative average of 26.0. All patients had improvements in their ASES scores. Patients had the most trouble with washing their back, reaching a high shelf and lifting 10 lbs above their shoulder. Only 59% of patients recorded "not difficult" for each of these three categories. Patients had the least trouble with putting on a coat and managing toilet. 82% of patients recorded "not difficult" to putting on a coat, while the remaining 18% recorded "somewhat difficult." 91% recorded "not difficult" to managing toilet, with 5% recording "somewhat difficult" and "very difficult" each. 45% of patients had perfect post-operative ASES scores of 30.

The Bear-Hug test was recorded as positive on just 9.1% of patients. The Napoleon test (Belly-Press test) was also recorded as positive on 9.1% of patients while the Lift-Off test was positive on 14% of patients. No patient was positive on all three tests; however, three patients were positive on two different tests. Patient 3 was positive on the Bear-Hug and Lift-Off tests but negative on the Napoleon test. Patient 4 was positive on only the Lift-Off test. Patient 8 was positive on both the Lift-Off and Napoleon tests, but negative on the Bear-Hug test while Patient 19 was positive for the Bear-Hug and Napoleon tests but negative for the Lift-Off test. All

Table 3

Patient	Age	R/L	Dom. Arm	Time Before Surgery	Post-Op Time	Method of Injury	Tear Size	Other Tears
1	53	R	R	6 months	16 months	Fall	Massive	None
2	38	R	R	3 months	14 months	Fall	Large	Supraspinatus, Infraspinatus
3	75	R	R	24 months	25 months	Fall	Large	Supraspinatus, Infraspinatus
4	59	R	R	5 months	15 months	Fall	Large	None
5	62	R	R	24 months	17 months	Degenerative	Upper 1/2	None
6	67	R	R	24 months	32 months	Fall	Upper 1/2	Supraspinatus, Infraspinatus
7	65	R	R	24 months	27 months	Degenerative	Fraying	None
8	62	R	R	13 months	33 months	Pulled Shoul.	Large	Supraspinatus, Infraspinatus
9	65	R	L	12 months	22 months	Throwing	Upper 1/2	Supraspinatus
10	50	R	R	1 month	12 months	Fall	Large	None
11	59	L	R	2 months	35 months	Fall	Upper 1/2	Supraspinatus, Infraspinatus
12	53	R	R	2 months	15 months	Fall	Large	Supraspinatus, Infraspinatus
13	59	L	R	2 months	21 months	Degenerative	Fraying	Supraspinatus
14	60	L	R	4 months	12 months	Lifting	Fraying	Supraspinatus, Infraspinatus
15	53	R	L	1 month	38 months	Fall	Fraying	Supraspinatus, Infraspinatus
16	54	R	R	24 months	25 months	Lifting	Lower 1/2	Supraspinatus
17	75	R	R	2 months	13 months	Lifting	Massive	Supraspinatus, Infraspinatus
18	57	L	L	4 months	24 months	Reaching Up	Upper 1/2	Supraspinatus
19	72	R	R	6 months	21 months	Dislocation	Large	Supraspinatus, Infraspinatus
20	55	R	R	4 months	33 months	Fall	Upper 1/2	Supraspinatus
21	53	R	R	3 months	42 months	Fall	Upper 1/2	Supraspinatus, Infraspinatus
22	75	R	R	10 months	13 months	Fall	Massive	Infraspinatus

Table 4

Patient #	Pre-Op UCLA	Post-Op UCLA	Pre-Op ASES	Post-Op ASES	Bear-Hug	Lift-Off	Napoleon
1	10	25	9	23	–	–	–
2	7	30	9	28	–	–	–
3	8	27	2	17	+	+	–
4	11	27	10	25	–	+	–
5	6	31	8	30	–	–	–
6	7	33	14	28	–	–	–
7	8	30	8	30	–	–	–
8	8	31	6	30	–	+	+
9	13	35	12	30	–	–	–
10	2	27	0	21	–	–	–
11	12	28	8	27	–	–	–
12	9	33	12	26	–	–	–
13	11	30	2	9	–	–	–
14	19	30	9	26	–	–	–
15	10	15	1	17	–	–	–
16	4	35	1	30	–	–	–
17	11	32	9	30	–	–	–
18	6	33	3	30	–	–	–
19	12	27	25	30	+	–	+
20	2	35	0	30	–	–	–
21	2	33	10	30	–	–	–
22	2	29	21	24	–	–	–

other patients were negative for all three tests. The two patients who were positive for the Bear-Hug test averaged post-operative UCLA and ASES scores of 27 and 23.5 respectively. These were lower than the overall post-operative UCLA and ASES scores of the entire group which were 29.8 and 26.0 respectively. The three patients with positive Lift-Off tests also averaged lowered post-operative UCLA and ASES scores, 28.3 and 24 respectively. The two patients with positive Napoleon tests averaged post-operative UCLA and ASES scores of 29 and 30 respectively.

The dominant shoulder was also the surgically repaired shoulder in 17 of the 22 patients. All five patients who injured their non-dominant shoulder had negative results for all three physical tests. However the 17 patients with injuries to their dominant shoulder had an overall increase in their average UCLA scores from 6.8 pre-operatively to 30.5 post-operatively. This is a greater increase than the non-dominant shoulder patients who had their average UCLA score increase from 13.0 pre-operatively to 27.6 post-operatively. The dominant shoulder patient also increased their average ASES scores from 8.4 pre-operatively to 27.2 post-operatively. This was also higher than the non-dominant patients who had their ASES score increase from a pre-operative average of 6.4 to a post-operative average of 21.8.

Seventeen of the 22 patients also had repair of at least one other rotator cuff tendon during the arthroscopy. Among those 17 patients, 11 had both the supraspinatus and infraspinatus also repaired. Included in these 11 patients were all three patients that had positives for at least two strength tests. These patients also averaged post-operative UCLA and ASES scores of 29.8 and 26.0 respectively. Each was similar to the overall post-operative averages. 5 patients had only the supraspinatus repaired in addition to the subscapularis. All 5 of these patients were negative for all three strength tests. They also had an average a post-operative average of 33.6 for the UCLA score and 25.8 for the ASES score. Only 1 patient had just the infraspinatus and subscapularis repaired. This patient was negative for all three strength tests and recorded a post-operative UCLA score of 29 and ASES of 24. Among the five patients that had no other rotator cuff repair, only Patient 4 was positive for any of the strength tests (Lift-Off only). These patients had a post-operative UCLA average of 28 and ASES average of 25.8.

Massive tears were described in 3 of the 22 total patients. None of these patients were positive for any of the three strength tests. They averaged 28.7 on the UCLA scale and 25.7 on the ASES scale post-operatively. Seven patients were described as having large tears. All four patients who had any positive strength tests had large tears. They also averaged post-operative scores of 28.9 on the UCLA and 25.3 on the ASES scale. Seven patients had tears of the upper half of the subscapularis tendon. Among these, none had any positive strength tests and had a post-operative UCLA average of 32.6 and ASES average of 29.3. Both of these were above their corresponding overall averages. Only one patient had a lower half tear of the subscapularis tendon. That patient had perfect post-operative UCLA and ASES scores of 35 and 30 respectively. The remaining four patients had fraying of the subscapularis tendon. They had low post-operative averages of 26.3 for the UCLA scale and 20.5 for the ASES scale.

Patient ages ranged from 38 to 75 with a mean of 60.1. The time between the patient's actual injury and surgery ranged from 1 to 24 months with a mean of 9.1 months. Additionally, the time between surgery and the physical examination ranged from 12 to 42 months with a mean of 22.3 months. Among the 22 patients examined, 12 sustained

their injuries from a fall, 4 had their injuries occur over time, 3 occurred while lifting items, 1 occurred during a dislocation, 1 occurred while pulling an object and 1 occurred while reaching up for an object.

Discussion

This study addresses the clinical results of arthroscopic repair on subscapularis tendons. The growing popularity of arthroscopy in rotator cuff repairs has led many Orthopaedic Surgeons to better identify subscapularis tendon tears.[8, 2] Additionally, arthroscopy has also shown to have better results in repairing rotator cuff injuries than did the previously used open-shoulder surgical technique.[11] As a result, it is important to continually evaluate the levels of success that are being reached with arthroscopic repairs of the subscapularis tendon.

Patients in this study generally had excellent results. All 22 patients showed improved post-operative UCLA and ASES scores. Additionally, according the post-operative UCLA scores, all 22 patients also claimed to be feeling "satisfied and better." 14% of patients reported perfect UCLA scores, while 68% fell into the categories of "good" or "excellent" according the UCLA scale's grading chart. The remaining 32% did, however, fall into the "poor" category, but these patients still showed improved scores from their pre-operative scores. 45% of patients recorded perfect post-operative ASES scores as well. In additional all 22 patients showed post-operative improvement in their ASES scores. The results of these two surveys suggest that shoulder function and range of motion can be improved through arthroscopic repair of the subscapularis tendon.

Only 18% of patients recorded a positive for any of the three strength tests used in this study. No patients recorded positives for all three tests. In fact, 82% of patients showed negative all of three tests. 91% of patients reported negative Bear-Hug tests.

The Napoleon test also came out negative in 91% of patients. 86% of patients were found to have negative Lift-Off tests as well. This suggests that arthroscopic repair can improve the overall strength of a damaged subscapularis tendon.

Patients also showed higher increases in their UCLA and ASES scores when the surgically repaired shoulder was their dominant shoulder. In fact the average post-operative UCLA score among patients that had their dominant shoulder surgically repaired was 30.5, which falls under the "good" category according the UCLA grading scale. Patients who had their non-dominant shoulder repaired averaged 27.2, which falls into the "poor" category, on their post-operative UCLA scores.

Conclusion

This study has demonstrated that arthroscopy can be successful in improving the range of motion and function of shoulders in which the subscapularis tendon has been torn. In addition, it also demonstrates that arthroscopy can be used as a way to successfully restore strength to the subscapularis tendon.

References

1. Barth JR, Burkhart SS, De Beer JF. The Bear-Hug Test: A New and Sensitive Test for Diagnosing A Subscapularis Tear. *Arthroscopy* 2006. 22(10):1070–5.
2. Bennett WF. Subscapularis, Medial, and Lateral Head Corocohumeral Ligament Insertion Anatomy. Arthroscopic Appearance and Incidence of "Hidden" Rotator Interval Lesions. *Arthroscopy* 2001. 17(2): 173–180.
3. Buess E, Steuber KU, Waibl B. Open Versus Arthroscopic Rotator Cuff Repair: A Comparative View of 96 Cases. *Arthroscopy* 2005. 21(9): 597–604.
4. Burkhart SS, Tehrany AM. Arthroscopic Subscapularis Tendon Repair: Technique and Preliminary Results. *Arthroscopy* 2002. 18(5):454–63.
5. Flury MP, John M, Goldhahn J, Schwyzer HK, Simmen BR. Rupture of the Subscapularis Tendon (Isolated or in Combination with Supraspinatus Tear): When Is a Repair Indicated? *J Shoulder Elbow Surg* 2006. 15(6):338–42.
6. Gilmer B, Edwards TB, Gartsman G, O'Connor DP, Elkousy H. Normalization of the Subscapularis Belly-Press Test. *J Shoulder Elbow Surg* 2007. 14(1):1–4.
7. Greis PE, Kuhn JE, Schultheis J, Hintermeister R, Hawkins R. Validation of the Lift-Off Test and Analysis of Subscapularis Activity During Maximal Internal Rotation. *Am J Sports Med* 1996. 24(5):589–93.
8. Kim Tk, Rauh PB, McFarland EG. Partial Tears of the Subscapularis Tendon Found During Arthroscopic Procedures on the Shoulder: A Statistical Analysis of Sixty Cases. *Am J Sports Med* 2003. 31(5):744–50.
9. Lyons RP, Green A. Subscapularis Tendon Tears. *J Am Acad Orthopaedic Surg* 2005. 13(5):353–63.
10. Romeo AA, Bach BR Jr, O'Halloran KL. Scoring Systems for Shoulder Conditions. *Am J Sports Med* 1996. 24(4):472–6.
11. Scheibel M, Nikulka C, Dick A, Schroeder RJ, Popp AG, Haas NP. Structural Integrity and Clinical Function of the Subscapularis Musculotendinous Unit After Arthroscopic and Open Shoulder Stabilization. *Am J Sports Med* 2007. 35(7):1153–61.
12. Sperling JW, Smith AM, Cofield RH, Barnes S. Patient Perceptions of Open and Arthroscopic Shoulder Surgery. *Arthroscopy* 2007. 23(4): 361–6.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

Use of a Single Dose of Intraoperative Heparin in Both Total Hip and Total Knee Arthroplasties in Reducing the Incidence of Deep Venous Thrombosis (DVT) as Evaluated by Doppler Ultrasound

Rupam Das, BS,[3] Easwaran Balasubramanian, MD,[1] Joseph Torg, MD,[1] Joseph Thoder, MD,[1] John P. Gaughan, PhD[2]

[1]*Department of Orthopaedic Surgery,* [2]*Biostatistics Consulting Center,* [3]*School of Medicine, Temple University, Philadelphia, PA*

Abstract

Deep Venous Thrombosis remains a common complication in Total Joint Arthroplasty even as anticoagulative treatment has become more aggressive. Heparin has been used intraoperatively at Temple University Hospital by a single surgeon since 2004 while other surgeons at Temple use more traditional prophylactic therapy including warfarin and enoxaparin. The surgeon using intraoperative heparin still uses postoperative prophylaxis also. Patient charts from patients undergoing THA and TKA either with intraoperative heparin added to standard prophylaxis or with standard prophylaxis alone were examined for occurrence of DVT. No statistical significant difference was observed in the incidence of DVT between patients receiving standard postoperative coagulation as compared to those also given intraoperative heparin. Also, the incidence of DVT was lower in THA compared to TKA regardless of what anticoagulant therapy was used. It appears that a dose of 1000 U intraoperative heparin does not improve anticoagulative therapy in TJR.

Introduction

Deep venous thrombosis (DVT) has been reported as the most common complication in Total Joint Replacement (TJR). Without prophylactic treatment, the incidence of DVT in total hip arthroplasty (THA) has been reported to be between 40% and 70%.[1] And for total knee arthroplasty (TKA) the incidence of DVT has been reported as high as 88% after surgery.[2] Thrombosis in the venous system is a risk for ischemia to local tissue but more critically has the potential to become a pulmonary embolus (PE), a potentially life threatening complication. Even with standard prophylactic treatment PE remains the most common cause of death after THA.[3]

Venous thrombosis occurs primarily because of one or more of the following three reasons: blood stasis, injury to the endothelial lining of blood vessels or hypercoagulation.[1] The current prevention strategy for DVT in TJR is multimodal (mechanical/pharmacological) postoperative prophylaxis to both reduce the stasis and coagubility of the patient's blood. The typical pharmacological treatment generally includes either warfarin, a low-molecular-weight heparin such as enoxaparin, or aspirin.[1, 2] For mechanical prophylaxis elastic compression stockings are typically worn on both lower limbs and movement of the surgically repaired limb is initiated shortly after surgery.[1] At Temple University Hospital, the standard care for DVT prophylaxis is to use Warfarin with an INR of between 1.5 and 2.5 bridged with Lovenox (enoxaparin) which is combined with pneumatic compression and early limb movement. We attempted to determine whether or not using intraoperative heparin at the most thrombophyllic time will lower the incidence of DVT thus lowering the chances that a patient will develop a life threatening PE.

The results of previous studies have been inconsistent as to whether or not intraoperative heparin is effective in reducing the incidence of DVT. Furthermore, there have been differences in administration of heparin as well as differences in other DVT prophylactics used in addition to intraoperative heparin. Also there remains the possibility that there are differences in effectiveness of heparin between patients who have undergone THA and TKA. These are reasons for evaluating the use of intraoperative heparin. The purpose of this study is to further evaluate whether or not using intraoperative heparin is effective by evaluating outcomes of its use in both TKA and THA.

Methods

For the purpose of this retrospective study, after gaining IRB approval, patient charts were reviewed from patients who underwent TJR between October, 2005 and May 31, 2007 at both Temple University Hospital and Northeastern Hospital with the goal of assessing the outcomes of patients who underwent surgery with either intraoperative heparin or with standard DVT prophylaxis. Patients undergoing surgery

with intraoperative heparin still received standard DVT prophylaxis postoperatively. A total of 411 procedures were identified as TJR of which 209 were performed with the use of intraoperative heparin and 201 used standard postoperative anticoagulation prophylaxis alone. Each patient who received intraoperative heparin received 1000 U either prior to deflation of the tourniquet in TKA or prior to reaming of the femoral canal in THA. These are moments during the surgery that have been identified as being the most thrombophyllic. If it was a bilateral TKA or THA then doses of 1000 U of heparin were given at the appropriate times for both sides being operated on. Each of the procedures in which intraoperative heparin was used were all performed by a single surgeon, Easwaran Balasubramanian, at Temple University Hospital or Northeastern Hospital.

For both study and control groups, we recorded what type of anesthesia was used; the age, weight and height of the patient; what procedure was performed; the length of surgery; the tourniquet time for TKA; and outcome measurements. Outcome measurements included any complications (PE, hemorrhage, bleeding, infection, myocardial infarction, stroke) the patient might have suffered and also the results of a Doppler Ultrasound indicating whether or not the patient had a DVT identified. The Doppler Ultrasound was performed before the patient was discharged. Also if a DVT was suspected at a later time a Doppler was performed and this was recorded. In addition, for the study group, the heparin amount and time of administration was recorded. The incidence of DVT was compared between patients who received intraoperative heparin and those that did not. We also looked to see if there was any difference in the effects of intraoperative heparin between TKA and THA.

Patients

Data from a total of 263 patient charts of patients who underwent total joint arthroplasty either at Temple University Hospital or Northeastern Hospital was included in this study. Patients were not included if the results of Doppler Ultrasound could not be found. The average age of all persons having total joint arthroplasty and who did not have heparin administered intraoperatively was 64.2 years and the average age of those persons receiving intraoperative heparin was 63.6 years. The average BMI of patients in the intraoperative heparin group and the non intraoperative group was 31 and 33 respectively.

Results

The results show that there is no significant difference in the incidence of DVT between groups of patients receiving intraoperative heparin as compared to those receiving standard anticoagulant prophylaxis. This can be seen on Figure 1 which shows the only statistically significant factors affecting the incidence of DVT were the Hospital where the surgery was performed and the type of surgery performed (THA vs. TKA).

The percentage of patients in which a DVT was identified is illustrated on Figure 2. There were 33 (21%) out of 155 patients who were reported to having a DVT in the intraoperative heparin group. In the standard prophylactic group 16 (15%) out of 108 patients were identified as having a DVT. For THA patients who received intraoperative heparin 5 (11%) out of 45 had a DVT identified by Doppler ultrasound. This compared to 2 (8%) out of 26 persons having undergone THA with standard anticoagulant prophylaxis with an identified DVT. For TKA patients who received intraoperative heparin 29 (26%) out of 110 had an identified DVT. This compared to 14 (18%) out of 78 persons who had a TKA with standard anticoagulant prophylaxis in which there was an identified DVT.

There is also little difference between the incidences of above the knee DVT post TKA in both surgical groups with the incidence for both approaching 3%. The incidence of above the knee DVT post THA was higher in the intraoperative group (6%) compared to patients who received standard anticoagulant prophylaxis (0%). However, no statistical difference was observed. It should be mentioned that there were only two (8%) post THA DVT's identified in the standard prophylactic group. The incidence of above the knee DVT is shown on Figure 3.

There was no difference in the ages of persons with or without a DVT in the intraoperative heparin group with the average age of those with a DVT and this can be seen on Figure 4. However, there was a slight difference in the ages of persons with a DVT in the standard prophylactic group with the average age of a person with an identified DVT being 69.5 years compared to 63.3 years for those with no identifiable DVT.

While there was statistical difference in the incidence of DVT between procedure types ($p = 0.02$) intraoperative heparin seems to have no clinical apparent affect in either procedure type. Although patients that received heparin had an average surgery length of 100 minutes vs. 172 minutes in the non intraoperative heparin group, there was no change in the incidence of DVT seen associated with length of surgery ($p = 0.08$).

There were few complications in either group other than venous thrombosis. It should be mentioned that no patients died from complications with surgery. The complications in the group who received intraoperative heparin included 2 patients with pulmonary emboli, 1 patient with pulmonary edema, 2 patients with anemia, one person with persistent wound drainage and one patient with a wound hematoma. The complications in the group receiving standard prophylactic care included one patient with persistent wound drainage, one patient with a right sided stroke involving the posterior and middle cerebral arteries, one patient with seizure like activity, and one person with a mild myocardial infarction.

Parameter	DF	Estimate	Standard Error	Wald Chi-Square	P	Odds Ratio Estimate	95% Confidence Limits	
DTB	1	0.7477	0.3367	4.9303	**0.0264**	2.112	1.092	4.086
BALAS	1	0.4156	0.3025	1.5629	0.2113	1.515	0.790	2.907
DRUNG	1	-0.3126	1.0816	0.0835	0.7746	0.732	0.086	6.224
MICRAL	1	-1.1470	0.6220	3.4004	0.0652	0.318	0.094	1.075
MOSAN	1	-0.3369	0.3643	0.3545	0.5515	0.714	0.236	2.158
VANET	1	0.4014	0.4403	0.8309	0.3620	1.494	0.630	3.541
DEX	1	-0.2268	0.3358	0.0062	0.9372	0.974	0.505	1.879
PROC	1	-0.9398	0.4335	4.7002	**0.0302**	0.391	0.167	0.914
SIDE	1	-0.1706	0.3146	0.2904	0.5900	0.843	0.453	1.568
AGE	1	0.0198	0.0138	2.0420	0.1510	1.020	0.993	1.048
ABSI	1	-0.2413	0.3166	0.5808	0.4460	0.786	0.422	1.461
BMI	1	0.00256	0.0224	0.0134	0.9079	1.003	0.959	1.048
DURATION	1	-0.00567	0.00323	3.0801	0.0793	0.994	0.988	1.001
HEP	1	0.4527	0.3323	1.8560	0.1731	1.573	0.820	3.016
HEPDOS	1	0.000505	0.000329	2.3489	0.1255	1.001	1.000	1.001
TOURTIM	1	0.00276	0.00749	0.1361	0.7121	1.003	0.988	1.019

Figure 1. Outcome = DVT, Univariate analysis

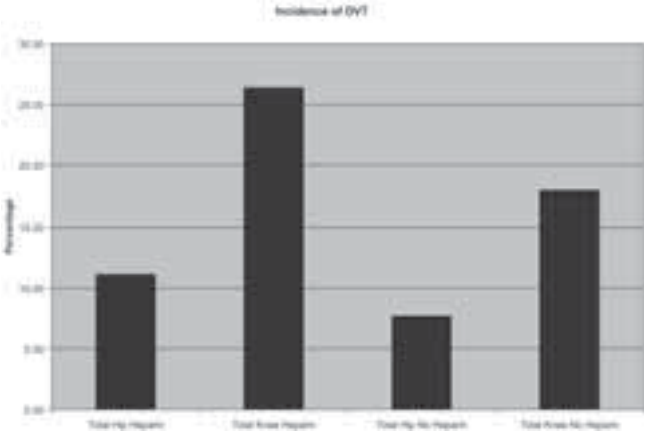


Figure 2. Incidence of DVT in total hip vs. total knee with and without intraoperative heparin.

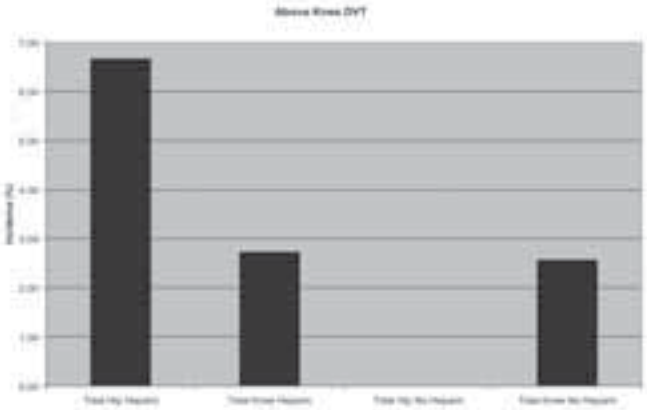


Figure 3. Incidence of above the knee DVT in THA and TKA for both patients receiving intraoperative heparin and those receiving standard prophylaxis.

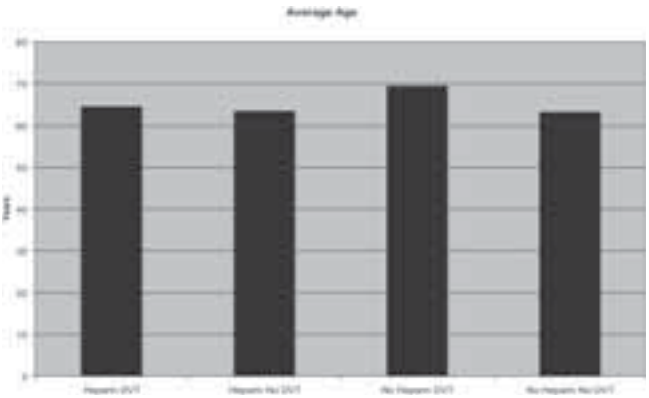


Figure 4. Average age of persons with and without a DVT in both the intraoperative heparin and standard prophylaxis groups.

Discussion

DVT prophylaxis has changed since the late 1980s and early 1990s when it was common to administer aspirin postoperatively as the sole DVT prophylactic treatment. Current standard care at most places is to use either warfarin or a LMWH in addition to pneumatic compression and very early limb movement postoperatively. The use of aspirin alone has been abandoned by most physicians although some do use aspirin combined with pneumatic compression and early limb movement.

Several studies at the Hospital for Special Surgery indicate that using heparin intraoperatively reduced the incidence of DVT and associated PE significantly.[1, 3–5] These studies however, compared the incidence of DVT when using heparin to a control group given aspirin postoperatively. Thrombogenesis has been reported to be most active

in THA during surgery on the femur, when several of the femoral vessels become obstructed because of the extreme flexion and rotation of the femur.[5–7] For Total Hip Arthroplasty (THA), Sharrock et al. demonstrated that the greatest risk for activation of the clotting cascade occurs during the insertion of the femoral component of the hip replacement.[5]

Previous studies have shown intraoperative heparin to show promise in decreasing the incidence of DVT. Heparin works by increasing the activity of antithrombin III which is a natural neutralizer for various coagulative factors in the coagulation cascade (Factors IIa, VIIa, IXa, Xa, and Xia — see Figure 5). Factor IIa is thrombin so thrombin-antithrombin complexes are the result of antithrombin III's activity. Fibrinopeptide A, prothrombin F1-2, D-dimer and thrombin-antithrombin complexes have all been shown to significantly elevate after reaming of the femoral canal in THA.[5] Sharrock et al. showed intraoperative heparin to be effective in lowering fibrinopeptide A and prothrombin F1+2 during surgery.[3] Fibrinopeptide A is a marker for the rate of conversion of fibrinogen to fibrin by thrombin and prothrombin F1+2 is an index for thrombin generation. Sharrock et al. also reported, in a separate study, a significant drop in DVT using a fixed dose

Figure 5. Coagulation Cascade. Heparin potentiates the activity of Antithrombin III which inhibits the formation of Factors IIa, VIIa, IXa, Xa, and XIa. (http://www.frca.co.uk/article.aspx?articleid=100805)

regimen (multiple doses) of Heparin intraoperatively when compared to their control group.[1] Only 8% of patients that received heparin were found to have DVT compared with 24% of patients in the control group.[1]

In our study, we were not able to show any reduction in incidence of DVT using intraoperative heparin as opposed to the standard prophylactic care. It appears that the combination of initial enoxaparin and prolonged warfarin with an INR goal of between 1.5 and 2.5 seem to reduce the incidence of DVT to a point that adding intraoperative heparin has no clinically observed benefits. The more recent studies using intraoperative heparin have tended to show this also.

While it is notable that the incidence of DVT is lower in THA compared to TKA there was no statistical difference due to the use of intraoperative heparin so this is merely a byproduct of the procedure being performed.

And though earlier studies have shown promise with intraoperative heparin there are some later studies that have shown little benefit to adding intraoperative heparin to DVT prophylaxis. Mant et al. reported no significant improvements using intraoperative heparin over using a postoperative low-molecular-weight heparin (enoxaparin) for total TKA patients.[8] Also a study by Westrich et al. showed no significant benefits using intraoperative heparin in addition to postoperative aspirin and pneumatic foot compression in TKA.[2] In a separate study by Westrich et al. the effects of intraoperative heparin were assessed by measuring DVT using Magnetic Resonance Venography (MRV).[9] Their results showed lower ipsilateral femoral DVT in patients receiving intraoperative heparin.[9] However, overall there was no statistically significant difference in the incidence of DVT in patients receiving heparin and patients in the control group, with patients receiving intraoperative heparin having a slightly higher incidence of pelvic thrombi.[9] This could be evidence that thrombi form later in the deep pelvic veins than in the deep femoral veins.

The reason that our study may have shown no reduction in the incidence of DVTs using intraoperative heparin may be due that warfarin and/or enoxaparin already significantly reduce the incidence of DVT when compared to aspirin or no DVT prophylaxis. In addition patients begin movement of the limb early and begin physical therapy almost immediately postoperatively. Intraoperative heparin at this dosage seems to offer no benefit over the standard DVT prophylactic treatment. Heparin has a relatively short half-life, about 90 minutes, and so the benefits of heparin as an anticoagulant are only realized at the most thrombophyllic time of surgery. This may indicate that reducing pro-thrombic factors during surgery has little to no effect on clotting potential that remains later postoperatively.

Conclusions

Our study seems to be more in line with some of the later research that has been done relating to intraoperative heparin use. The move to more aggressive postoperative anticoagulation therapy appears to have decreased the incidence to a point that the effect of adding intraoperative heparin has no observable effects. It is possible that a higher dose of intraoperative heparin could have an effect as some of the earlier studies used variable amounts of heparin and showed increased response with higher doses but this may come at a cost with increased risks from higher doses of heparin.

References

1. Sharrock NE, Brien WW, Salvati EA, et al. The effect of intravenous fixed-dose heparin during total hip arthroplasty on the incidence of deep-vein thrombosis. *J Bone and Joint Surgery* 72:1456–61, 1990.
2. Westrich GH, Menezes A, Sharrock NE, et al. Thromboembolic Disease Prophylaxis in Total Knee Arthroplasty Using Intraoperative Heparin and Postoperative Pneumatic Foot Compression. *J Arthroplasty* 14(6):651–56, 1999.
3. Sharrock NE, Go G, Sculco TP, et al. Dose Response of Intravenous Heparin on Markers of Thrombosis During Primary Total Hip Replacement. *J Anesthesiology* 90:981–87, 1999.
4. Huo MH, Salvati EA, Sharrock NE, et al. Intraoperative Adjusted-Dose Heparin Thromboembolic Prophylaxis in Primary Total Hip Arthroplasty. *J Clinical Orthopaedics and Related Research* 277:188–96, 1992.
5. Sharrock NE, Go G, Harpel PC, et al. Thrombogenesis During Total Hip Arthroplasty. *J Clinical Orthopaedics and Related Research* 319:16–27, 1995.
6. DiGiovanni CW, Restrepo A, Della Valle AG, et al. The Safety and Efficacy of Intraoperative Heparin in Total Hip Arthroplasty. *J Clinical Orthopaedics and Related Research* 379:178–85, 2000.
7. Nassif JM, Merrill AR, Meding JB, et al. The Effect of Intraoperative Intravenous Fixed-Dose Heparin During Total Joint Arthroplasty on the Incidence of Fatal Pulmonary Emboli. *J Arthroplasty* 15(1):16–21, 2000.
8. Mant MJ, Russell DB, Johnston DW, et al. Intraoperative heparin in addition to postoperative low-molecular-weight heparin for thromboprophylaxis in total knee replacement. *J Bone and Joint Surgery* (Br) 82(B1):48–9, 2000.
9. Westrich GH, Salvati EA, Sharrock NE, et al. The Effect of Intraoperative Heparin Administered During Total Hip Arthroplasty on the Incidence of Proximal Deep Vein Thrombosis Assessed by Magnetic Resonance Venography. *J Arthroplasty* 20(1):42–50, 2005.
10. Parvizi J, Mui A, Purtill JJ, et al. Total Joint Arthroplasty: When Do Fatal or Near-Fatal Complications Occur? *J Bone and Joint Surgery* 89(A1):27–32, 2007.
11. Canale ST. Campbell's Operative Orthopaedics, 10th edition. Mosby Inc 2003.
12. Mauermann WJ, Shilling AM, Zuo Z. A Comparison of Neuraxial Block Versus General Anesthesia for Elective Total Hip Replacement: A Meta-Analysis. *J Regional Anesthesia* 103(4):1018–1025, 2006.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

The Dynamic Hip Screw and Four-Hole Fixation Plate: Still the Gold Standard for Intertrochanteric Hip Fracture Stabilization?

Nathan Tiedeken, BS,[3] Pekka Mooar, MD,[1]
Joseph S. Torg, MD,[1] John P. Gaughan, PhD[2]

[1]*Department of Orthopaedic Surgery,* [2]*Biostatistics Consulting Center,* [3]*School of Medicine, Temple University, Philadelphia, PA*

Abstract

Determining the best surgical hip stabilization procedure which decreases complication rates is a currently debated topic in the literature. A retrospective analysis of patients who underwent either a 4-hole fixation plate with dynamic hip screw (DHS) or intramedullary nail (IM) stabilization by the Department of Orthopaedic Surgery at Temple University Hospital and Northeastern Hospital was performed. One-hundred and forty-one patients from June 2003 through January 2006 were analyzed with regard to postoperative complications and time until initial weight bearing. There was no significant difference in complication rates ($p = 0.4366$) or weight bearing ($p = 0.8426$) between the two procedures. For both procedures, blood loss ($p = 0.0325$) was a significant factor in contributing to postoperative wound infections. A history of heart disease ($p = 0.0422$) and ASA level ($p = 0.0383$) were found to increase the postoperative time until weight bearing. Surgeons should evaluate each patient on an individual basis and consider the increased risks when deciding on which hip stabilization procedure to perform.

Introduction

Hip fracture is one of the most prevalent osteoporotic fractures in the elderly population and can be a very serious medical condition.[1, 3] For nearly five decades, the dynamic hip screw and fixation plate has remained the most preferred and common implant for treatment of intertrochanteric hip fracture stabilization.[2] Schumpelick and Jantzen first reported using a DHS with a two-hole fixation plate in the early 1950s.[1] It is unclear when or why a transition to a four-hole fixation plate evolved, but this implant is currently considered the gold standard for intertrochanteric hip fracture stabilization. Continuing advancements and the goal to reduce complication rates have recently led to the development of newer implants. Such innovations as intramedullary (IM) devices, have led to debates over which implants are the most beneficial for the treatment of intertrochanteric hip fracture stabilization.

Proposed advantages of an IM device are a smaller incision, lower blood loss, and a shorter operating time.[5, 6] The development of IM nails for intertrochanteric hip fracture fixation offer the theoretical benefits of improved load transfer due to the medial location of the implant, a shorter lever arm, reduced blood loss, and shorter operative time.[4, 11] First generation IM nails demonstrated a higher complication rate when compared to compression screws and were sparingly used.[7, 9] Subsequent revisions in surgical techniques and alterations in the IM nail structure reduced complications, and some authors now recommend its use in clinical practice.[8, 10–12]

The use of hip fracture stabilization implants is frequently discussed in current literature. Olson stated that the overall goal of internal fixation is to achieve solid bone healing, restore length and alignment of the affected limb, and to preserve limb function.[13] Determining the best implant to treat hip fractures would be a great benefit to the medical and elderly communities. Bone quality, fragment geometry, fracture reduction, implant design, and choice of implant are the five variables which Kaufer believes determines the strength of the fracture implant assembly.[14] While bone quality and fragment geometry are not controlled by the physician, fracture reduction and implant choice and design are crucial aspects that the surgeon controls. Determining the best implant for stabilization can have a direct effect on the clinical outcome of a hip fracture patient.

Our goal was to retrospectively perform a multivariable analysis to examine the "gold standard" DHS four-hole fixation plate procedure and compare it with the newer IM implants. This study's main objective was to determine which implant had the best clinical results and lowest complication rates for the fixation of intertrochanteric hip fractures.

Materials and Methods

This study was a retrospective analysis of patients who sustained an intertrochanteric hip fracture which required

surgical stabilization with either a DHS and fixation plate or IM nailing. Following IRB approval, 117 patient charts from Temple University Hospital from June 2003–January 2006 were reviewed. The operative reports, discharge notes, anesthesia reports, and history/physical therapy progress notes were reviewed using the Alpha Systems computer program. Other postoperative clinical follow up documents used for this study were retrieved from the orthopaedic medical records department. Twenty-four surgical hip stabilization patients were reviewed through Alpha Systems from Northeastern Hospital from the time period of September 2005–January 2006.

Age, sex, body mass index (BMI), blood loss, airway sedation assessment (ASA) classification, length of hospital stay, and operating time for each patient were determined. Incision length for each procedure was recorded from the operative reports. In addition to the entry point incision for the IM nail, there are two small incisions for the lag screw and the locking screw. Co-morbidities, postoperative time until weight bearing, and complications were also recorded. Weight bearing was determined by reviewing post operative history/physical therapy progress notes to determine the first time the patient was reported standing or walking. Co-morbidities included hypertension, osteoporosis, arthritis, diabetes, renal and liver and heart disease, cancer, and history or presence of stroke or heart disorder (congestive heart failure and history of myocardial infarction). Postoperative complications included; implant hardware failure, infection, deep venous thrombosis (DVT), and pulmonary embolism.

Univariate and multivariable linear and logistic regression with stepwise selection were used to evaluate predictors of each outcome. Each potential risk factor was evaluated alone and in combination (blood loss, complication, time to weight bearing, etc.). Statistically significant factors ($p < 0.05$) indicate increase (or decrease) in the outcome variable being tested.

Results

One hundred forty-one patients (average age = 67.24 years) were involved in this study, 79 were female (56.03%) and 62 male (43.97%). The average age for males and females were 59.24 and 75.04 years, respectively. Thirty-eight underwent a hip stabilization procedure involving a DHS 4-hole fixation plate and 103 had the implantation of an IM device. There were 20 complications in 16 patients with an overall patient complication rate of 11.35%.

Complication rates for the 4-hole fixation plate and the IM nail procedures were 7.89% and 12.62% ($p = 0.4366$) respectively *(see Table 1 and Figure 1).* The IM procedure had 5 wound infections (4.85%) and the DHS 4 hole fixation plate had 0 wound infections ($p = 0.9574$) [61% power]. There were 6 IM procedure complications (5.83%) caused by hardware failure and 2 DHS hardware complication failures (5.26%) ($p = 0.4505$). A pulmonary embolism occurred in one patient who received an IM device.

Table 1. Overall Patient Procedures, Sex, and Complications

	Patients	Overall %
Male	62	43.97
Female	79	56.03
IM Nail	103	73.05
4 Hole DHS	38	27.95
Complications	16	11.35

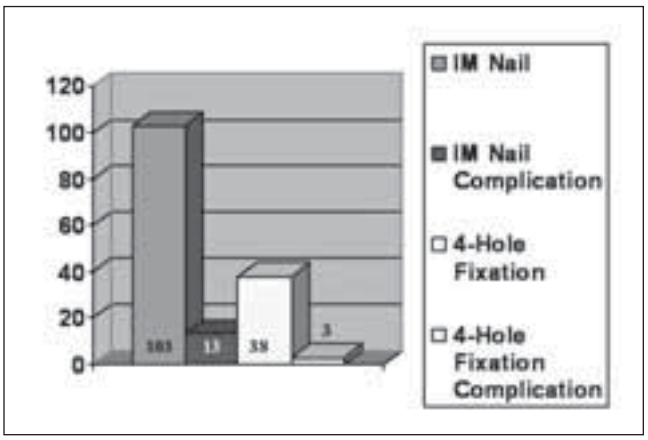


Figure 1. Total patients in each procedure and complications.

One patient had a myocardial infarction postoperatively (IM procedure patient). Four patients in the IM nail category had a DVT (3.88%) versus one patient in the DHS group (2.63%) ($p = 0.9290$) *(see Table 2 and Figure 2).*

Our results demonstrated no significant difference between the two procedures in blood loss ($p = 0.4217$), operative time ($p = 0.2020$), initial time to weight bearing ($p = 0.8426$), hardware failure ($p = 0.4505$), DVT ($p = 0.9290$), myocardial infarction ($p = 0.9572$), infection ($p = 0.9574$), or pulmonary embolism ($p = 0.9572$) *(see Table 2).* A statistical significance was found with incision size. The 4-hole fixation plate had an average 3.675 cm larger incision per procedure than the IM nail ($p < 0.0001$).

Table 2. Procedure Comparison

	4 Hole DHS	IM Nail	Both Procedures	Total % Complication
Total Patients	38	103	141	n/a
Complications	3	17	20	n/a
Wound Infections	0	5	5	3.55
Hardware Failures	2	6	8	5.67
DVT	1	4	5	3.55
Pulmonary Embolus	0	1	1	0.71
Heart Attack	0	1	1	0.71
Blood Loss (ml) Avg. per procedure	217.30	275.57	n/a	n/a
OR Time (minutes) Avg. per procedure	89.46	103.89	n/a	n/a

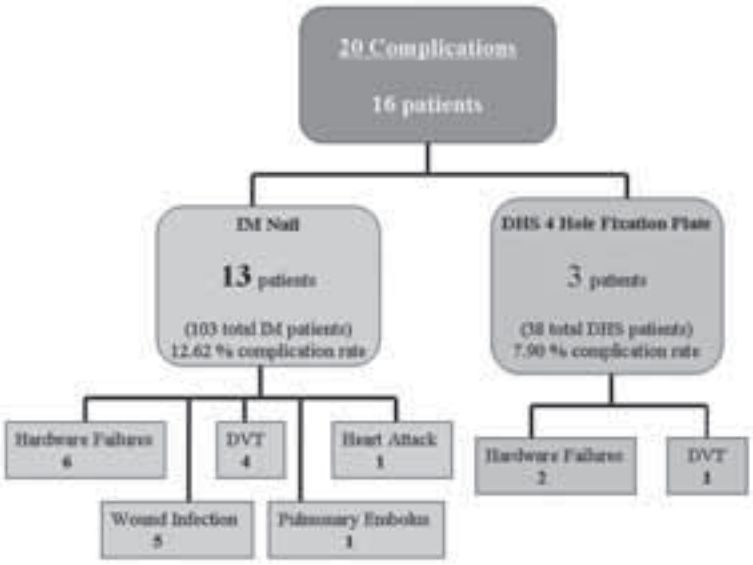


Figure 2. Flowchart of complications.

Using univariate analysis of blood loss, we found no statistical difference between procedures (p = 0.422). Statistically significant predictors for blood loss using the combined group were operative time and incision size. For each minute increase in the operating room, blood loss increased 1.56 ml (p = 0.0347). Each centimeter increase in incision size resulted in an 18.20 ml increase in blood loss (p = 0.0498).

Using the combined group, incision size was a statistically significant predictor of operative time. For each centimeter increase in incision size, the operating room time increased by 3.977 minutes (p = 0.0351).

With reference to co-morbidities, a history of a heart disease (p = 0.0422) and the ASA level (p = 0.0383) were significant predictors of time to weight bearing. The presence of heart disease increased time to weight bearing by 1.389 days. For each increase in ASA level, the postoperative time to weight bearing increased approximately one day (0.918 days).

Statistically significant predictors of a postoperative infection were blood loss (p = 0.0325), renal disease (p = 0.0255), and arthritis (p = 0.00780). A multivariate analysis with stepwise selection showed that the two most important predictors of a postoperative infection were arthritis (p = 0.00840) and blood loss (p = 0.0230). A patient's risk of infection increased by 0.50% (odds ratio = 1.005, CI = 1.001, 1.010) for each ml of blood loss during surgery.

Discussion

Our study showed no significant difference in complication rates between IM and 4-hole DHS procedures (p = 0.4366). The 4-hole DHS had a significantly larger incision size (p < 0.0001), but this did not lead to a significant increase in blood loss compared to the IM nail. Our outcome was similar to the study performed by Patel A., et al. with respect to no significant increase in operating time or complication rates between procedures.[15]

Determining which procedure to use for hip stabilization of intertrochanteric fractures should be evaluated by the physician on a patient to patient basis. There are several predictors which the physician must consider when performing these procedures in order to minimize the risk of complication. Postoperative time until weight bearing time significantly increased with the presence of heart disease (p = 0.0422) and high ASA values (p = 0.0383). Operative time and incision size should be minimized as much as possible when performing surgical hip stabilization. Increases in operative time (p = 0.0347) and incision size (p = 0.0498) significantly increase blood loss, which can lead to increased postoperative wound infections (p = 0.0230). Our data supports studies in the literature which conclude that selecting the procedure in which the surgeon feels the most confident can help reduce complications.[14, 15] Reduction in complications can occur since the surgeon will be more efficient, which will result in decreased operating time and blood loss.

Our data suggests a clinical trend toward increased infections with the IM nail procedure, but this difference was not statistically significant (p = 0.9574). This study achieved 61% power and needed 107 patients in each procedure group in order for the differences to be statistically significant. With sufficient statistical power, future studies should focus on possible etiologies for this increase.

It was difficult to obtain retrospective follow up data for a majority of these patients. For this reason, our study focused on the surgical complications reported until the patient was discharged. A future study perform a longitudinal analysis of

a larger group of patients in order to analyze the time until complete recovery and estimate infection rates with greater power.

Conclusions

Our study demonstrated no significant difference between complication rates and time until weight bearing for the IM nail and 4-hole DHS procedure. In considering complications, blood loss and OR time should be minimized as much as possible to decrease wound infections. Time until weight bearing is affected by a history of heart disease and a high ASA level. Further investigation is required to determine the significance of the clinical trend toward increased IM nail wound infections. Surgeons should evaluate each patient individually and choose the procedure in which they feel most comfortable when performing a hip stabilization.

References

1. Laohapoonrungsee, A, Arpornchayanon, O, Phornputkul, C. Two-hole side-plate DHS in the treatment of intertrochanteric fracture: results and complications. *Injury.* 2005;36(11):1355–60.
2. Harrington, P, Nihal, A, Singhania, AK, Howell, FR. Intramedullary hip screw versus sliding hip screw for unstable intertrochanteric femoral fractures in the elderly. *Injury.* 2002;33(1):23–8.
3. Verhofstad, MH, van der Werken, C. DHS osteosynthesis for stable pertrochanteric femur fractures with a two-hole side plate. *Injury.* 2004;35(10):999–1002.
4. Ricci, WM. New Implants for the Treatment of Intertrochanteric Femur Fractures. *Techniques in Orthopaedics.* 2004;19(3):143–152.
5. DiPaola, M, Razbruch, SR, Helfet, DL. Minimal Incision Technique using a two hole plate for fixation of stable intertrochanteric hip fractures. *Orthopaedics* 2004;27(3):270–4.
6. Bolhofner BR, Russo PR, Carmen B. Results of intertrochanteric femur fractures treated with a 135-degree sliding screw with a two-hole side plate. *J of Orthop Trauma.* 1999;13(1):5–8.
7. Valverde, JA, Alonso, MG, Porro, JG, Rueda, D, Larrauri, PM, Soler, JJ. Use of the gamma nail in the treatment of fractures of the proximal femur. 1998. *J of Orthop Trauma.* 2003;17(8 Suppl):S51–6.
8. Harrington, P, Nihal, A, Singhania, AK, Howell, FR. Intramedullary hip screw versus sliding hip screw for unstable intertrochanteric femoral fractures in the elderly. *Injury.* 2002;33(1):23–8.
9. Parker, MJ, Pryor, GA. Gamma versus DHS nailing for extracapsular femoral fractures. Meta-Analysis of ten randomized trials. *Int Orthop* 1996;20:163–8.
10. Baumgaertner, MR, Curtin, SL, Lindskog, DM. Intramedullary versus extramedullary fixation for the treatment of intertrochanteric hip fractures. *Clinical Orthopaedics & Related Research.* 1998;348:87–94.
11. Utrilla, AL, Reig, JS, Munoz, FM, Tufanisco, CB. Trochanteric gamma nail and compression hip screw for trochanteric fractures: a randomized, prospective, comparative study in 210 elderly patients with a new design of the gamma nail. *Journal of Orthopaedic Trauma.* 2005; 19(4):229–33.
12. Crawford, CH, Malkani, AL, Cordray, S, Roberts, CS, Sligar, W. The trochanteric nail versus the sliding hip screw for intertrochanteric hip fractures: a review of 93 cases. *Journal of Trauma-Injury Infection & Critical Care.* 2006;60(2):325–8; discussion 328–9.
13. Olson, S, Hahn, D. Surgical treatment of non-unions: A case for internal fixation. *Injury.* 2006;37(8):681–90.
14. Kaufer H. Mechanics of the treatment of hip injuries. *Clin Orthop* 1980;146:53–61.
15. Patel, A, Boyes, C, Shur, V. Treatment of stable extra-capsular hip fractures with a sliding screw versus a gamma nail: a retrospective study of 102 patients. *Eur J Orthop Traumatol.* 2007;17:51–56.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

The Incidence and Contributing Factors of Partial Cartilage Delamination Injuries in the Knee

THOMAS D. RILEY, IV, MBS,[3] PEKKA MOOAR, MD,[1] JOHN P. GAUGHAN, PHD[2]

[1]*Department of Orthopaedic Surgery,* [2]*Department of Biostatistics,* [3]*School of Medicine, Temple University, Philadelphia, PA*

Abstract

Objective: Partial articular cartilage delamination injuries (PACDI) are a common finding during knee arthroscopy. Clinical observation has revealed a distinct increase in presentation of partial delamination injuries in patients greater than 37 years of age. This study delineates the incidence and contributing factors of partial cartilage delamination injuries in the knee and provides insight into potential mechanisms of injury.

Methods: Post-operative reports of patients, ages 15 to 93, who have undergone knee arthroscopy at Temple University Hospital from April 2003 to December 2006 were reviewed. Those presenting with cartilage injuries were further evaluated for the presence or absence of partial delamination. Relevant correlating factors were analyzed for strength of contribution to the incitement of partial delamination injury.

Results: Review of post-operative reports demonstrated a diagnosis of articular cartilage pathology in 62.4% of all arthroscopies. PACDI was discovered in 17.4% of patients. Age, race (African-American vs. non-African-American) and tobacco use were identified as significant risk factors for PACDI.

Conclusions: Clinical observations regarding the onset of PACDI presentation in patients aged 37 and greater was validated. Analysis of relevant incidence and contributing factors suggests a significant relationship between age-related changes in the molecular and cellular composition of articular cartilage and PACDI.

Introduction

Partial articular cartilage delamination injuries (PACDI) are poorly defined and have the potential to produce long-term disability in active patients. Clinical observation has indicated an age-related dependence on the incidence of PACDI in the knee. Such observations invariably raise questions regarding the incidence and contributing factors of cartilage delamination injuries. The intimate association of chondral lesions with various concomitant knee injuries has been validated.[1–3] Biomechanical, biochemical and physiological factors have also been included as prevalent contributors to cartilage injury.[4–6] As we continue to identify the dependence of articular cartilage integrity on surrounding structures in the knee it is clinically important to understand the context in which such relationships exist. The age-related effects of oxidative stress may be the first step in the mechanism of partial delamination injury, which leads to chondrocyte apoptosis and the deterioration of extracellular matrix. Therefore, aging patients with associated injury and structural instability in the knee are expected to be at great risk for PACDI.

Gaining a greater understanding of the clinical associations between aging and PACDI will be of value in injury prevention and the refinement of specific treatment regimens. Effective management of future research in treatment options applicable to partial delamination injuries will require a thorough understanding of the types of patients who stand to benefit from such innovations. Thus, the incidence of PACDI in the knee remains a critical element of understanding required for the effective management of patient care and clinical research. This study delineates the incidence and contributing factors of partial cartilage delamination injuries (PACDI) in the knee and provides insight into potential mechanisms of injury.

Methods

This retrospective study evaluated 873 patients between the ages 15 and 93 that had undergone knee arthroscopy at Temple University Hospital from April 2003 to December 2006. Patients were determined to require arthroscopy following evaluation and likely diagnosis of tibiofemoral joint injury by the attending physician.

Defining the Partial Articular Cartilage Delamination Injury (PACDI)

Patient operative reports were reviewed and cartilage injuries were classified on a four grade scale based on the Outerbridge classification system.[7, 8] Grade 1 cartilage degeneration was assigned to chondral injuries described as minimal or mild by the operating surgeon. Cartilage injury, which included fraying or fibrillation of superficial chondral layers were assigned Grade 2. Damage of articular cartilage which penetrated to the deep chondral layers was designated Grade 3. Osteochondral injuries in which all layers of cartilage were removed from the underlying subchondral bone were

characterized as Grade 4 injuries. PACDI was defined as an injury that included the splitting and removal of cartilage layers without the exposure of subchondral bone. In delamination the damaged cartilage characteristically displays an "orange peel" morphology in which the separated cartilage layers hang free in the synovial space. As a result, only operative reports that noted the presence of grade 2 or 3 injuries could be included as a positive diagnosis of PACDI. In the event that an operative report did not define the apparent cartilage injury, a grade level was assigned based on intraoperative arthroscopic images. The operative reports were also the primary source of information for patient demographic, medical and social information.

Table 1. Articular Cartilage Injury Grading System Based on the Outerbridge Method of Chondral Injury Classification[7, 8]

Grading	Characteristics
Grade I	• Minimal/mild chondral injury • Minor fibrillation or softening of articular cartilage
Grade II	• Mild to severe fraying, fibrillation or delamination of chondral layers • Damage isolated to the outermost chondral layers (superficial/transitional zones)
Grade III (Delamination)	• Chondral erosion or delamination extending to the deep layer of articular cartilage • Separation/"orange peeling" of cartilage layers without subchondral exposure
Grade IV	• Osteochondral injuries • Complete erosion of all chondral layers leading to the exposure of subchondral bone

Determining the Relative Angle of Anatomical Axis in the Tibiofemoral Joint

The relative tibiofemoral angle for each injured knee joint was calculated using the PACS Radiographic imaging system at Temple University Hospital. Radiographs examined approximated the distal 1/3 of the femur to the proximal 1/3 of the tibia. Only weight bearing AP standing or erect images were used. The physiologic tibiofemoral angle was calculated to compare each patient's knee to the average 5° to 7° valgus variation. A 90° reference angle was produced at the center of the knee joint by placing a line perpendicular to the approximated mechanical axis of the tibia. The femoral shaft center was calculated at the most proximal level possible. The femoral anatomic axis was inferred by a line drawn from the base of the 90° reference angle to the femoral shaft center. The incident angle between the reference line and the femoral anatomical axis was recorded as the relative tibiofemoral axis.

Results

Partial articular cartilage delamination injury (PACDI) was discovered in 17.4% of all knees explored arthroscopically. Cartilage pathology of any nature, including delamination, was noted in 62.4% of all patients during arthroscopic evaluation. The average age of arthroscopy patients without any noted articular cartilage defect was 34 years. Patients presenting with PACDI were an average of 48 years (Fig. 3c) old while patients presenting with non-delamination articular cartilage injuries (NDACI) were an average age of 45 (Fig. 3b). There proved to be significant variation in the relative age of onset dependant on the type of injury incurred. Relative to the hypothesized baseline of 37 years 13.8% of PACDI, 26.1% of NDACI and 60.4% of non-articular (meniscal/ligamentous) cartilage injuries consisted of patients under the age of 37 (Table 2).

A large majority of PACDI were located on the medial femoral condyle (77%). A similar but smaller percentage (67.5%) of NDACI were also found on the medial femoral condyle. In contrast, delamination and non-delamination patients were just as likely to present with an injury on the lateral femoral condyle. Similar results were found for injuries located on the patella, which made up a greater proportion of the injuries than those in the lateral femoral condyle. Non-delamination patients were more likely to present with an injury located on the medial and lateral tibial plateau than those with partial delamination (Table 2).

A large number of patients presenting with articular cartilage injuries were also found to suffer comorbid pathologies including meniscus and ACL damage. Medial meniscus damage was the most common comorbidity noted in all patients with articular cartilage injuries. A greater proportion of delamination patients (72.4%) were concomitantly diagnosed with a medial meniscus injury during arthroscopy than non-delamination patients (62.1%). However, lateral meniscus damage accompanied delamination and non-delamination injuries at a relatively equal rate. ACL damage was not a common finding with articular cartilage injuries appearing in less than 10% of both delamination and non-delamination patients. In contrast, more than 40% of all patients presenting without articular cartilage injury were diagnosed with ACL damage (Table 2).

Patient race (African American vs. non-African American) revealed a strong relationship with PACDI ($p < 0.0001$). Regarding patients with noted articular cartilage injuries African Americans were found to have 2.34 times the risk of delamination compared to non-African Americans in this study. Slightly greater than one fourth (27.5%) of all arthroscopy patients reviewed were African American. Of all patients presenting with NDACI 26.1% were African American, however, a significantly greater proportion of patients with PACDI (46.1%) were African American (Table 2).

Body composition does appear to play a role as a predictor of cartilage injury; however, its relationship to partial delamination is unclear. Nearly 43% of patients with NDACI and a similar percentage of patients with PACDI were categorized as obese (BMI ≥ 30). In contrast, only 21% of all patients without articular cartilage injuries were obese. However, among patients with articular cartilage injuries the proportion of overweight patients (BMI 25 to 29.9) with and without delamination did not vary significantly (Table 2).

Table 2. Statistical Analysis Based on Patient Categorization by Injury Type

Patient Category by Injury Type	Number	Percentage (%)	P-Value
Partial Delamination (n = 152)			
Under age 37	21	13.8	
Injury location			
Medial femoral condyle	117	77	**0.036**
Lateral femoral condyle	45	29.6	1.000
Medial tibia	36	23.7	0.038
Lateral tibia	29	19.1	0.418
Patella	63	41.5	0.845
Comorbidity			
Medial meniscus	110	72.4	**0.028**
Lateral meniscus	32	21.1	0.498
ACL	8	5.1	0.122
Race			
African American	70	46.1	**<.0001**
Non-African American	82	53.9	
BMI			
Obese (≥30)	66	43.4	0.064
Overweight (25–29.9)	61	40.1	0.195
Medication			
Any medication	130	85.5	**0.033**
Anti-Inflammatory	76	50	0.104
Tobacco Use			
Past or current users	61	40.1	**0.014**
Non-Delamination (n = 394)			
Under age 37	103	26.1	
Injury location			
Medial femoral condyle	266	67.5	
Lateral femoral condyle	116	29.4	
Medial tibia	129	32.7	
Lateral tibia	88	22.3	
Patella	158	40	
Comorbidity			
Medial meniscus	245	62.1	
Lateral meniscus	95	24.1	
ACL	38	9.6	
Race			
African American	103	26.1	
Non-African American	291	73.9	
BMI			
Obese (≥30)	166	42.1	
Overweight (25–29.9)	133	33.8	
Medication			
Any medication	303	76.9	
Anti-inflammatory	166	42.1	
Tobacco Use			
Past or current users	114	28.9	
No Articular Cartilage Injury (n = 328)			
Under age 37	198	60.4	
Type of injury			
Medial meniscus	205	62.5	
Lateral meniscus	97	29.6	
ACL	136	41.5	
Race			
African American	67	20.4	
Non-African American	261	79.6	
BMI			
Obese (≥30)	70	21.3	
Overweight (25–29.9)	127	38.7	
Medication			
Any medication	203	61.9	
Anti-Inflammatory	116	35.4	
Tobacco Use			
Past or current users	81	24.7	

The relative tibiofemoral axis was statistically not a strong predictor for partial delamination injury; however, certain differences between patient groups were noticed. An average of 4.1° valgus was calculated for all patients included in the study whose relative tibiofemoral axis was determined. Those with partial delamination injuries showed an average of 3.7° valgus, a hypothesized outcome, although not statistically significant. An average relative tibiofemoral angle was consistently found to be slightly more varus than normal when patients were compared by gender. Males proved to have a more varus average tibiofemoral angle (3.7°) than women (4.6°), however, despite such variation male and female patients reported with delamination injuries at relatively equal frequencies. Men and women with PACDI reported average relative tibiofemoral angles that were more varus than those with NDACI (Table 3).

Table 3. Relative Tibiofemoral Axis

Patient Category by Injury Type	Relative Tibiofemoral Angle (° Valgus)
All Patients	
Total (n=294)	4.1
Men (n=167)	**3.7**
Women (n=127)	**4.6**
Partial Delamination	
Total (n=64)	3.7
Men (n=31)	3.1
Women (n=33)	4.2
Non-Delamination	
Total (n=147)	4.3
Men (n=82)	3.7
Women (n=65)	5.1
No Articular Cartilage Injury	
Total (n=85)	4.1
Men (n=55)	4.0
Women (n=30)	4.4

The prior use of anti-inflammatory medications as reported by the patient history at presentation to the hospital is a potential contributor to delamination injury. Patient groups with delamination were more likely (50%) than those with non-delamination injuries (42.1%) to have reported previous use of anti-inflammatory medication. Furthermore, when the patient groups were compared based on the prior use of any type of medication (including anti-inflammatory) partial delamination patients (85.5%) were significantly more likely to have been previously medicated than non-delamination injury patients (76.9%).

Tobacco use proved to be a significant risk factor for the onset of PACDI in the knee ($p < 0.013$). Patients who reported the current and past use of tobacco were found to have nearly two times the risk of delamination compared to non-smokers. A significantly greater proportion of delamination patients were smokers (40.1%) compared to non-

delamination patients (28.9%) and those who did not present with articular cartilage pathology (24.7%).

Discussion

Articular cartilage lesions, including partial and full-thickness delamination, are a common finding during knee arthroscopy.[9, 10] Partial articular cartilage delamination injuries (PACDI) include the splitting and removal of chondral layers ("orange peel) without the exposure of subchondral bone. Articular cartilage repair is complicated by the tissue's avascular nature and poor ability to reconstitute original matrix composition following injury.[11] An array of surgical treatment options have been developed including debridement, radiofrequency energy probes, microfracture, osteochondral autograft and allograft transplantation and autologous chondrocyte implantation.[12] As current treatments are unable to produce repair cartilage with normal structure future methods aim to utilize growth factor administration and tissue engineering techniques.[12] Due to the poor efficacy of currently available treatment options PACDI have the potential to produce long-term disability in patients. The goal of this study is to define PACDI and develop a potential mechanism of injury based on the incidence and relevant contributing factors.

The primary hypothesis of this study points to age-related changes in chondrocyte senescence and apoptosis as a potential mechanism of PACDI. The ability of articular cartilage to maintain it's integrity against loading and shearing forces in the knee is derived from its molecular and cellular composition.[11] Resistance to forces associated with everyday activities relies on the uniform composition of articular cartilage constituents including water, collagen, proteoglycans, glycoproteins and chondrocytes. Healthy cartilage ascertains its form and tensile strength from its collagen fibrillar meshwork and collagen fiber cross-linking while proteoglycans provide cartilage with the ability to resist compressive forces.[11] Chondrocytes assume a dynamic role in both the general and fine-tuned construction of cartilage matrix. We suggest that the predisposition for partial delamination injury arises from a loss of a uniform matrix density due to the age-related changes involving chondrocyte senescence and apoptosis. As loading and shearing forces are transmitted across the articular cartilage matrix partial delamination occurs as force distribution is interrupted in those regions, which no longer contain structurally and metabolically viable chondrocytes. This study has revealed that age is one of several contributing factors related to the incidence of PACDI. Further analysis of the relationships between these contributing factors indicates that aging and biomechanical instability are major aspects of PACDI in the knee. Subsequently, each contributing factor will be discussed in the context of the potential age-related changes in articular cartilage of the tibiofemoral joint.

The tibiofemoral axis was considered a potential risk factor for PACDI due to its relationship to the localization of weight-bearing and loading forces in the knee.[13] For a normal valgus tibiofemoral angulation of 5° to 7° the force load distribution within the knee joint is predominantly medial indicating a propensity for medial compartment injuries.[13] A tibiofemoral angle deviating from the normal valgus angulation will redistribute load across the knee joint. An exaggerated valgus angulation will distribute a greater than normal amount of load on the lateral compartment while in a varus deformity the load on the medial compartment rapidly approaches 100% of the total load in the knee.[13] Based on the biological and physiological nature of partial delamination as viewed during arthroscopy shear forces were considered a relevant parameter leading to the induction of this type of injury. Therefore, the tibiofemoral angle was expected to correlate with the location and potential for delamination injury. The relative tibiofemoral axis calculated in this study can only be considered an approximation since the radiographic images did not permit the inclusion of the mechanical axis of the tibia. Furthermore, the femoral head was not visible preventing exact depiction of the femoral anatomic axis. However, localization of weight-bearing forces in the knee were well approximated since a relative tibiofemoral angle could be determined from patient radiographs (Figure 2). Articular cartilage injury in the knee has already been shown to occur most commonly in the medial femoral condyle, consistent with the findings of this study.[9] Therefore, the relative tibiofemoral angle for PACDI patients was expected to be on average less valgus than those without delamination injuries. Although the variations in tibiofemoral angle were not statistically significant a consistent average valgus deviation was noted (Table 3). While the relative tibiofemoral axis was suspected to play a more functional role in predicting delamination injury there were inherent flaws associated with its calculation. However, despite the limitations, the noted consistencies warrant further investigation into this matter under more stringent experimental controls.

The presentation of pathology concomitant with articular cartilage damage was a common finding in this study. Such associations have been noted previously and were an expected outcome.[1–3] The significance of comorbid pathology lies in what these relationships indicate regarding the mechanism of PACDI. Medial meniscus damage was the most consistent injury noted along with all articular cartilage pathology (Table 2). Although the nature of meniscal damage was not a focus of this study, age-related variations in degenerative versus non-degenerative meniscus tears have been defined.[1] The average age of articular cartilage injury (46.3 years) closely follows that of patients with degenerative meniscal injuries (45.5 years).[1] The relationship between articular cartilage pathology and the relative time course of degenerative changes in meniscus damage indicate a depen-

dence of articular cartilage integrity on that of the meniscus tissue. The onset of meniscus damage and resulting exposure of adjacent articular cartilage to relatively increased loading and shearing forces may predispose the incitement of cartilage damage including partial delamination. However, such relationships do not imply that partial delamination is the result of continual erosion down to the deep layers of articular cartilage in these newly exposed areas following meniscal damage. Through arthroscopic imaging PACDI show an "orange peel" morphology displaying well-defined boarder of superficial articular cartilage with an abrupt loss of superficial and transitional zones and the subsequent exposure of the deep zone (Figure 1c). This description of injury implies a type of damage, which is characteristically the result of sudden impact involving shear forces concentrated on a weakened region of cartilage. Therefore, factors contributing to the structural weakening of articular cartilage, such as age-related changes, were suspected among the most probable risk factors involved in predisposing patients to delamination injuries.

Articular cartilage undergoes a number of biochemical changes during aging that lead to the increased risk of joint injury. Articular cartilage pathology is often defined though grading systems suggesting the progression of a single mechanism of injury to greater severity. Unfortunately, the unique nature of PACDI has caused its definition to often be restricted to the terms of the grading systems rather than gaining distinction as a specific type of injury. Nonetheless, each type of cartilage injury may represent variations in the manifestation of age-related changes. Fibrillation, including the mild splitting and fraying of the superficial cartilage layers, is indicative of cyclic loading and frictional deterioration.[11] Without therapeutic intervention fibrillation may progress to deeper layers of cartilage and ultimately to the subchondral bone. Fibrillation may be well localized but often does not maintain consistency in depth. This type of

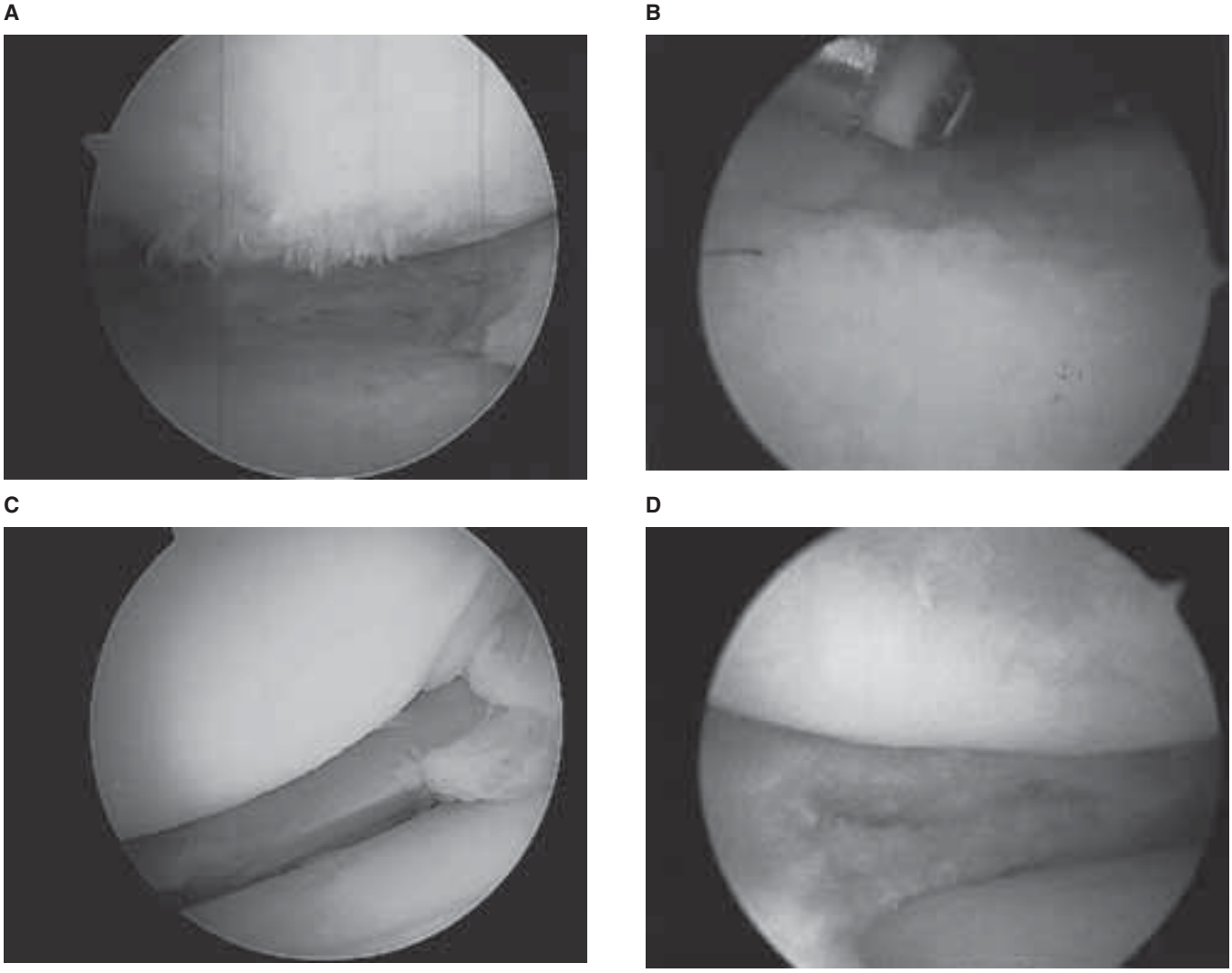


Figure 1. (A) Cartilage fibrillation and fraying indicating a grade I–II injury. **(B)** Grade III chondral erosion without delamination. **(C)** Grade III partial cartilage delamination injury. **(D)** Grade IV cartilage erosion revealing exposed subchondral bone.

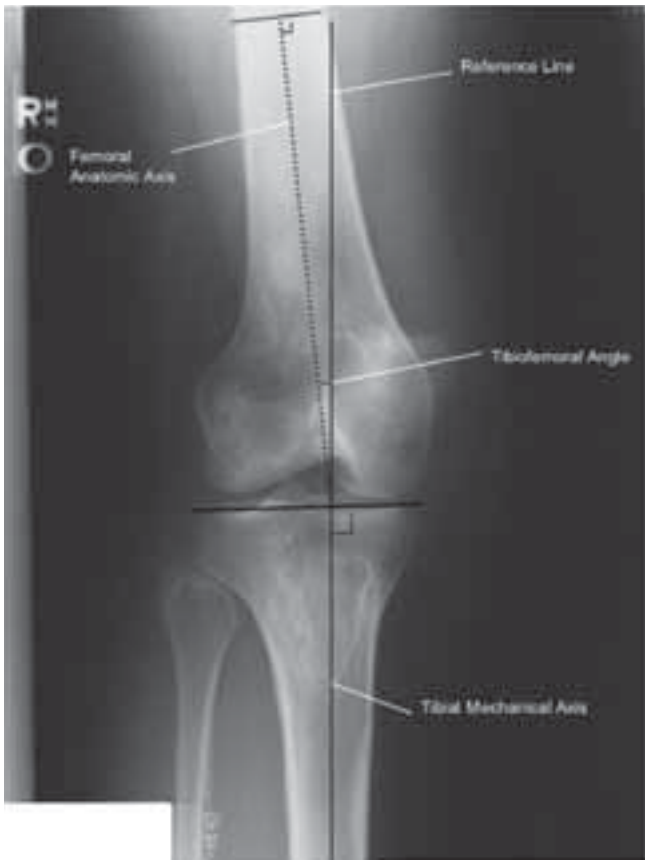
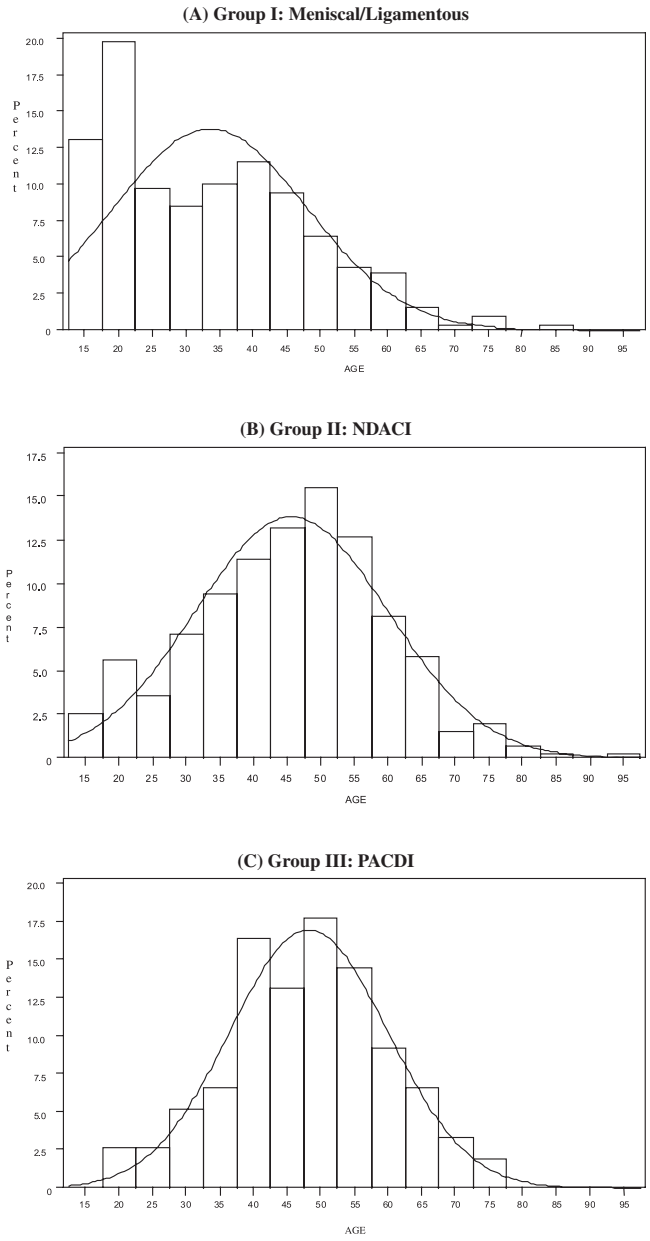


Figure 2. Standing AP radiograph of a right knee joint illustrating construction of the relative tibiofemoral angle.

pathological progression does not appear to account for PACDI due to their well-defined boarders and uniform exposure of deep layers. Thus, it is suggested that PACDI relies heavily on the isolated degeneration of cellular and molecular constituents prior to experiencing the mechanical shearing forces in the knee that ultimately result in injury.

Chondrocytes, which are responsible for the synthesis and maintenance of the extracellular matrix throughout life, are a vital component in the degenerative processes involved in articular cartilage aging. The decline in chondrocyte numbers with age has been correlated with the increased frequency of fibrillation in cartilage of the femur.[14] Due to the lack of macrophages and the isolation of individual or small groups of chondrocytes in articular cartilage it is likely that apoptotic bodies eventually release their contents.[11, 14] As a result, constituents such as proteases released from the apoptotic bodies may be responsible for the deterioration of the surrounding extracellular matrix.[14] As deep layer extracellular matrix surrounding apoptotic chondrocytes begins to weaken the cartilage may become predisposed to delamination.

The process by which aging effects chondrocyte apoptosis is potentially linked to the accumulation of oxidative stress. Human articular cartilage chondrocytes actively produce reactive oxygen species (ROS), which are capable of induc-



Age Distribution:

Group	N	Mean	Std Dev	Minimum	Maximum
I	152	48.17	11.73	18.00	74.00
II	393	45.57	14.40	15.00	93.00
III	328	33.53	14.44	16.00	86.00

Figure 3. Age distribution organized by patient group. Patient groups are defined by injury type: **(A)** *Group I:* non-articular cartilage (meniscal/ligamentous) injury, **(B)** *Group II:* non-delamination articular cartilage injury (NDACI), **(C)** *Group III:* partial articular cartilage delamination injury (PACDI).

ing cellular apoptosis.[15] Cellular defenses against oxidative stress and free radical production include antioxidants such as oxidized glutathione and glutathione reductase. Studies indicate that the ratio of oxidized glutathione to reduced forms is greater in old versus young chondrocytes, indicat-

ing that older articular cartilage is predisposed to damage by ROS.[15] Smoking, which was found to be a significant risk factor for delamination, has been indicated as a contributor to oxidative stress and the increase in carbon monoxide levels leading to tissue hypoxia in articular cartilage.[16]

In conclusion, this study has indicated that significant risk factors for partial articular cartilage delamination injury (PACDI) in the knee include age, smoking and race. Of the 873 arthroscopic procedures reviewed 17.4% of patients were found to have a partial delamination injury. A possible mechanism of injury includes the localized deterioration of cartilage extracellular matrix following chondrocyte senescence and apoptosis due to the cumulative effects of oxidative stress on articular cartilage. The development of oxidative stresses by age-related changes in combination with tobacco use may significantly predispose patients to PACDI. This study has validated the clinical observation that there is a distinct increase in presentation of PACDI for patients greater than 37 years of age.

References

1. Christoforakis, J, Pradan, R, Sanchez-Ballester, J, Hunt, Neil, Strachan, RK. Is There an Association Between Articular Cartilage Changes and Degenerative Meniscus Tears? *Arthroscopy* 21(11):1366–1369, 2005.
2. Geissler, WB, Whipple, TL. Intraarticular abnormalities in association with posterior cruciate ligament injuries. *Am J Sports Medicine* 21(6): 846–849, 1993.
3. Piasecki, DP, Spindler, KP, Warren, TA, Andrish, JT, Parker, RD. Intraarticular Injuries Associated with Anterior Cruciate Ligament Tear: Findings at Ligament Reconstruction in High School and Recreational Athletes. *Am J Sports Medicine* 31(4):601–605, 2003.
4. Martin, JA, Brown, TD, Heiner, AD, Buckwalter, JA. Chondrocyte Senescence, Joint Loading and Osteoarthritis. *Clinical Orthopaedics and Related Research* 42(7S):96–103, 2004.
5. Bellucci, G, Seedhom, BB. Mechanical behavior of articular cartilage under tensile cyclic load. *Rheumatology* 40:1337–1345, 2001.
6. Gelber, AC, Hochberg, MC, Mead, LA, Wang, N, Wigley, FM, Klag, MJ. Body Mass Index in Young Men and the Risk of Subsequent Knee and Hip Osteoarthritis. *Am J Med* 107:542–548, 1999.
7. Outerbridge, RE. The etiology of chondromalacia patellae. *J Bone and Joint Surg* 43B:752–775, 1961.
8. Noyes, FR, Stabler, CL. A system for grading articular cartilage lesions at arthroscopy. *Am J Sports Medicine* 17(4):505–513, 1989.
9. Asbjorn A, Sverre L, Stig H, Elling A, Arne E, Granlund OG, Engebretsen L. Articular Cartilage Lesions in 993 Consecutive Knee Arthroscopies. *Am J Sports Medicine* 32(1):211–215, 2004.
10. Walton WC, Krome J, Gordon S, Rushing J, Smith BP, Poehling GG. Cartilage Injuries: A Review of 31,516 Knee Arthroscopies. *Arthroscopy* 13(4):456–460, 1997.
11. Buckwalter JA, Mow VC. Articular Cartilage. In: DeLee JC, Drez D, Miller MD, editors. DeLee and Drez's Orthopaedic Sports Medicine: Principals and Practice. 2nd edition. Philadelphia: Saunders: 2003. p. 67–87.
12. Morelli M, Nagamori J, Miniaci A. Articular lesions in the knee: evaluation and treatment options. *Current Opinion in Orthopaedics* 13:155–161, 2002.
13. Johnson, F, Leitle, S, Waugh, W. The Distribution of Load Across the Knee: A Comparison of Static and Dynamic Measurements. *J Bone and Joint Surg* 62B(3):346–349, 1980.
14. Mobasheri, A. Role of chondrocyte death and hypocellularity in ageing human articular cartilage and the pathogenesis of osteoarthritis. *Med Hypo* 58(3):193–197, 2002.
15. Del Carlo, M, Loeser, RF. Increased Oxidative Stress with Aging Reduces Chondrocyte Survival. *Arthritis & Rheumatism* 48(12):3419–3430, 2003.
16. Amin, S, Guermazi, A, Grigoryan, M, Hunter, DJ, Clancy, M, LaValley, MP, Genant, HK, Felson, DT. Cigarette smoking and the risk for cartilage loss and knee pain in men with knee osteoarthritis. *Ann Rheum Dis* 66:18–22, 2007.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

Management of Tarsal Navicular Stress Fractures: Conservative vs. Surgical Treatment — A Meta Analysis

James Moyer, BA, MS,[1] John P. Gaughan, PhD,[2] Joseph S. Torg, MD[3]

[3]*Department of Orthopaedic Surgery,* [2]*Biostatistics Consulting Center,*
[1]*Temple University School of Medicine, Philadelphia, PA*

Abstract

Objective: The purpose of this paper is to provide a statistical analysis of previously reported tarsal navicular stress fracture studies regarding the outcome and effectiveness of conservative and surgical management.

Methods: A systematic review of the published literature was conducted utilizing MEDLINE through Ovid, PubMed, ScienceDirect, and EBSCOhost. Case reports of studies that provided the type of tarsal navicular stress fracture, i.e. complete or incomplete, type of treatment, result of that treatment, and the amount of time required to return to full activity were selected for analysis. Using a Mixed Generalized Linear Model with study as a random effect and treatment as a fixed effect, cases were separated and compared based on three different types of treatment: Conservative, weight-bearing permitted (WBR); Conservative, non weight-bearing (NWB); and Surgical treatment. The outcome of the treatment was recorded as either successful or unsuccessful based on radiographic and/or clinical healing of the fracture and time from onset of treatment to return to activity.

Results: There is no statistically significant difference between NWB conservative treatment and surgical treatment regarding outcome ($P = .6441$). WBR as a conservative treatment was shown to be significantly less effective than either NWB or surgical treatment ($P < 0.0001$).

Conclusion: Non-weight-bearing conservative management should be considered the standard of care for tarsal navicular stress fractures. Our study suggests that patients are undergoing unnecessary surgical management for these injuries.

Introduction

The purpose of this paper is to provide a systemic review and meta-analysis of previously reported tarsal navicular stress fracture (TNSF) studies regarding the outcome effectiveness of conservative and surgical management by evaluating four parameters: 1) the success rate and time of return to activity when incomplete and complete tarsal navicular stress fractures are managed with cast immobilization for six weeks or surgery; 2) the success rate for management of tarsal navicular stress fractures utilizing non-weight-bearing cast immobilization for six weeks, weight-bearing cast and/or rest, and management consisting of ORIF and/or bone grafting; 3) differences regarding return to activity between conservative management consisting of non-weight-bearing cast mobilization for six weeks, weight- bearing cast and/or rest, and surgical management; and; 4) complication rates for conservative and surgical treatment.

The stress fracture of the tarsal navicular was first described in humans in a 1970 case study by Towne et al.[1] Early studies showed that it was a rare injury, accounting for only .7 to 2.4 percent of all stress fractures.[2] As awareness of the injury has increased, so have the reported number of cases, with tarsal navicular stress fractures currently representing up to 14 percent of stress fractures in some series.[3–5]

In 1982, a retrospective study of 21 cases demonstrated that both uncomplicated, partial stress fractures and non-displaced, complete stress fractures of the tarsal navicular heal with conservative treatment.[10] Conservative treatment consisted of non-weight-bearing cast immobilization for 6–8 weeks, followed by gradual weight-bearing in a boot for 2–6 weeks until pain free. The effectiveness of this treatment has been reaffirmed by several subsequently published studies.[6, 9] It appears however that current management of this injury more frequently utilizes surgical intervention both as a first line treatment or following failed treatment with weight-bearing conservative management due to pressure on both the athlete and the physician to have the athlete more quickly return to competition.[7, 8] Saxena et al., in 2000, suggested that surgical intervention will decrease the amount of time for an athlete to return to their activity level prior to injury.[12] The most recently reported data by Saxena et al. in 2006 contradicts this, demonstrating there is no significant difference between surgical and conservative management.[11] In 1992, Khan et al. reported that non-weight-bearing cast treatment compares favorably with surgical treatment following failed weight-bearing treatment.[6] A meta-analysis of previously reported outcomes of conservative and surgical management of tarsal navicular stress fracture studies may clarify the issue.

Materials and Methods

A systematic review of the published literature of tarsal navicular stress fractures was conducted. We searched MEDLINE through Ovid, PubMed, ScienceDirect, and

EBSCOhost Reseach Database. The following search terms were entered and modified according to the requirement of each database: "tarsal navicular" and "stress fracture" or "injury;" and "treatment" or "surgery" or "management." In addition, we consulted reference lists. There were no restrictions on date of publication, publication status, or language. The search generated 31 articles, with 21 reports of 19 different trials.

The data is presented as three subsets depending on parameter documentation. Subset I included studies that, in addition to fracture types and outcomes, reported details of patient history and imaging findings. Subset II included studies that documented fracture types, successful/unsuccessful outcomes, and time to return to activity. Subset III included reports limited to documentation of fracture type and successful/unsuccessful outcomes.

Case reports or series that provided the type of stress fracture (complete or incomplete), type of treatment, result of that treatment, the amount of time required to return to full activity, and complications were selected. For purposes of analysis, the type of stress fractures reported were classified as either "incomplete," or "complete," based upon the radiographic and/or imaging information provided. The outcome of the treatment was considered "unsuccessful" if the patient: 1) continued to have pain following the end of treatment; 2) was unable to return to their previous sporting level; or 3) experienced a recurrence of the fracture. A "successful" outcome was one in which the patient was pain free, able to return to previous activity level, and did not have recurrence of the fracture.

The cases were separated into three groups based on the type of treatment: 1) conservative, weight-bearing permitted; 2) conservative, non weight-bearing; and 3) surgical treatment. The cases were classified based upon whether or not the treatment modality was the initial treatment, or secondary treatment following a failed initial therapy. The majority of cases with failed initial therapy involved weight-bearing, therefore our analysis primarily compares non weight-bearing conservative treatment with surgical intervention. The outcome was recorded as either successful or unsuccessful, based on the stated criteria. Sources of variation within and among the groups examined include: type of fracture, time elapsed until onset of treatment; type of treatment; age; and gender. Statistical analysis was performed using a mixed generalized linear model with study analyzed as a random effect (assumes heterogeneity among studies) and treatment, fracture type, age and sex as fixed effects. The 9 SAS v9.1 statistical software (SAS institute, Cary NC) was used for all analyses. ANOVA and Fisher's exact test was calculated for comparisons using a two-tailed p value significance level of ≤0.05.

Results

Two hundred and eighty-one tarsal navicular stress fractures were identified in the peer review literature and included in this analysis.

Subset I

In subset I, seventeen trials with 120 cases that met the inclusion criteria were analyzed. As described, the cases were separated into three groups, and the mixed generalized linear model was used to examine random effect. It was determined that of the variations examined, only the type of treatment was statistically significant regarding a successful outcome (P = .0002). The data indicates the propensity of tarsal navicular stress fractures to respond to treatment was independent of fracture type, i.e. partial vs. complete. Fifty incomplete fractures and twelve complete fractures were treated conservatively, compared to thirteen incomplete fractures and twelve complete fractures treated surgically. The type of fracture was not a statistically significant when comparing NWB-conservative and surgical treatment with regards to a successful outcome (P = 0.994) (Table 2).

Comparing the modes of treatment there was no statistically significant difference between NWB Conservative treatment and Surgery (P = 0.6441). There was a statistically significant difference between WBR conservative treatment, and NWB conservative (P = 0.0001) and surgical treatment (P = 0.0003) (Table 1).

Table 1. Differences of Treatment Least Square Means

Treatment 1	Treatment 2	P
NWB	SURG	0.6441
NWB	WBR	<0.0001
SURG	WBR	0.0003

Analysis of Subset I data further determined the outcomes (fracture healing) were not statistically different comparing fracture type (P = 0.9943), time of onset of treatment (P = 0.7008), age of patient (P = 0.3323) or sex of patient (P = 0.1255) (Table 2).

Table 2. Analysis of Subset I

Effect	F Value	P
Fracture Type	0.00	0.9943
Onset of Treatment	0.15	0.7008
Type of Treatment	9.25	0.0002
Age	0.95	0.3323
Sex	2.39	0.1255

Subset II

Having demonstrated that the type of fracture was not a statistically significant variable regarding success of outcome, a more comprehensive data analysis was performed incorporating other published studies which provided statistical summaries of fracture healing and time to return to activity outcomes. Data analysis included outcome success and return to activity for two-hundred fifty tarsal navicular stress fractures reported in the literature between 1970 and 2005. Seventy of the seventy-three fractures (96%) initially treated with non-weight-bearing cast immobilization for 6 weeks had a successful outcome with return to activity on an

average 4.9 months. Only forty-one of the ninety-two (44.5%) initially treated with weight-bearing rest and/or cast immobilization experienced a successful outcome with return to activity on an average 5.7 months. Fifty-four of sixty-six fractures (82%) initially treated surgically had a successful outcome with return to activity on an average 5.2 months (Tables 3 and 4).

We further analyzed and compared the effectiveness of non-weight-bearing treatment with surgical intervention as secondary treatment modalities followed failed weight-bearing management. The same sources of variation were examined as for the cases of initial treatment. Again, there was no statistically significant difference between the treatment methods (P = 0.5783) (Table 5).

Subset III

Potter et al. reported 32 fractures in 26 subjects. Treatment outcomes were not statistically significant for pain (P = 0.984) or function (P = 0.170) between non-weight-bearing cast immobilization and surgical fixation.[31]

Analysis of Secondary Treatment

We further analyzed and compared the effectiveness of non weight-bearing treatment with surgical intervention as secondary treatment modalities followed failed weight-bearing management. The same sources of variation were examined as for the cases of initial treatment. Again, there was no statistically significant difference between the treatment methods (P = .5783) (Table 5).

Discussion

There is strong evidence supporting the effectiveness of proper conservative management for both partial and non-displaced, complete stress fractures of the tarsal navicular. Case series or reports from Ostlie,[24] Alfred,[23] Murray,[22] Towne,[1] Goergen,[14] Ariyoshi,[15] Miller,[28] and Ting[13] all reported a 100% success rate when non-weight-bearing management of at least six weeks was utilized. The data also strongly reaffirms that weight-bearing rest or limited activity as a conservative treatment often leads to an unsuccessful outcome, including: delayed or non-union, re-fracture, fracture progression, or recurrence of symptoms.[1, 6–8, 10, 16, 27]

In 1982, Torg et al., in a multi-institutional study, analyzed twenty-one stress fractures of the tarsal navicular bone in nineteen patients with particular reference to the clinical and radiographic characteristics, the results of treatment, and the complications associated with the fracture.[10] In addition,

Table 3. Summary of Subset I and Subset II Reports and Success of Various Initial Treatment Modalities

	Torg 1982 21	Fitch 1989 22	Kahn 1992 86	Bojanic 1997 18	Saxena 2000 22	Saxena 2006 19	Burne 2005 20	Others* 30	Totals 250
NWB/cast 6 wks	10/10		19/22	18/18		6/6	2/2	15/15	70/73 96%
NWB/cast <6 wks			9/13				4/5	4/4	17/22 77%
WBR	2/9	13/18	9/34		8/13		8/13	1/5	41/92 45%
Surgery**	2/2	12/16	12/20		9/9	13/13		6/6	54/66 82%

*"Others" include authors: Ostlie, Alfred, Murray, Goergen, Ariyoshi, Miller, Gordon, Ting, Towne, Dennis, and Roper.
**Surgery includes ORIF and/or bone grafting, and ossicle excision.

Table 4. Summary of Subset I and Subset II Reports on Average Time to Return Activity in Months

	Torg 1982 21	Fitch 1989 22	Kahn 1992 86	Bojanic 1997 18	Saxena 2000 22	Saxena 2006 19	Burne 2005 20	Others* 23	Totals 250
NWB/cast 6 wks	3.9		5.6	6		4		5.7	4.9
NWB/cast <6 wks			3.7					4.2	3.7
WBR	5.5	10	5.8		4.3			3	5.7
Surgery**	6	8	5.4		3.1	3.7		4.9	5.2

*"Others" include authors: Ostlie, Alfred, Murray, Goergen, Ariyoshi, Miller, Gordon, Ting, Towne, Dennis, and Roper.
**Surgery includes ORIF, bone grafting, and ossicle excision.

Table 5. Results of Secondary Treatment Following Failure of Initial Weight Bearing Rest/Cast Management

Treatment	Variable	N	Mean	Std. Dev.	Min.	Max.
NWB	Age	3	17.6	4.04	14	22
	Onset Tx*	3	6	7.0	1	14
	Weeks in Cast/Boot	3	4.6	1.2	4	6
	Time to Full Activity Return**	3	7.6	3.5	4	11
SURG	Age	18	23.5	8.0	15	45
	Onset Tx*	18	4.27	6.1	—	24
	Weeks in Cast/Boot	17	16.8	13.4	2	44
	Time to Full Activity Return**	17	6.82	1.8	3	8

*The number of months from the time of injury to the onset of treatment.
**The number of months it took the patient to return to full activity.

microangiographic studies were done on five fresh human cadaver specimens to determine the vascular patterns peculiar to the tarsal navicular bone.

The fractures occurred predominantly in young male athletes (mean age 21.8 years). Because routine radiographs failed to show the fracture, or showed it diagnosis ranged less than one month to thirty-eight months (mean interval, 7.2 months). For fourteen of the twenty-one lesions, radionuclide bone scans were needed to locate the abnormality in the tarsal navicular and for seventeen, anteroposterior tomograms made with the dorsum of the foot parallel to the diagnosis of fracture (in fourteen) or to evaluate further the stage of healing (in three).

The characteristic fracture was oriented in the sagittal plane and located in the central one-third of the bone, and was either partial or complete. Initially, nineteen fractures were treated conservatively and two were treated surgically. Treatment included immobilization in a non-weight-bearing cast for six to eight weeks for ten fractures; immobilization in a weight-bearing cast for four; limitation of activity with continued weight-bearing for five; open reduction and internal fixation for one acute displaced fracture; and an autogenous bone graft for one non-union. All ten fractures that were initially treated in non-weight-bearing casts healed without complications. Seven of the nine patients whose fractures were treated by limitation of activity but continued weight-bearing or by immobilization in a weight-bearing cast were unable to resume vigorous activity after that treatment because of pain associated with delayed union, nonunion, or recurrence of the fracture.

In 1989, Fitch et al. reported on the management of thirty-seven stress fractures of the tarsal navicular.[8] Thirteen of the eighteen fractures treated with either plaster immobilization or rest with continued weight-bearing received a satisfactory result with resumption of activities on an average of ten months. They reported successful outcomes with twelve of the sixteen fractures treated surgically with an average return to activities of eight months. After reviewing the results of Torg et al., the paper stated that they now treat recent fractures with eight to ten weeks of non-weight-bearing in a cast. However, Fitch et al. still consider autogenous bone graft as the treatment of choice for complete fracture and those that develop a medullary cyst.

In 1992, Kahn et al. reported on the outcomes of conservative and surgical management of eighty-six navicular stress fractures of athletes.[6] Nineteen of twenty-two patients (86%) who had initial non-weight-bearing cast immobilization returned to sports activities on an average 5.6 months as compared to only twelve of the forty patients (30%) who initially had continued weight-bearing with limited activity with an average return to activity time of 9.3 months. They also reported a successful outcome for 5 of the 6 patients (83%) who initially underwent surgical treatment with average return to activities of 3.8 months. It should be noted that two of these patients simply had small ossicles removed, with no reported fracture. As a secondary treatment following failed weight-bearing conservative management, 9 of the 10 patients (90%) treated with non weight-bearing cast immobilization healed in comparison to 13 of the 21 patients (61%) who underwent surgery. These results led the authors to conclude that non-weight-bearing cast immobilization is the treatment of choice for tarsal navicular stress fractures, and that this treatment also compares favorably with surgical treatment in patients who present after failed weight-bearing treatment.

In 1997, Bojanic reported on eighteen tarsal navicular stress fractures treated with a non-weight-bearing short leg cast for six to eight weeks, all of whom returned to resumption of full athletic activities on the average of six months.[26]

Saxena et al. reported two series, one consisting of twenty-two navicular stress fractures, nine of which underwent ORIF with average return to activity of 3.1 months (range 1.5–5 months).[11, 12] Thirteen patients were treated conservatively with a weight-bearing regiment and eight of the thirteen fractures had favorable outcome with a return to activity of 4.3 months (range 2–13 months). Five of the 13 had an unsatisfactory outcome and surgery was recommended for both incomplete and complete fractures as well as those with cystic changes and sclerosis.

In 2006, Saxena[11] presented a second series of nineteen fractures in athletes. Six who where treated successfully in a non-weight-bearing plaster cast with an average return to activities at 4 months and thirteen of who were treated by ORIF with an average return to activity in 4.1 months. Combining the findings of these two series, twenty-three have had surgery and eighteen were treated non-operatively. The difference in return to activity between the treatment groups was not statistically significant, and they concluded that tarsal navicular stress fractures take four months to heal with non-operative or operative treatment.

In 2005, Burne et al. reported on twenty tarsal navicular stress fractures and observed that "the published recommendation of minimum of six weeks non-weight-bearing cast treatment does not appear to be translated into clinical management; few patients seem to receive this treatment today."[7]

Burne et al. found that the clinical outcome of alternative therapies were inferior to that which is reported for cast immobilization. They also stated that "there is limited evidence to support surgical intervention as a first line of management" and suggest that the large variance in different surgical approaches "may reflect a lack of consistently satisfactory outcomes." They also noted that tarsal navicular stress fractures prevented almost half of the participants in their study from returning to sports at their previous level.

In 2004, Lee and Anderson published a case report in which they observed that "because most injuries occur in the dedicated athlete, prolonged conservative treatment options may be unsatisfactory."[25] They reported a case of a twenty-eight year old professional football player, who spent two weeks in non-weight-bearing cast, in whom surgical intervention was under taken because of his high demand and his "desire to return to professional level as soon as possible." Also to be noted, to justify the cause of surgical intervention, they have misinterpreted Kahn's data stating that the average return to activity was 3.8 months, when actually it was 5.4 months, the same as the 5.6 months return to activity for non-weight-bearing cast immobilization for six weeks.

Worthy of note was Ronald Quirk, MD's Presidential Guest Lecture to the North American Foot and Ankle in 1998 when he stated that "all patients, no matter how long their history, are to be placed for six weeks on crutches and a below knee non-weight-bearing cast. This has been successful even in several patients who previously failed surgery." He also pointed out that post operative complications include non-union, recurrence of a fracture, and progress and partial fracture to complete fracture.[30]

The recent literature suggests that patients are undergoing surgery or are receiving weight-bearing conservative management as a first line treatment option with the expectation that they will return to their activity more quickly.[7, 11, 12] Although surgical treatment seems increasingly common, it remains largely underreported in the literature. It is the contention of the authors that many patients are undergoing unnecessary surgical management for these injuries.

Conclusion

There is no statistically significant difference between non-weight-bearing conservative management and surgical fixation regarding successful outcome (P = 0.6441) or time to return to activity. It is concluded that conservative non-weight-bearing management is the standard of care for initial treatment of both partial and complete stress fractures of the tarsal navicular.

References

1. Towne LC, Blazina ME, Cozen LN. Fatigue fracture of the navicular. *J Bone Joint Surg Am* 1970; 52:376–8.
2. Coris EE, Lombardo JA. Tarsal navicular stress fractures. *Am Fam Physician* 2003; 67:85–90.
3. Khan KM, Brukner PD, Keanney C, Fuller PJ, Bradshaw CJ, Kiss ZS. Tarsal navicular stress fracture in athletes. *Sports Med.* 1994; 17: 65–76.
4. Brukner P, Bradshaw C, Khan KM, White S, Crossley K. Stress fractures: A review of 180 cases. *Clin J. Sports Med.* 1996; 6:85–9.
5. Bennel KL, Malcolm SA, Thomas SA, Wark JD, Brukner PD. The incidence and distribution of stress fractures in competitive track and field athletes. A twelve-month prospective study. *Am J Sports Med.* 1996; 24; 211–7.
6. Khan KM, Fuller PJ, Brukner PD, Kearney C, Burry HC. Outcome of conservative and surgical management of navicular stress fracture in athletes: Eighty-six cases proven with computerized tomography. *Am J Sports Med.* 1992; 20; 657–666.
7. Burne SG, Mahoney CM, Forster BB, Koehle MS, Taunton JE, Khan KM. Tarsal navicular stress injury: long-term outcome and clinicoradiological correlation using both computed tomography and magnetic resonance imaging. *Am J Sports Med.* 2005; 33; 1875–1881.
8. Fitch KD, Blackwell JB, Gilmour WN. Operation for non-union of stress fractures of the tarsal navicular. *J Bone Joint Surg [Br]* 1989; 71-B: 105–110.
9. Hulkko A, Orava S, Peltokallio P, Tulikoura I, Walden M. Stress fracture of the navicular bone: Nine cases in athletes. *Acta Orthop Scand.* 1985; 56: 503–5.
10. Torg JS, Pavlov H, Cooley LH, et al. Stress fractures of the tarsal navicular: A retrospective review of twenty-one cases. *J Bone Joint Surg [Am].* 1982; 64-A; 700–12.
11. Saxena A, Fullem B. Navicular stress fractures: A prospective study on athletes. *Foot Ankle Int.* 2006; 27(11): 917–21.
12. Saxena A, Fullem B, Hannaford D. Results of treatment of 22 navicular stress fractures: A new proposed radiographic classification system. *J Foot Ankle Surg.* 2000; 39:96–103.
13. Ting A, King W, Yocum L, Antonelli D, Moynes D, Kerlan R, Jobe F, Wong L, Bertolli J. Stress fractures of the tarsal navicular in long-distance runners. *Clinics in Sports Medicine* 1988: Vol. 7, No. 1; 89–101.
14. Goergen TG, Venn-Watson EA, Rossman DJ, Resnick D, Gerber KH. Tarsal navicular stress fractures in runners. *Am J Roentgenol* 1981; 136:201–3.
15. Ariyoshi M, Nagata K, Kubo M, Sonoda K, Yamada Y, Akashi H, Sato S. MRI monitoring of tarsal navicular stress fracture healing: A case report. *Kurume Medical Journal* 1998; 45:223–225.
16. Dennis L, Lombardi CM. Stress fracture of the tarsal navicular: Two unusual case reports. *J Foot Surg.* 1988; Nov-Dec; 27(6):511–4.
17. Roper RB, Parks RM, Haas M. Fixation of a tarsal navicular stress fracture: A case report. *J Am Podiatr Med Assoc.* 1986; Sep; 76(9):521–4.
18. Hunter, LY. Stress fracture of the tarsal navicular: More frequent than we realize? *Am J Sports Med.* 1981; 9:217–219.
19. Kiss ZS, Khan KM, Fuller PJ. Stress fractures of the tarsal navicular bone: CT findings in 55 cases. *Am J Roentgenol* 1993; 160:111–115.
20. Choi LE, Chou LB. Surgical treatment of tarsal navicular stress fractures. *Oper Tech Sports Med* 2006; 14:248–251.
21. Coughlin, MJ. tarsal navicular stress fractures. *Techniques in Foot and Ankle Surgery.* 2002; 1(2):112–122.
22. Murray SR, Reeder M, Ward T, Udermann BE. Navicular stress fractures in identical twin runners: high risk fractures required structured treatment. *Physician and Sports Medicine.* 2005; Jan 33(1):28–33.
23. Alfred RH, Belhobek G, Bergfeld JA. stress fracture of the tarsal navicular: A case report. *Am J Sports Med.* 1992; 20:766–8.
24. Ostlie DK, Simons SM. Tarsal navicular stress fracture in a young athlete: case report with clinical, radiological, and pathophysiologic correlations. *J Am Board Fam Pract.* 2001; 14:381–5.
25. Lee S, Anderson RB. Stress fracture of the tarsal navicular. *Foot Ankle Clin N Am.* 2004; 9:85–104.
26. Bojanic I, Pecina MM. Algorithm for non-operative treatment of partial tarsal navicular stress fractures in athletes. *Rev Chir Orthop Reparatrice Appar Mot.* 1997; 82(2):133–8.
27. Helstad PE, Ringstrom JB, Erdmann BB, Jacobs PM, Julsrud ME. Bilateral stress fractures of the tarsal navicular with associated avascular necrosis in a pole vaulter. *J Am Podiatr Med Assoc.* 1996; Nov. 86(11):551–4.
28. Miller JW, Poulos PC. Fatigue stress fracture of the tarsal navicular: A case report. *J Am Podiatr Med Assoc.* 1985; Aug. 75(8):437–9.
29. Gordon GM, Solar J. Tarsal navicular stress fracture. *J Am Podiatr Med Assoc.* 1985; Jul. 75(7):363–6.
30. Quirk, R. Stress fractures of the navicular: President's guest lecture. *Foot Ankle Int.* 1998; Jul. 19(7): 494–6.
31. Potter, NJ, Brukner PD, Makdissi M, Crossley K, Kiss ZS. Navicular Stress Fractures: Outcomes of surgical and conservative management. *Br J Sports Med.* 2006; Aug. 40(8):692–695.

Medical Student Research Project *Supervised by the Office of Clinical Trials*

Gunshot Extremity Fractures with Neurologic Injury

Omar Beidas, BS,[1] John Parron, MD,[2] Heather Kulp, BSN, MPH,[3]
Joanne Donnelly,[2] Saqib Rehman, MD[2]

[1]*School of Medicine,* [2]*Department of Orthopaedic Surgery,* [3]*Department of Surgery,*
Temple University, Philadelphia, PA

Introduction

Greater than 30,000 fatal and 70,000 non-fatal injuries result from firearms each year in the US.[1] The number of civilian deaths in the US due to gunshot injuries is greater than the combined total of US soldiers killed in all the wars ever fought.[2] With the increasing numbers of civilian gunshot injuries it is becoming increasingly important for surgeons to understand the complications that may accompany them. Orthopaedic injuries from gunshot wounds with bone, vascular, muscle, joint, or soft tissue involvement has been thoroughly studied.[9–15, 18] The incidence and prognosis for neurologic injury from civilian low velocity gunshot wounds is not well documented. Furthermore, risk factors for neurological injury and poor outcomes have not been well-identified. The purpose of this study is to determine the incidence of gunshot wounds to the extremities with concomitant neurological injury and whether or not fractures are risk factors for neurologic injury. It is our hypothesis that neurologic injuries are more likely to occur with concomitant fracture and that neurologic function typically recovers in these patients.

Materials and Methods

The study was conducted at Temple University Hospital (TUH), an urban level 1 trauma center with a high volume of low velocity civilian gunshot injuries. Medical records were reviewed during the period between January 2002 and June 2007. Three methods were used to identify patients with gunshot injuries to the extremities (with and without fractures) with peripheral neurological injury.

Four separate hospital medical record searches were performed with the following criteria: (1) upper extremity gunshot wounds with nerve injury; (2) upper extremity gunshot wounds with nerve injury and open fractures; (3) lower extremity gunshot wounds with nerve injury, and (4) lower extremity gunshot wounds with nerve injury and open fractures.

An orthopaedic inpatient database was utilized to retrieve additional records. Using the search term "GSW," patients with gunshot injuries were identified. These were then reviewed and patients with concomitant neurological injury were identified.

Finally, the TUH Pennsylvania Trauma Systems Foundation (PTSF) database was searched using Report Wrighter (Digital Innovations) using the ICD-9 codes (both diagnosis codes and E-codes) for gunshot wounds, neuropathy, nerve injuries, and extremity fractures.

Various demographics were recorded for each patient: age, gender, race, and date of injury. In addition, injury-related information such as wound location; number of wounds; injury severity score (ISS). Finally, other pertinent information was noted including but not limited to patient history and complications.

All patients were sent a letter with return envelope via postal mail in order to follow-up with their condition since their accident date. If patients agreed to return to the hospital to fill out questionnaires, they were contacted to set up an appointment. At that time, they signed consent forms and filled a questionnaire regarding their post-injury status the short musculoskeletal function assessment (sMFA) to determine the current health status of each patient in the study.[21, 22] Nerve recovery was determined according to the widely used and accepted Medical Research Council Grading System for Nerve Recovery.

Results

Results from all three sources (hospital medical records, orthopaedic database, trauma database) were cross-referenced. The hospital medical record search identified thirty-six patients: 14 with upper extremity open wounds, 13 with upper extremity open fractures, 8 with lower extremity open wounds, and 1 with lower extremity open fractures. Since there were some duplicate patients, the final list came out to 29 patients. The orthopaedic database identified 453 patients during this same period, 27 of which also had peripheral nerve injury. The PTSF database search identified a total of 28 patients from the same time period. Amongst the three sources, patients found on more than one list were eliminated.

During the study period, a total of 1851 patients aged 18 and older were admitted with gunshot injuries. Of these, 895 (46%) involved at least one extremity and 382 (21%) had concomitant fractures. A total of 74 patients were identified as having gunshot injuries to the extremities with neurologi-

cal injuries. Of these patients 53 (72%) patients had at least one accompanying bone fracture and 15 (20%) patients suffered additional vascular injury, with eleven (15%) of those having both types of injuries. Over this five-year period, we therefore report a 14% incidence of gunshot extremity fractures resulting in neurologic injuries. Neurologic injury from gunshot injuries to the extremities without fractures, on the other hand, occurred with an incidence of only 4%.

Patient questionnaires (sMFA) and clinical evaluation (Medical Research Council Grading) are ongoing at this time and not completed.

Discussion

Firearms are the leading cause of death for Americans between the ages of 15 and 24, second only to unintentional injuries. As the number of firearms in the US passes 300 million, or almost half the total firearms worldwide, our emergency departments are receiving more and more patients with injuries inflicted by these dangerous weapons. Studies have shown that possession of a firearm increases the chances of being murdered by 41 percent for every individual in the household[4] and 22 times more likely to be shot with a gun in the household.[6]

Most urban gunshot violence is due to low velocity handguns. Handguns account for one third of the firearms amongst civilians in the US but are the cause of more than two-thirds of gun-related deaths,[5] highlighting the need for the medical community to be familiar with the prognosis and nature of gunshot injuries. The City of Philadelphia sees an average of more than one gun-related fatality each day and a crime rate almost three times the national average.[7, 8] It is imperative that orthopedic surgeons be aware of these findings as Brown et al. reported that gunshot injuries consume a large portion of orthopedic resources: 24% of all admissions, 14% of all surgery cases, 15% of all fractures requiring surgical intervention, 26% of all trauma cases, 32% of inpatient days, and 33% of the average daily census at certain urban trauma centers.[20]

Neurologic damage from projectile missiles can occur due to blast effect or less commonly due to physical disruption of the nerve itself. However, neurologic injury can also occur with fractures typically due to stretch injury resulting in neurapraxia. Sunderland showed in 1972 that in military gunshot injuries, 25% of these injuries resulted in neurologic injury.[17] Furthermore, he documented that peripheral nerve injuries recovered in 68% of these patients. However, this phenomenon has not been well described in civilian gunshot injuries despite its relative common occurrence in urban trauma centers. Furthermore, it can be speculated that since nerve injury is more likely to occur in the presence of skeletal instability, gunshot fractures should have a higher rate of neurologic injuries than gunshot injuries to the extremities without fractures. Indeed, we demonstrated an incidence of neurologic injury in 14% of patients who had a gunshot extremity fracture compared with 4% of patients with gunshot injuries to the extremities. We can conclude that fractures are a risk factor for neurologic injury in patients with civilian gunshot violence to the extremities. Unfortunately, we have not yet completed our patient follow-up and are not able to report on the rate and degree of neurologic recovery or patient outcomes. Nevertheless, the retrospective data from this study highlights this increased risk and the importance of careful neurologic examination upon presentation.

References

1. Centers for Disease Control and Prevention. Accessed June 18, 2007. Available online at http://www.cdc.gov/ncipc/wisqars/.
2. The Violence Prevention Task Force of the Eastern Association for the Surgery of Trauma. Violence in America: A Public Health Crisis — The Role of Firearms. *J Trauma* 38(2):163–168, 1995
3. International Action Network on Small Arms. 2006: Bringing the global gun crisis under control. Accessed June 20, 2007. Available online at http://www.iansa.org/members/IANSA-media-briefing-low-res.pdf
4. Wiebe, Douglas J. Homicide and Suicide Risks Associated with Firearms in the Home: A National Case-Control Study. *Ann Emerg Med* 41(6):771–782, 2003.
5. Kellerman, AL and Roberta K. Lee et al. The Epidemiological Basis for the Prevention of Firearm Injuries. *Annual Review of Public Health* 12:17–40, 1991.
6. Kellerman AL, et al. Suicide in the Home in Relation to Gun Ownership. *NEJM* 327(7):467–472, 1992.
7. US Census Bureau. Accessed June 28, 2007. Available online at http://factfinder.census.gov/servlet/ACSSAFFFacts?_event=&ActiveGeoDiv=geoSelect&pctxt=fph&_lang=en&_sse=on&geo_id=16000US4260000&_state=04000US42.
8. Federal Bureau of Investigation. Accessed June 28, 2007. Available online at http://www.fbi.gov/ucr/05cius/offenses/violent_crime/index.html.
9. Norman J, Gahtan V, Franz M, Bramson R. Occult vascular injuries following gunshot wounds resulting in long bone fractures of the extremities. *Am Surg* 61(2):146–50, 1995.
10. Volgas DA, Stannard JP, Alonso JE. Current orthopaedic treatment of ballistic injuries. *Injury* 36:380–386, 2005.
11. McHenry TP, Holcomb JB, Aoki N, Lindsey RW. Fractures with Major Vascular Injuries from Gunshot Wounds: Implications of Surgical Sequence. *J Trauma* 53(4):717–721, 2002.
12. Dicpinigaitis PA, Fay R, Egol KA, Wolinsky P, Tejwani N, Koval KJ. Gunshot wounds to the lower extremities. *Am J Orthop* 31(5):282–93, 2002.
13. Bartlett CS, Helfet DL, Hausman MR, Strauss E. Ballistics and gunshot wounds: effects on musculoskeletal tissues. *J Am Acad Orthop Surg* 8(1):21–36, 2000.
14. Ganocy K 2nd, Lindsey RW. The management of civilian intra-articular gunshot wounds: treatment considerations and proposal of a classification system. *Injury* 29(S):S1–6, 1998.
15. Bowyer GW, Rossiter ND. Management of gunshot wounds of the limbs. *J Bone Joint Surg* 79-B(6):1031–6, 1997.
16. Department of Health. Firearm-related Injuries in Pennsylvania. Research Briefs Issue 6, 2005.
17. Sunderland S. Nerves and nerve injury. New York: Churchill Livingstone; 1972.
18. Brettler D, Sedllin ED, Mendes DG. Conservative treatment of low velocity gunshot wounds. *Clin Orthop* 140:26–31, 1979.
19. Seddon HJ. Three types of nerve injury. *Brain* 66(4):238–88, 1943.
20. Brown TD et al. The Impact of Gunshot Wounds on an Orthopaedic Surgical Service in an Urban Trauma Center. *J Orthop Trauma* 11(3):149–153, 1997.
21. Department of Orthopaedic Surgery, University of Minnesota. Clinical and Outcomes Research. Accessed June 28, 2007. Available online at http://www.ortho.umn.edu/ortho/research.html.
22. Swiontkowski et al. Short Musculoskeletal Function Assessment Questionnaire: Validity, Reliability, and Responsiveness. *Journal of Bone & Joint Surgery* 81:1245–60, 1999.

Case Report

Endoscopic Leg Fasciotomy for the Treatment of Exertional Compartment Syndrome: A Case Report

Carlos E. Moreyra, MD,[1] James R. McCarthy, AS,[2] John D. Kelly, IV, MD[1]

[1]*Department of Orthopaedic Surgery,* [2]*Department of Perioperative Services, Temple University Hospital, Philadelphia, PA*

Abstract

Exertional compartment syndrome of the leg is a condition in which an individual can have signs and symptoms, such as pain, swelling, tightness, from transiently elevated intracompartmental pressures of the leg. The condition may require fasciotomies in order to prevent recurrent symptoms with activities. Fasciotomies can be performed with the use of mini-incisions, which can decrease the morbidity of the surgery, but may risk injury to neurovascular structures due to compromised visualization. We report a novel way of performing a mini-incision compartment fasciotomy of the leg using an endoscopic vein harvester.

A standard mini-incision was made during surgery. However, the fasciotomy was able to be performed under endoscopic visualization at all times with the use of the endoscope and electrocautery. Postoperatively the patient had no signs of neurovascular damage from the surgery. Our patient was able to return to running at approximately two weeks. We believe that a lower extremity fasciotomy using an endoscopic vein harvester is promising in that direct visualization is afforded and bleeding is minimized with electrocautery.

Introduction

The mini-incision compartment fasciotomy of the leg is usually undertaken for the treatment of exertional or exercise-induced compartment syndrome. This procedure entails making a small incision laterally on the leg for the relief of the anterior and lateral compartments. Occasionally, a medial incision is also utilized for relief of the less common posterior exertional compartment syndrome. Once the lateral incision is made, the intermuscular septum is identified. Small incisions are made anterior and posterior to the septum on each of the compartments. These fasciotomy incisions are then normally extended proximally and distally with either a fasciotome or scissors. The cuts are usually made blindly, relying completely on anatomical knowledge for the avoidance of the neurovascular structures. In addition, they do not allow for the control of bleeding in the case of a transection of a vessel.

We report a novel way of performing a mini-incision compartment fasciotomy of the leg using an endoscopic vein harvester. This allows for endoscopic visualization of the fasciotomy as well as cauterization, rather than sharp dissection of tissue.

The endoscope used in our case was the Datascope ClearGuide System (Datascope Corporation, Montvale, NJ). This endoscopic instrument is commonly used for the harvesting of GSV grafts during CABG surgeries. It consists of an endoscope with a clear plastic hemi dome superiorly at its tip. The floor of the tip of the endoscope is free and allows for working in the tissues with the use of the ClearGuide Precision Bipolar electrocautery. The endoscope has a pistol shaped handle at its end that allows for easy maneuverability (Figure 1). The electrocautery is held with the opposite hand. It functions for both electrocautery as well as cutting. The bipolar instrument has a notched tip with a blade that can be extended into the notch. Electrocautery is applied through the blade which is one pole of the bipolar electrodes. The end of the bipolar instrument is also an alligator jaw which is used to apply cautery to any vessels not cauterized by the blade. The endoscope allows for working space underneath its dome with the tip of the electrocautery in the middle.

Carbon dioxide gas is delivered through a port in the endoscope retractor at 2–3 liters of flow. The gas clears fog

Figure 1

and plume from the operative field created by the cautery bipolar blade.

Case

The patient is a 17-year-old female avid soccer player who complained of pain to bilateral lower legs with exertion. Radiographs and a bone scan were negative for fractures. Compartment pressures measured in the office suggested exertional compartment syndrome. A mini-incision anterior and lateral compartment fasciotomy was planned and proper consents were obtained.

After induction of general anesthesia, tourniquets were placed in both lower extremities. The lower extremities were prepped and draped in the usual sterile fashion. A 4-centimeter (cm) longitudinal incision was made at the upper and mid-third junction of the lateral leg midway between the lateral crest of the tibia and the fibula. The anterior intermuscular septum was palpated and the incision was attempted to be centered over this area. Dissection with the Metzenbaums was done down to the fascia. The intermuscular septum was visually identified. Right angle retractors were used to facilitate visualization of the fascia. A #15 blade was then used to make a small transverse incision at the anterior and lateral compartment, each incision about 1 cm away from the septum. The vein harvesting endoscope was then introduced into the wound (Figure 2). A subcutaneous dissection plane was created while directing the endoscope in the direction of the great toe distally (Figure 3). Dissection of the anterior muscular fascia was then performed under direct visualization via the endoscope monitor (Figure 4). By transillumination through the subcutaneous tissue and the skin, the location of the endoscope edge was easily visualized from the outside of the leg. Hemostasis was achieved by the extended blade or by applying the endoscopic bipolar forceps. Once the fascia was satisfactorily opened distally and hemostasis assured, the endoscope was the introduced proximally while aiming it towards Gerdy's tubercle. In a similar fashion, the lateral compartment was then released using the same skin incision. The lateral fasciotomy was undertaken by dissecting distally with the endoscope and endoscopic electrocautery while aiming the instruments towards the calcaneus. Once a satisfactory fasciotomy was achieved distally, the endoscope was redirected proximally while aiming it towards the fibular head but staying 4 cm distal to it.

The skin wounds were irrigated and closed in layers. The subcutaneous tissue was approximated with a braided absorbable suture and at the skin with a subcuticular non-absorbable suture. Compression dressings were placed. Once awake, the superficial and deep peroneal nerves were examined to be intact. The patient was discharged home on aspirin for deep venous thrombosis prophylaxis.

At 2 weeks postoperative, the patient was already engaging in light running. Figure 5 shows her left leg scar at 6 weeks after the operation. At this time, full unrestricted sports activity was permitted.

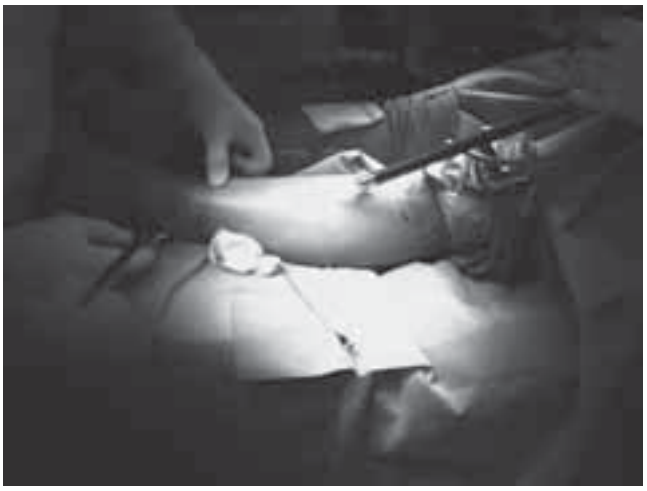


Figure 2. The endoscope is introduced through the mini-incision over the anterior intermuscular septum.

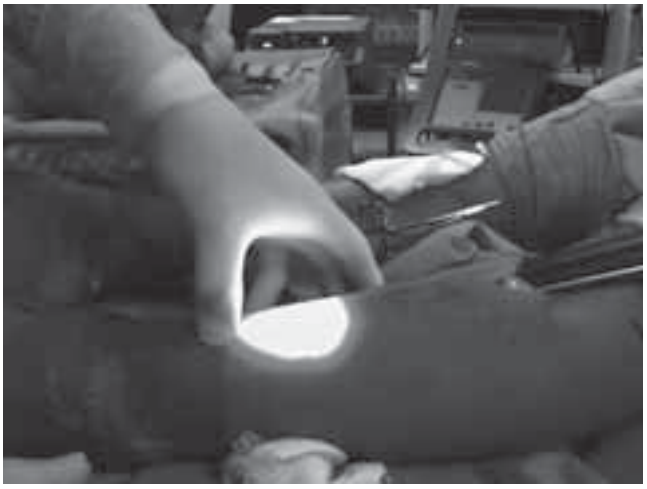


Figure 3. The endoscope is advanced in the direction of the assistant's thumb, towards the great toe, while dissecting the anterior compartment of the leg.

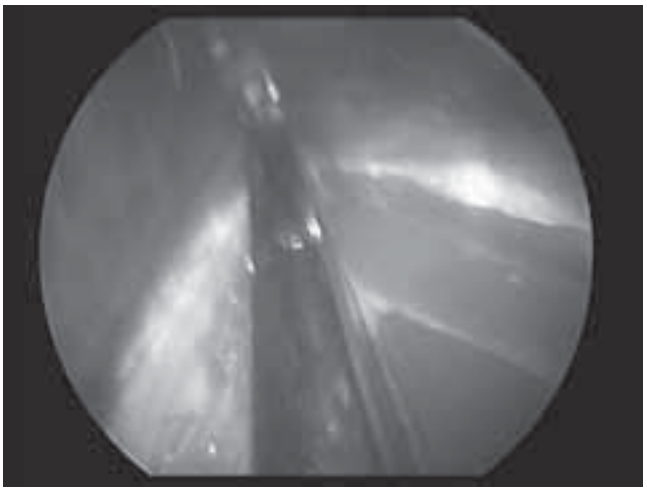


Figure 4. The endoscope is advanced while maintaining visualization of the fascia as well as any nearby neurovascular structures.

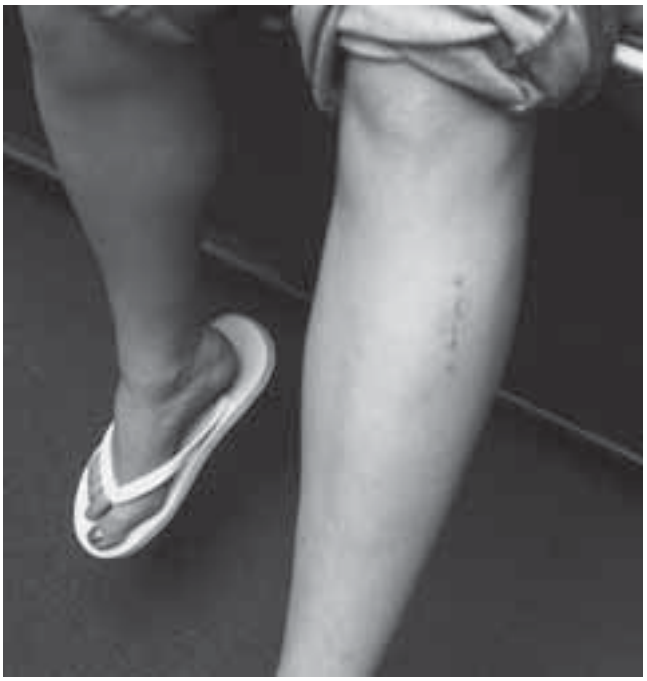


Figure 5. Endoscopic fasciotomy incision on left leg at six weeks after surgery.

Discussion

We report the use of an endoscopic vessel harvester for the performance of a mini-incision compartment fasciotomy of the leg. While this instrument is commonly used in the field of cardiothoracic surgery, no report in the literature shows its use in the performance of a lower leg compartment fasciotomy. Recent papers in the literature have reported on similar endoscopic fasciotomies for exertional compartment syndrome using standard arthroscopes. In some of the reports with larger case numbers, Fontes and group present a retrospective review of 41 forearm decompressions for chronic exertional compartment syndrome of the forearm.[1] They reported on four complications — two hematomas and two lateral epicondylitis, with no adverse long-term effects. More specific to the lower extremity, several reports in the literature have discussed the use of the arthroscope in the performance of endoscopic-assisted lower extremity fasciotomy in both cadaveric specimens and patients.

In 1999, Ota and group described a technique to release the anterior fascia using a transparent outer tube from Universal Subcutaneous Endoscope (Biomet, Warsaw, IN) and a 4.0 mm arthroscope.[2] This allowed for visualization of the working tissue. The fascial cut was performed with the use of a retrograde arthroscopic blade. They reported a successful result.

In 2002, Leversedge et al.[3] performed anterior and lateral compartment fasciotomies in 14 matched, fresh-frozen, cadaveric specimens using a 30 degree endoscope, Metzenbaum scissors, and an endoscopic retractor. Their study initially began with a single 4-cm incision at the mid level of the leg and over the anterior intermuscular septum. Due to difficulty with visualization and unpredictable effectiveness of the compartment release, their study was modified to incorporate a two-incision method. Despite their abandonment of a single-incision for the release of both anterior and lateral compartments, they reported no nerve, vascular, or muscular injuries to any of the single-incision specimens. In addition, they reported no nerve, muscle, or vascular injuries during the course of endoscopic fasciotomies using the two-incision technique. Their only two complications were related to a soft tissue mass on one specimen, allowing only an incomplete lateral compartment release, and an avulsion of the intermediate dorsal cutaneous branch of the superficial peroneal nerve, which the authors believed was caused by retractor placement rather than the endoscopic fascial release.

A year later, Hutchinson and group reported on an endoscopically-assisted fascial compartment release of the leg performed in cadaver specimens.[4] In their study, a standard 30-degree arthroscope was used with the help of skin retraction. Their results showed that the superficial peroneal nerve was less likely to be injured with the endoscopically-assisted releases than with the percutaneous approach. Their results were compared to percutaneous fascial release controls.

In 2005, Stein and Sennett reported on anterior and lateral compartment releases performed also with a 30 degree arthroscope in four patients.[5] In their paper, they report excellent results with the use of a single-portal endoscopically-assisted fascial release with the arthroscope along with an Army-Navy instrument and a switching stick for retraction, and a Metzenbaums scissors for fasciotomy.

More recently, Lohrer and Nauck reported a case series of 17 patients who underwent endoscopic fascial releases for exertional compartment syndrome.[6] Ten of the patients had anterior compartment involvement and two had lateral involvement. Given the bilaterality of some of the patients, 16 anterior and 3 lateral fascial releases were performed. In their study, the soft tissue dissection was performed with Metzaunbaum, a 30 degree endoscope was utilized for visualization, while a specialized pair of scissors (32 cm in length, bent at the shank, and an immobile lower blade) was employed for the dissection. A single-blade gynecological speculum was used to assist with retraction. Their results showed 3 patients who had complications related to bleeding in the deep posterior compartment. No complications were noted for the anterior or lateral fascial releases. Although the authors concluded that the safety and effectiveness of endoscopic fasciotomies is inferior when compared to open surgery data, they nonetheless stated that the procedure is safe in the anterior and lateral compartments.

While the use of a vessel-harvesting endoscope may require a steep learning curve when it comes to its original use in cardiothoracic surgery, its use for compartment fasciotomies appears to us to require much less training. Patients

who undergo CABG surgery can oftentimes be obese, have poor vascular beds, peripheral edema, or other conditions that make the use of the endoscope more difficult. In addition, the harvesting of the GSV requires ligation of its branches during its course through the leg. In contrast, patients undergoing mini-incision fasciotomies of the leg are oftentimes athletes who suffer from exertional compartment syndromes. These patients are younger and have a leaner body habitus. Thus it would seem that the tissue bed for performing endoscopic fasciotomies for exertional compartment syndrome would be much more easily navigated. In addition, the use of a vessel harvesting endoscope facilitates retraction and visualization of the working field regardless of the distance between the entry skin incisions and the end of the endoscopes. Since the endoscope comes with a clear plastic hemi dome at its end, there is no need to insert long retractors into the wound.

A drawback of our report is the fact that only anterior and lateral compartment releases were performed in our patient. Although the anterior compartment is the most commonly involved compartment in compartment syndrome of the leg, it is possible to have posterior compartments involvement in exertional compartment syndrome. Since some of the studies discussed here relate to the present danger of complications with posterior compartment releases endoscopically, we hypothesize that release of such compartments with the use of the endoscope would also prove promising, but this would have to be a focus of future study.

Conclusion

We have reported a case of a mini-incision fasciotomy for the treatment of exercise-induced compartment syndrome utilizing a vessel harvester endoscope. The main advantages of performing this procedure endoscopically are direct visualization of the fasciotomy and nearby neurovascular structures and control of bleeding. Although the instruments used were developed for the harvesting of veins for CABG surgery, we have found them to be useful on the performance of endoscopic fasciotomy of the lower extremity.

Acknowledgments

The authors would like to acknowledge the gracious contribution of Rosario T. Moreyra for the redaction of reference 1 from the French language.

References

1. Fontes D, Clement R, Roure P. Endoscopic aponeurotomy for chronic exertional compartmental syndrome of the forearm: report of 41 cases. *Chir Main.* 2003 Aug;22(4):186–96.
2. Ota Y, Senda M, Hashizume H, Inoue H. Chronic compartment syndrome of the lower leg: a new diagnostic method using near-infrared spectroscopy and a new technique of endoscopic fasciotomy. *Arthroscopy.* 1999 May;15(4):439–43.
3. Leversedge FJ, Casey PJ, Seiler JG 3rd, Xerogeanes JW. Endoscopically assisted fasciotomy: description of technique and in vitro assessment of lower-leg compartment decompression. *Am J Sports Med.* 2002 Mar-Apr;30(2):272–8.
4. Hutchinson MR, Bederka B, Kopplin M. Anatomic structures at risk during minimal-incision endoscopically assisted fascial compartment releases in the leg. *Am J Sports Med.* 2003 Sep-Oct;31(5):764–9.
5. Stein DA, Sennett BJ. One-portal endoscopically assisted fasciotomy for exertional compartment syndrome. *Arthroscopy.* 2005 Jan;21(1):108–12.
6. Lohrer H, Nauck T. Endoscopically assisted release for exertional compartment syndromes of the lower leg. *Arch Orthop Trauma Surg.* 2007 Nov;127(9):827–34.

Review

Elbow Fracture-Dislocations: Review of Pathoanatomy, Treatment, and Complications

Asif M. Ilyas, MD,[1] Jesse B. Jupiter, MD[2]

[1]*Department of Orthopaedic Surgery, Temple University, Philadelphia, PA,*
[2]*Department of Orthopaedic Surgery, Massachusetts General Hospital, Boston, MA*

Introduction

Elbow dislocations can be divided into two broad categories: simple-dislocations and fracture-dislocations. Simple-dislocations of the elbow can usually be treated with closed reduction and early range of motion with minimal sequelae.[1] In contrast, elbow fracture-dislocations often require operative treatment and are associated with several complications. There have been many descriptions of what defines an elbow fracture-dislocation. Ring & Jupiter reviewed their institutional experience and identified four common patterns:[2]

(1) Posterior elbow dislocation with fracture of the radial head (see Figure 1).
(2) Posterior elbow dislocation with fracture of the radial head and coronoid process (aka, the "Terrible Triad") (see Figure 2).
(3) Anterior elbow dislocation with fracture of the olecranon (see Figure 3).
(4) Posterior elbow dislocation with fracture of the proximal ulna (aka, a posterior Monteggia fracture) (see Figure 4).

The first two types (Types 1 and 2) are true dislocations where there is loss of ulno-humeral articulation. The second two types (Types 3 and 4) may have the relationship between the ulna and humerus maintained and instead represent an ulno-humeral disruption. Despite not being a true dislocation, Types 3 and 4 injuries result in sufficient disruption that their treatment and sequelae warrant their inclusion as elbow fracture-dislocations.

Complications frequently compromise results from elbow fracture-dislocations. Complications can be divided into early and late. Early complications include instability, stiffness, and heterotopic ossification. Late complications include fracture malunion/nonunion, radio-ulnar synostosis, and post-traumatic arthrosis. Understanding the fracture, institution of appropriate treatment, and awareness of the complications can help optimize results.

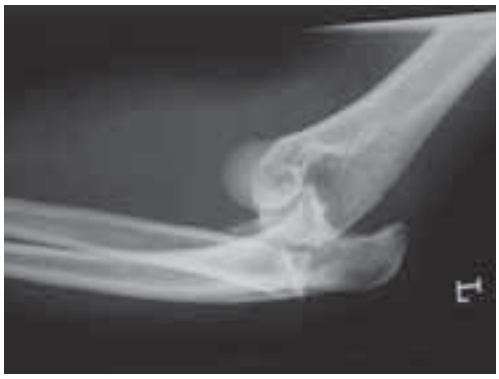


Figure 1. A Type 1 elbow fracture-dislocation with posterior dislocation and fracture of the radial head. Integrity of the coronoid process must be confirmed.

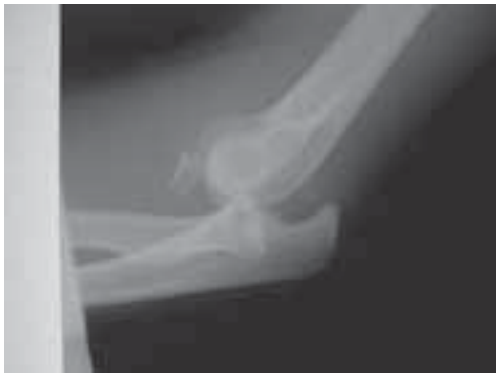


Figure 2. A Type 2 injury representing the "terrible triad" with a posterior elbow dislocation, coronoid fracture, and radial head fracture.

Anatomy

The anatomy of the elbow illustrates an elegant balance between the functional requirements of positioning the hand in space and the stability required for manipulating objects, bearing weight, and throwing. Motion at the elbow can be broken down broadly into flexion-extension of the elbow and rotation of the hand at the wrist. There are three anatomic components that provide stability and facilitate elbow function:

(1) Osseous articulation
(2) Capsulo-ligamentous complex
(3) Musculo-tendinous units

Osseous Articulation

The elbow is a highly congruent joint with significant inherent stability. The distal humerus is angled approximately 30 degrees anteriorly and has two articulations: the

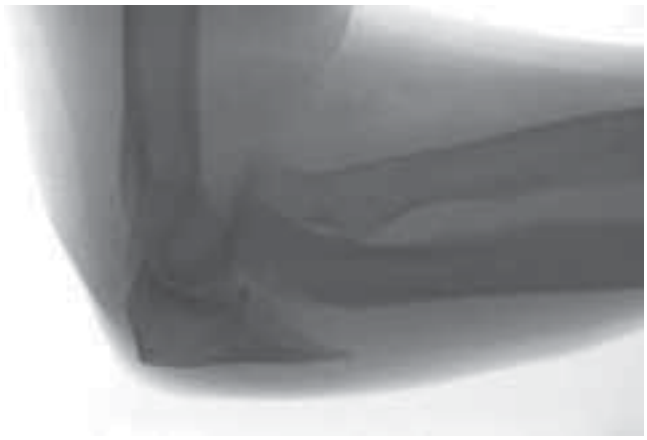


Figure 3. A Type 3 anterior or trans-olecranon fracture-dislocation with the relationship of the radius and the ulnar shaft maintained distally.

Figure 4. A Type 4 injury representing a proximal posterior Monteggia fracture with posterior dislocation of the elbow.

capitellum and trochlea. The capitellum articulates with the radial head providing rotation. The trochlea, which is covered by articular cartilage over an arc of 300°, is highly conformed to the proximal ulna and provides flexion-extension. This articulation alone provides the predominant stability of the elbow.[3] The anterior angulation allows for increased flexion prior to impingement. Furthermore, the olecranon and coronoid fossa on the distal humerus allows additional motion as well as increased stability with interlocking of their corresponding processes at the extremes of elbow motion. Stability is further enhanced at the ulnohumeral articulation by the "spool-shaped" anatomy of the trochlea that interdigitates with the central groove in the corresponding ridge of the trochlear notch of the olecranon, and the height of the coronoid process. Large coronoid fractures compromise the stability of the trochlear notch as well as the integrity of the medial collateral ligament, which inserts at the base of the coronoid process at the sublime tubercle.[4] Consequently, the ulno-humeral articulation provides significant stability in the anterior-posterior plane of the elbow. In addition, the highly congruent nature of the ulno-humeral joint also provides varus-valgus and rotational stability.

The radial head also contributes to stability of the elbow while providing for rotation of the hand and force transmission. As much as 60% of a load seen by the hand is transmitted to the humerus through the radio-capitellar articulation.[5] In addition, the radio-capitellar joint aids in resisting valgus stress of the elbow. There is approximately a 30 degree decrease in the resistance to valgus load by the elbow with resection of the radial head.[6] This valgus stability becomes paramount when the medial collateral ligament is compromised.[7] The radial head has been considered expendable when injured or dysfunctional, but in cases where there are concomitant injuries to the interosseous membrane of the forearm or medial collateral ligament of the elbow, significant instability can ensue with its loss.

Capsulo-ligamentous Complex

The medial collateral ligament (MCL) originates from the medial epicondyle and inserts on the ulna at the base of the coronoid process. The MCL has three components consisting of the anterior, posterior, and transverse bundles. The posterior and transverse bundles are subtle thickenings of the medial joint capsule, but the anterior bundle is readily identifiable. Several studies have examined the valgus strength provided by the MCL and have suggested that the anterior band of the MCL provides 33% to 50% of the resistance to valgus stress depending on the amount of elbow flexion.[6–9] Incompetence of the MCL can occur in several forms: frank rupture, chronic attenuation as with throwing sports, or fractures of the coronoid process or medial epicondyle.

The lateral collateral ligament (LCL) originates from the lateral epicondyle and inserts on the annular ligament over the radial head and the ulna posteriorly. Its components include the radial collateral, annular, accessory, and lateral ulnar collateral ligaments (LUCL). The LCL complex provides varus and posterolateral rotatory stability to the elbow, where tension in the LCL complex and the overlying musculotendinous structures maintains apposition of the radial head to the capitellum.[10, 11] Incompetence of the LCL, and particularly of the LUCL component, has been used to explain recurrent elbow dislocation or instability through a posterolateral route without an associated fracture.

Musculo-tendinous Units

The muscles crossing the elbow joint provide dynamic stability to the joint. Muscular contractions help maintain the ulno-humeral articulation. A cadaveric study showed that in elbows with sectioned MCL complexes, simulated physiologic muscle action was partially able to restore normal joint kinematics.[7]

Mechanism of Injury

In simple elbow dislocations the articular relationship is disrupted by way of soft tissue injury. The injury begins laterally and extends medially involving both the anterior and posterior soft tissue envelope and has been described to occur in three stages.[12]

(Stage 1) The LCL complex is partially or completely torn (PL subluxation).

(Stage 2) Anterior and posterior soft tissue is torn (PL dislocation).

(Stage 3) The MCL complex is torn (True dislocation).

With each progressive stage of soft tissue injury, the elbow experiences increasing instability from posterolateral subluxation to frank dislocation. As long as the anterior band of the MCL is left intact the joint can be reduced and stability can be attained through reduction of the bony articulations, despite the significant soft tissue injury. In contrast, elbow fracture-dislocations incorporate both a ligamentous and bony injury and thereby eliminate the hopes of stability with reduction.

Fracture & Treatment

Elbow fracture-dislocations incorporate both ligamentous and bony injury and in our opinion require operative treatment. Both the ligaments and fracture must be managed during treatment. The treatment steps include: (1) Reduction of the dislocation, (2) Treatment of the fracture (fixation versus replacement), and (3) Repair of the collateral ligaments.

Posterior Elbow Dislocation with Fracture of the Radial Head

Anteroposterior and lateral radiographs will readily identify posterior elbow dislocation with associated radial head fracture. The radiograph must be initially scrutinized for associated coronoid fracture. This may be evident as a small fragment in the soft tissue or may also become incarcerated within the trochlear groove.

In the absence of a coronoid process fracture, treatment options include non-operative and operative. Non-operative treatment after closed reduction of elbow dislocations with fractures of the radial head has been reported with success.[13] However with increasing severity of radial head injuries, operative fixation is recommended to avoid restricted forearm rotation and malunion. Displaced or comminuted fractures of the radial head have traditionally been excised. Recent understanding now indicates that a radial head fracture should be fixed or replaced when a ligamentous injury is suspected, as is the case of elbow dislocations, to avoid instability.[6, 7] For small displaced radial head fractures the authors treat the fracture with internal fixation. In comminuted cases, radial head replacement is performed. A lateral approach is utilized to access the radial head. The LCL complex is evaluated and reattached to the lateral epicondyle with drill holes or suture anchors. The elbow is also evaluated medially and the MCL is examined and repaired if injured. The ulnar nerve may also be released if indicated through this approach.

The "Terrible Triad" (Posterior Dislocation with Fracture of the Radial Head and Coronoid

With the addition of a coronoid fracture, the operative treatment becomes more involved. Ring & Jupiter advocate fixing all fractures of the coronoid regardless of size due to the instability and historically poor results from this injury.[2]

Multiple exposures and fixation options for the coronoid process are available.[14] The authors advocate a midline posterior approach again facilitating access to both the medial and lateral sides. The coronoid fracture is approached first through the medial side. The ulnar nerve is identified and released. The split in the two heads of the flexor carpi ulnaris through which the ulnar nerve travels is utilized. The anterior head is raised off of the ulna while protecting the ulnar nerve thereby exposing the coronoid process. Fixation of the coronoid can be accomplished with a suture passed through a drill hole or screw fixation from posterior to anterior. Attention is then turned laterally where the radial head is repaired or replaced and the LCL is repaired (see Figure 5). Stability is checked through range of motion examination. If instability exists in the mid-range of motion a hinged external fixator may be applied.

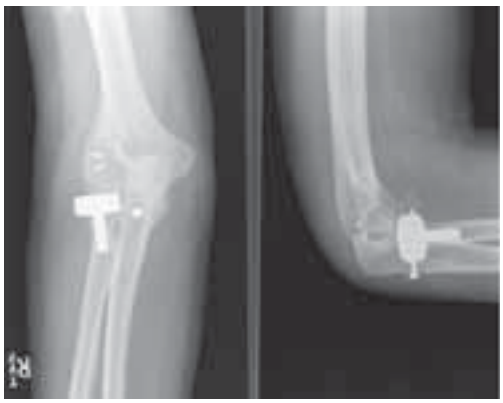


Figure 5. A Type 2 terrible triad injury after undergoing open reduction internal fixation of the coronoid fracture, radial head replacement, and repair of the LCL complex with suture anchors resulting in a stable and congruent joint.

Anterior Elbow Dislocation with Fracture of the Olecranon

The elbow dislocates anteriorly with anterior olecranon fracture-dislocations occurring through the proximal ulna, most commonly trans-olecranon. This pattern is easily confused with an anterior Monteggia fracture (fracture of the proximal ulnar shaft with radial head dislocation), but is distinguished by the fact that both the radius and the ulna

dislocate anteriorly and maintain their relationship.[15] Although this is not a true dislocation of the ulno-humeral joint, the stability of the ulno-humeral articulation is disrupted and therefore should be considered and treated as an elbow fracture-dislocation.

The fracture of the proximal ulna is often complex and can be associated with a large coronoid fragment. In contrast, the capsulo-ligamentous restraints may remain intact since the dislocation occurs predominantly from loss of osseous articulation rather than ligamentous incompetence. We utilize a midline posterior approach. The coronoid is directly visualized through the olecranon fracture and fixed with screws. The olecranon is then reduced. Fixation of the ulna is performed with plates and screws applied to the dorsal surface of the ulna while wrapping around the olecranon proximally. Often significant comminution exists in the proximal ulna and should be bridged with a plate of adequate length. Despite being a severe injury, 15 of 17 patients in Ring et al.'s series treated as outlined above achieved good or excellent results.[15]

Posterior Elbow Dislocation with Fracture of the Proximal Ulna (aka, a Posterior Monteggia Fracture)

Posterior olecranon fracture-dislocations may be considered in the spectrum of posterior Monteggia fractures.[15, 16] The pattern includes a proximal ulna fracture, again often trans-olecranon, with apex posterior angulation of the fracture and posterior dislocation of the radial head. Although again not a true dislocation, the stability of the ulno-humeral articulation is disrupted sufficiently to warrant its inclusion.

In addition to the proximal ulna fracture and possibly a coronoid fracture, the radial head dislocates posteriorly and is often fractured. The LCL is also often injured, predisposing to posterolateral rotatory instability. We utilize a midline posterior approach. The coronoid is examined through the proximal ulna fracture and fixed with screws. The radial head is repaired or replaced, and then reduced. The LCL is then repaired. The ulna is subsequently plated. Jupiter et al. reported their experience with 11 cases of posterior Monteggia lesions and yielded 6 good or excellent results.[16] The inferior results were related to inadequate reduction of the ulna and coronoid with persistent posterior subluxation of the radio-capitellar joint.

Rehabilitation

The intra-operative goal is restoration of elbow stability. If this is achieved then early motion can be instituted after a brief (less than 2 weeks) period of immobilization. When fixation is more tenuous or stability is guarded, then the period of immobilization may have to be increased, or more preferably, motion can be initiated with the protection of a hinged elbow fixator.

Complications

Complications after elbow fracture-dislocations can be divided into early and late. Early complications include instability, stiffness, and heterotopic ossification. Late complications include fracture malunion/nonunion, radio-ulnar synostosis, and arthrosis. Complications are best treated by avoidance of risk factors.

Instability

Early instability after operative fixation is best treated with diligent examination under intra-operative fluoroscopy. In addition, adequate reduction and fixation of the fracture and ligamentous repair must be re-confirmed. In the presence of persistent instability a hinged external elbow fixator may be applied. In contrast, chronic instability may be secondary to malunion, nonunion, bony defects, or attenuation or inadequate repair of the soft tissue.

Stiffness

Loss of motion is common following any elbow injury and including both simple and complex dislocations. Immobilization for beyond two weeks has been shown to greatly increase the risk for stiffness and is best avoided by early motion.[1] In the face of elbow fracture-dislocations, prolonged immobilization would only be considered if the repair was tenuous. In this situation, both protection of the repair and early immobilization is best managed with a hinged elbow fixator.

Stiffness after fracture healing can be treated with static progressive splinting. Open release of the elbow capsule can also be used with reliably good success assuming the articular anatomy is well-reduced.[17]

Heterotopic Ossification

Risk factors for heterotopic ossification include severe trauma, burns, and brain injuries.[18] Other less well defined risk factors include gender and genetics. The relationship between operative treatment of elbow fracture-dislocations and the risk for heterotopic ossification remains controversial. Traditionally it was considered that early operative fixation increased the risk. More recently, it has been shown that the timing of surgery and the risk of heterotopic ossification are not related.[19]

Drawing from the trauma and joint arthroplasty literature, radiation therapy and non-steroidal anti-inflammatory medications have been shown to be effective against heterotopic ossification.[20] Use of these modalities must be tempered against the risk of compromised wound healing with radiation therapy and medical morbidity with anti-inflammatory medications.

Resection of heterotopic ossification is successful in returning motion, but the timing of surgery has historically been controversial. Early resection avoids formation of

elbow contracture and joint degeneration, but risks return and exacerbation of the process. In cases of isolated elbow trauma without head injury, resection has been shown to be successful without recurrence when the heterotopic bone assumes a well-defined trabecular pattern on plain radiographs.[21, 22]

Arthrosis

Post-traumatic arthrosis occurs secondary to the severity of the injury, articular injury, and residual instability. Treatment of symptomatic arthrosis resistant to non-operative management is directed by the age of the patient. Total elbow arthroplasty is effective in treating older patients with less demands on the involved extremity.[23] In younger patients, debridements and fascial interposition arthroplasty may allow for maintenance of a more active lifestyle.[24]

Summary

Elbow fracture-dislocations are complex injuries encompassing both soft tissue and bony injury to the elbow. The result is inherent instability to the intricate relationship and function of the distal humerus, proximal ulna, and the radial head. Understanding the significance of the bony articulation, soft tissue complex, and the support of the musculotendinous units is central to the pathoanatomy. We routinely recommend operative treatment of these injuries. Complications are common and include instability, stiffness, heterotopic ossification, and arthrosis. Complications are best avoided by achieving sound soft tissue and bony repair, stable reduction of the articulations, and early motion.

References

1. Melhoff TL, Noble PC, Bennet JB, et al. Simple dislocation of the elbow in the adult: Results after closed treatment. *J Bone Joint Surg* 1988;70A:244.
2. Ring D, Jupiter JB. Fracture-dislocations of the elbow. *J Bone Joint Surg* 1998;80A:566–580.
3. Morrey BF: Anatomy of the elbow joint, in Morrey BF (ed): The Elbow and Its Disorders, ed 3. Philadelphia, PA: WB Saunders, 2000, pp 13–42.
4. Cage DJN, Abrams RA, Callahan JJ, Botte MJ. Soft tissue attachments of the ulnar coronoid process. An anatomic study with radiographic correlation. *Clin Orthop Rel Res* 1995:320;154–158.
5. Halls AA, Travill A. Transmission of pressures across the elbow joint. *Anat Rec* 1964;150:243–7.
6. Hotchkiss RN, Weiland AJ. Valgus stability of the elbow. *J Ortho Res* 1987;5:372–377.
7. Morrey BF, Tanaka S, An KN. Valgus stability of the elbow. A definition of primary and secondary constraints. *Clin Orthop Rel Res* 1991;265:187–195.
8. Morrey BF, An KN. Articular and ligamentos contributions to the stability of the elbow joint. *Am J Sports Med* 1983;11:315–319.
9. Sojbjerg JO, Ovesen J, Gundorf CE. Experimental elbow instability after transection of the medial collateral ligament. *Clin Orthop Rel Res* 1987;218:186–190.
10. O'Driscoll SW, Bell DF, Morrey BF. Posterolateral rotatory instability of the elbow. *J Bone Joint Surg* 1991;73:440–446.
11. Cohen MS, Hastings HH. Rotatory instability of the elbow. The anatomy and role of the lateral stabilizers. *J Bone Joint Surg* 1997; 79A:225–233.
12. O'Driscoll SW, Jupiter JB, Cohen MS, Ring D, McKee MD. Difficult elbow fractures: pearls and pitfalls. *Instr Course Lect.* 2003;52: 113–34.
13. Broberg MA, Morrey BF. Results of treatment of fracture-dislocations of the elbow. *Clin Orthop Rel Res* 1987;216:109–119.
14. Ring D. Fractures of the coronoid process of the ulna. *J Hand Surg [Am].* 2006;31(10):1679–89.
15. Ring D, Jupiter JB, Sanders RW, Mast J, Simpson NS. Transolecranon fracture-dislocation of the elbow. *J Orthop Trauma* 1997;11:545–550.
16. Jupiter JB, Leibovic SJ, Ribbans W, Wilk RM. The posterior monteggia lesion. J Orthop Trauma 1991;5:395–402.
17. Husband JB, Hastings H. The lateral approach for operative release of post-traumatic contracture of the elbow. *J Bone Joint Surg* 1990; 72A:1353–8.
18. Garland DE. A clinical perspective on common forms of acquired heterotopic ossification. *Clin Orthop Rel Res* 1991;263:13–29.
19. Noblin JD, Geissler WB, Bass D. The incidence of heterotopic ossification with elbow injuries. *Orthop Trans* 1995;19:162.
20. Kjaersgaard-Andersen P, Ritter MA. Current concepts review. Prevention of formation of heterotopic bone after total hip arthroplasty. *J Bone Joint Surg* 1991;73A:942–7.
21. Jupiter JB, Ring D. Operative treatment of post-traumatic proximal radioulnar synostosis. *J Bone Joint Surg* 1998;80A;248–57.
22. McAuliffe JA, Wolfson AH. Early excision of heterotopic ossification about the elbow followed by radiation therapy. *J Bone Joint Surg Am.* 1997 May;79(5):749–55.
23. Morrey BF, Adams RA, Bryan RS. Total replacement for post-traumatic arthritis of the elbow. *J Bone Joint Surg* 1991;73B:607–12.
24. Morrey BF. Post-traumatic contracture of the elbow. Operative treatment including distraction arthroplasty. *J Bone Joint Surg* 1990;72: 601–18.

Review

Coding and Billing for Orthopedics — The Office: How to Get Paid for What You Do

BRUCE B. VANETT, MD

Department of Orthopedic Surgery, Temple University School of Medicine, Philadelphia, PA

Abstract

The business side of orthopedic surgery is not often discussed during our training programs. Most orthopedists learn something about this topic with on the job training. In truth correct coding and billing are the backbones of any successful practice. It is incumbent upon each physician to become familiar with these concepts to insure proper reimbursement for their work effort. This paper lays the groundwork for understanding these modalities in the office practice. It is important to keep in mind that this information is relative to the billing and reimbursement in Pennsylvania; other states may have a different reimbursement pattern.

The practice of orthopedic surgery is a complex and ever changing profession — new procedures, new technology, and evidence-based outcomes help us to modify our treatments to always provide the best care possible for our patients. Yet, very little is ever taught during our residency training or even in our practice careers about the business of orthopedics. Economics is not a dirty word; it is a fact of our professional lives. Insurance companies, employers, employees, and the government all understand the business side of orthopedics; it is imperative, therefore, for us to also learn how to maximize our reimbursement for what we really do. On the job training from an office manager, billing company, or partner may help; but grasping it yourself is far superior. This paper will attempt to explain the basics of coding and billing in the office.

To begin with, the diagnosis of a medical problem is defined by an ICD-9 code from the International Classification of Diseases, 9th Revision, which is readily available.

Procedures which we perform are defined in the CPT-4 or Current Professional Terminology, 4th Revision, which is also published and updated yearly. Procedures include not only operations, but also office visits, consults, x-rays, injections, medicines, and casting among others; it includes everything we do in caring for a patient. The ICD-9 and CPT-4 must be linked; the claim will be rejected if the procedure does not relate to the diagnosis chosen (e.g. ICD-9 code 729.5 = knee pain with CPT code = hip x-ray or ICD-9 code 717.7 = chondromalacia patellae with CPT code = arthroscopic medial menisectomy; these two examples are not linked). Different insurers allow different numbers of CPT codes per day of visit. As I will state several times in the course of this discussion, the insurer's goal and your goals are often quite opposite; therefore, it is very important to submit a "clean" claim from the start as you want to get paid quickly and completely. All insurers have "timely limits" on billing — if you don't get the claim processed in a finite length of time, it will be denied and you will have to have "proof of timely filing" to appeal; if you have no proof of filing, the claim will not be paid. For the most part, insurers will not allow you to bill the patient for a billing error which caused a denial; remember you will most probably be a "participating provider" and if a claim is denied because your office did not submit it on time, you can not bill the patient — this amount will have to be written off. Your only defense is to get it right and correct any errors as quickly as possible; resubmit and follow up carefully or you will lose out!

There are two components of each patient's bill. Evaluation and Management (E/M) services cover your initial new patient visits, follow up visits, consultations as an inpatient or outpatient, and hospital care visits. The second part of the chare includes Procedures. These can be x-rays, casts, supplies, medical reports, or surgical procedures. It is very important for each of us to know the components of these services so that they are clearly documented and billed correctly. Just by taking three extra minutes of dictating what you actually did can significantly impact your level of reimbursement.

Three main factors contribute to the level of billing going from Level 1 to Level 5. History, physical examination, and medical decision making are critical. Contributing, but less important, factors include counseling, coordination of care, nature of the problem, and actual time spent in the face-to-face communication with the patient.

The history ranges from the lowest level of problem focused to the highest level of comprehensive history. All levels start with chief complaint and history of present illness and then add review of systems, past medical history, family history, social history, and complete medical and surgical history to increase the complexity of the visit. Beware! Most orthopedists do not perform a review of systems but it can be done quickly and correctly (see Table 1). Physical exam also was devised and made for internists, not orthopedists.

Table 1. Organ Systems

Constitutional	Skin	Eyes	Ears, Nose, Throat	Cardiovascular	Respiratory
Musculoskeletal	Neurological	Hematologic Immunologic	GU Male	GU Female	Psychiatric

We always fully examine the body part (e.g. knee, shoulder) that is involved; this regimen asks for a complete organ system (e.g. musculoskeletal, cardiac) or multisystem exam to get the highest level of coding. What are the "body systems" being investigated? It is generally true that we all do observe and/or examine these areas; you must document that you did actually do this exam. The constitutional system includes vital signs (these can be done by your assistant) and general appearance; such as nutrition, habitus, deformity, grooming. We don't normally evaluate Head and Face, Eyes, ENT, Respiratory, Cardiac, GI or GU systems. We do Vascular evaluations looking for varicose veins, swelling, temperature, edema and tenderness as well as palpation of peripheral pulses. The Skin counts also and it is important to comment on scars, rashes, lesions or ulcers. Neurologic system evaluation includes coordination, deep tendon reflexes, sensation, orientation, mood, and affect such as depression, anxiety or agitation. We almost always compare one extremity to the other — this must be recorded in your dictation also.

The Musculoskeletal system is our home base; yet, it must be fully covered.

This examination includes:

1. Gait and Station — limp, crutches, or cane.
2. Inspection and Palpation — malalignment, crepitus, tenderness or effusion.
3. Range of Motion — pain, crepitus, or contracture.
4. Stability — ligament laxity.
5. Muscle strength and tone — atrophy, spasticity or weakness.

The more points or "bullets" covered, the higher the level of the visit. For a problem focused physical exam, you need 5 bullets in 1 system. The next level needs 6 bullets; the next needs 12 bullets in 2 systems or 6 different systems; the highest level of comprehensive exam requires 9 organ systems with 2 bullets in each one — daunting, but not impossible. Always keep in mind, the more extensive your exam, and subsequent documentation, the higher the level you may bill. If you are doing the work, just document it — if you don't document it, you can not code higher.

The last major component of level of coding is complexity of decision making. The more diagnoses (comorbidities) the patient has, the more complex is the decision making code. Note also that closed treatment of a fracture with no reduction is graded as moderate; any proposed surgery is considered high complexity. Include in your notes diagnostic testing which was ordered or reviewed, old records reviewed, tests and/or x-rays reviewed by you or discussed with another doctor. Document discussion of risks of any procedures planned.

A brief note about using time to determine level of coding. Table 2 includes time spent on the visit; this parameter is not usually applicable in our orthopedic practice. However, a major scoliosis or back surgical procedure discussion with the patient and their family, a revision total joint procedure, or a worker's compensation patient with multiple records to review and then subsequent discussion could invoke these time parameters. If you are using time as your parameter for level of coding, write it down in the record and document actual time spent with the patient.

Some special circumstances warrant separate notations. If counseling or coordination of care takes greater than 50% of face to face time with the physician/patient or physician/family, then record the time in the note. Note that a new patient means that there are no notes or contacts from a physician or anyone in his group within three years — even if it is a new problem. Level 5 visits (99205) for a new patient are billed at a 4 x higher level than level 1 visits (99201) in one series (personal communication, BBV). Established or "old" patient visits have less required elements and move the documentation requirements down one level — i.e. expanded history, expanded physical exam, low decision making = Level 3 visit, not Level 2, in established patients. This fact means that most office revisits for orthopedic care are Level 3 and must include Chief Complaint, HPI, ROS, and appropriate physical exam. Hospital care for nonoperative conditions like hand infection, sciatica, etc. are billed at 3 levels, again using history, physical exam, and decision making parameters. Consultations are billed on the 5 level system. A consult is service provided by a physician whose opinion or advice is requested by another physician or other source, such as an insurance company, nursing home, or other third party. Almost all HMOs require a referral asking for your orthopedic opinion and therefore, they should be charged as consultations, not new patient visits. (NB — The exception to this tenet is when the referral is for a known fracture; this should be billed as a new patient visit but then also bill for the fracture care). Consultations require the UPIN of the referring physician, a note in your dictation stating this is a consultation and a letter or note sent back to the original consulting physician. Follow up consults for hospital inpatients should be billed under the hospital care codes if you initiate treatment and continue treatment; only use follow up inpatient consults if you have finished initial treatment and then are asked by the referring doctor to see the patient again. Physicians do code differently for consults. My protocol is

Table 2

Requirements	a) Problem focused history b) Problem focused physical exam c) Straightforward medical decision making (CC, HPI)	a) Expanded problem focused history b) Expanded problem focused physical exam c) Straightforward medical decision making (Add ROS)	a) Detailed history b) Detailed physical exam c) Low medical decision making (Add PMH, FH, SH)	a) Comprehensive history b) Comprehensive physical exam c) Moderate medical decision making (Add — complete PMH)	a) Comprehensive history b) Comprehensive physical exam c) High complexity medical decision making
Problem Level	Self limited or minor	Low to moderate severity	Moderate severity	Moderate to high severity	Moderate to high severity
Time	10 minutes face to face contact	20 minutes	30 minutes	45 minutes	60 minutes
Level of Service	**1**	**2**	**3**	**4**	**5**

to list as the first diagnosis the reason you were asked to see the patient (e.g. knee pain, back pain) and next to list your diagnosis (e.g. torn meniscus, herniated nucleus pulposus.). Most billing forms allow 4 diagnoses and I do list comorbidities (e.g. hypertension, NIDDM, COPD) on the forms to show that I did thoroughly examine the patient.

The other half of the patient encounter includes procedures. Everything you do to the patient has codes and you must include them or do them for nothing. Arthrocentesis, injection with Cortisone, application of a cast, fracture treatment with no reduction, applying a wrist splint, application of external coils for a nonunion and everything else requires a code for proper billing. Just as important as doing these procedures is adding a modifier to your code. If you do not use a modifier, the insurance company will choose to pay you for the lowest paying procedure and disregard the office visit charge (if applicable). There are over 25 modifiers listed in the CPT-4 book; it is incumbent upon you to familiarize yourself with them. The most common include -25, significant and separate evaluation and management service on the same day of procedure/service; -51, multiple procedures on the same day at the same session by the same provider, -57 decision for surgery on day of or day before surgery; and -58 related procedure during global period. These codes are added to the procedure codes and complete the billing process. For example, a new patient who comes in with degenerative arthritis of her knee and gets a low complexity evaluation and knee joint injection with Kenalog would be coded as ICD-9 715.6 and CPT-4 99203 -25 20610, J3301.

Another important consideration is the Global Fee Period. This time normally runs anywhere from 30 to 90 days from the date of the procedure; surgery and fracture care are both included. X-rays and injections can be billed in the global period; most cast changes are lumped into the global fee, but insurers vary on paying for repeat casting and should be individualized. A different complaint in the global period of another problem should be billed with the modifier -24. Cast applications cannot be billed separately if the cast is part of the original fracture care code; then you can only bill a "Q" code for the cast supplies. However, if the cast is applied for a bruise or a sprain and not a fracture, then you should bill for the cast application as a procedure and use the -25 modifier; the cast supply charge is included in the application fee.

You can truly see that office coding and billing is mildly complex. It is crucial that all of us become familiar with this topic, just as we all do with any area of orthopedics. Reading the basic ICD-9 and CPT-4 books can introduce the topic; it also helps to attend a coding course and many are offered by the Academy. The key to fair and adequate reimbursement is to be correct and complete with a "clean" claim; this treatise should get you started. Remember that every insurance company has different "fee schedules" and if you are a participating physician with a particular insurer you will only get paid per their "fee schedule" regardless of additional coding and documentation. However, it is a good practice to code fully and accurately throughout your practice for all of your insurers as commercial, worker's comp and no fault each pay differently than your contracted rates. It is encumbent for each physician to learn how to handle these topics to get reimbursed correctly for the work that you actually do.

Abstract

A Comparison of the Correction of Rib Prominence for Vertebral Body Derotation Versus Thoracoplasty

Jahangir Asghar, MD, Patrick Cahill, MD, Amer F. Samdani, MD,
David H. Clements MD, Joshua M. Pahys, MD, Randal R. Betz, MD

Shriners Hospital for Children, Philadelphia, PA

Introduction

The purpose of this study is to compare objective clinical measures for correction of rib prominence using thoracoplasty versus direct vertebral body derotation.

Methods

Our prospective adolescent idiopathic scoliosis database was reviewed for patients with structural thoracic curves treated with posterior spinal fusion and thoracoplasty (TP) or vertebral body derotation (VBR). Furthermore, for inclusion, they had to have preoperative and postoperative scoliometer readings. The postoperative scoliometer readings were done at two years. 107 patients met the inclusion criteria for the study. There were 61 patients in the VBR group and 47 in the TP group. No statistical difference was noted between the groups for thoracic curve magnitude, flexibility, preoperative scoliometer reading.

Results

The average preoperative reading was similar between the two groups (TP-14.2, VBR-15.1, $p = 0.41$). The average postoperative correction was similar between the two groups (TP-5.31, 4.25, $p = 0.29$). The percent correction showed a trend toward statistical significance difference with 63% correction in TP group and a 72.1% in the VBR group ($P = 0.12$). When comparing a subgroup of curve magnitude less than 75 degrees and thoracic curve flexibility of greater than 50%, the percent correction of the rib prominence showed a significant difference with 67.2% correction in TP group and to 80% in VBR group ($P < 0.05$).

Conclusions

At two years, the percent correction between vertebral body derotation and thoracoplasty in correcting rib prominence are statistically similar. However, for thoracic curves measuring less than 75 degrees and flexibility greater than 50%, the percent correction was statistically greater in the vertebral body derotation group compared to the thoracoplasty group.

Abstract

Increased Tendon Calcification and a Bone Mineralization Protein in Musculoskeletal Tissues with Repetitive Reaching Task

Ann E. Barr, PT, PhD,[2] Harry K. Hobbs,[1] Mamta Amin,[1]
Fayez F. Safadi, PhD,[3] Mary F. Barbe, PhD[1, 3]

[1]*Department of Physical Therapy, Temple University, Philadelphia, PA,*
[2]*Department of Physical Therapy, Thomas Jefferson University, Philadelphia, PA,*
[3]*Department of Anatomy and Cell Biology, Temple University, Philadelphia, PA*

Introduction

Work-related musculoskeletal disorders (WMSDs) arise from repeated performance of tasks at submaximal levels of physical exertion that eventually lead to tissue damage due, perhaps, to insufficient recovery of tissues between bouts of performance. Our laboratory has developed a rat model of repetitive and forceful reaching and grasping. Our results indicate that performance of a high rate, low force (HRLF) task regimen results in injury, inflammation and fibrosis in bone, muscles, tendons, nerves and associated loose connective tissues.[1–3] Osteoactivin (OA) is a recently identified factor that plays a role in bone mineralization and possibly in wound healing and inflammation. Enhanced expression of this protein would suggest that repetitive and/or forceful tasks lead to accelerated bone remodeling and tendon matrix changes, which would further our understanding of the etiology of MSDs. The purpose of this current study was to examine the production of OA in musculoskeletal tissues and tendon calcification following performance of these repetitive and/or forceful tasks for up to 12 weeks.

Methods

Young adult, female Sprague-Dawley rats were used. Experimental rats were trained in one of two repetitive tasks. These tasks consisted of reaching forward to pull a lever at a rate of 4 reaches/min at either 15% of maximum grip strength (HRLF) for 2 hours/day in 30 min sessions, 3 days/week for up to 12 weeks. Results were compared to control rats, which are considered week 0 in this study.

Following euthanasia using Nembutal (120 mg/kg body weight), rats were perfused intracardially with 4% paraformaldehyde. Musculoskeletal tissues were harvested. Soft tissues were dissected out and frozen sectioned en bloc into 15 micrometer longitudinal sections, while bones were paraffin embedded and cut into 5 micrometer sections, before mounting on coated slides. Tissue sections on slides were analyzed for the presence of calcium salts using von Kossa staining. Sections with tendons were stained in 3% silver nitrate solution for 1.5 hours under intense light, rinsed in distilled water, 5% sodium thiosulfate for 2 minutes, and counterstained with nuclear red.

For localization of OA, sections were blocked for endogenous peroxidase, washed, permeabilized with 0.05% Pepsin solution in 0.01N HCL, washed and blocked for nonspecific binding with 10% goat serum for 20 minutes. Primary antibody raised against the c-terminal sequence of osteoactivin was diluted 1:100 with PBS and incubated on slides overnight at room temperature. After washing, sections were incubated with appropriate secondary antibody conjugated to HRP, and visualized using DAB with or without cobalt (black versus brown, respectively). Percent area with OA immunoreactivity was quantified using the Osteo II Bioquant program using methods described previously.[3] Two-way ANOVA ($p \leq 0.05$) was used to examine differences across weeks and between regions, followed by Bonferonni post hoc analysis.

Results

Discrete sites of von Kossa staining were present in forelimb tendons at the level of the wrist in week 6 and 12 HRLF rats (Fig. 1B), but not in controls (Fig. 1A). Von Kossa staining was greatest in HRLF week 12 forelimb tendons in matrix regions surrounding tendon fibroblasts. Supraspinatus tendons were also examined, but no von Kossa staining was present at any time point in either exposure group.

OA immunoreactivity increased in osteoclasts, periosteal cells, osteoctyes and osteoblasts (Fig. 1C), as well as in chondrocytes, tendon fibroblasts and mast cells, in 6–12 week HRLF rat radius and ulna. The highest OA immunoreactivity was seen in radius periosteum at sites of muscle and tendon attachments in week 5 (Fig. 2A), and in forelimb tendons at the level of the wrist in week 8 (Fig. 2B).

Discussion

Increases in osteoactivin (OA) staining in the periosteum parallels previously reported inflammatory responses in this same tissue, suggesting that OA may play a role in inflammation-induced bone remodeling by a repetitive reaching

and grasping task. The tendon OA increases in week 8 indicate matrix remodeling changes that are delayed compared to bony tissues possibly due to the avascular nature of tendon. Tendon von Kossa staining may indicate the onset of pathological calcific tendonitis as a result of performing repetitive and forceful tasks. Thus, this study shows that repetitive tasks catalyze changes at the cellular level in a variety of tissues.

References

1. Barbe MF, Barr AE, Gorzelany I, Amin M, Gaughan JP, Safadi FF. Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J Orthop Res* 2003, 21:167–176.
2. Barr AE, Safadi FF, Gorzelany I, Amin M, Popoff SN, Barbe MF. Repetitive, negligible force reaching in rats induces pathological overloading of upper extremity bones. *J Bone Mineral Res* 18(11) 2003, 2023–2032.
3. Clark BD, Al-Shatti TA, Barr AE, Amin M, Barbe MF. Performance of a High-repetition, high-force task induces carpal tunnel syndrome in rats. *J Orthop Sports Phys Ther,* 2004, 34(5):244–254.
4. Selim AA, Abdelmagid SM, Kanaan RA, Smock SL, Owen TA, Popoff SN, Safadi FF. Antiosteoactivin antibody inhibits osteoblasts differentiation and function in vitro. *Crit Rev Eukaryot Gene Expr* 2003; 13(2–4):265–75.

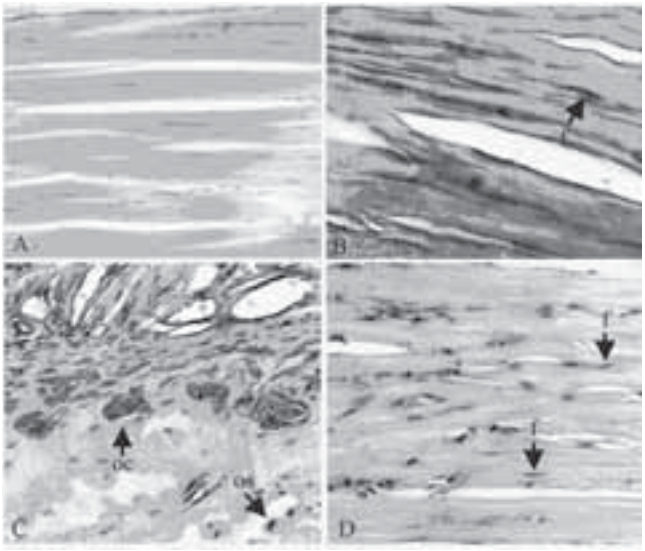


Figure 1. Flexor forelimb tendon vonKossa staining dramatically increased in HRHF 12 week rat tendon **(B)** compared to controls **(A). (C)** In HRLF week 12, OA increased in bone osteoclasts (oc) and osteocytes (os). **(D)** OA also increased in fibroblasts (f) in HRLF 12 week tendon.

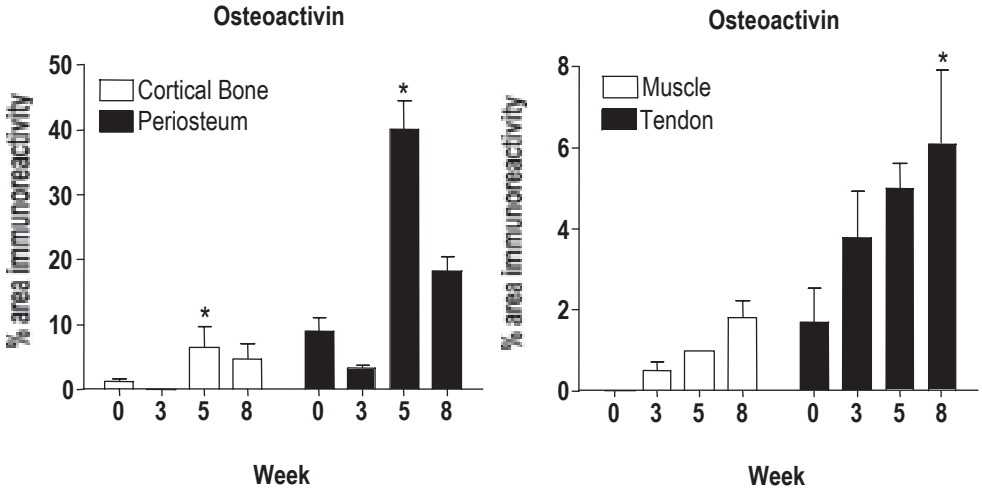


Figure 2. Graph shows that % area of osteoactivin immunoreactivity significantly increased in week 5 in cortical bone and periosteum, and in week 8 in tendon of HRLF rats. *$p < 0.001$.

Abstract

Gender Differences in Hip Strength, Muscle Activation, and Dynamic Stability During a Functional Landing Task

David J. Stearne, PhD, ATC,[2, 1] Keith F. Davis, MS, ATC,[1]
Michael R. Sitler, EdD, ATC,[1] Ryan T. Tierney, PhD, ATC,[1] John McNamara, PhD[3]

[1]*Department of Kinesiology, Temple University, Philadelphia, PA,*
[2]*Department of Kinesiology, West Chester University, West Chester, PA,* [3]*Saint Francis College, Brooklyn Heights, NY*

Purpose

Dynamic instability has been associated with altered neuromuscular control and increased demand on joint stabilizing structures. Gender differences in hip sensorimotor control strategies used to achieve stabilization may reflect a risk factor for acute non-contact knee injury. The purpose of this study was to examine gender differences in hip muscle strength and activation, and time to center of mass stabilization (TCMS) on a functional landing task.

Methods

A post-test only design was used in a controlled laboratory setting. Forty healthy NCAA Division I collegiate and club sport athletes (20 males, 21.1 ± 1.7 years, height = 181.2 ± 8.9 cm, mass = 85.3 ± 21.3 kg; and 20 females, 19.6 ± 1.4 years, height = 171.2 ± 8.8 cm, mass = 65.4 ± 7.4 kg) volunteered for the study. Isometric strength and strength ratios for the hip extensors, flexors, abductors, adductors, and internal and external rotators were measured with a hand-held dynamometer. Participants then performed a two-legged takeoff jump-to-one-legged landing, from a horizontal distance equal to 50% of their standing height, over a foam hurdle 10% of their standing height. Participants landed on a force plate and were instructed to attain a stable position on the landing leg as quickly as possible. Electromyography (EMG) preparatory (150 ms) and reactive (250 ms) area and EMG co-activation area was collected for the gluteus maximus, biceps femoris, gluteus medius, iliopsoas, rectus femoris and adductor longus; and TCMS was measured on a force plate. Hip strength was analyzed using Independent t-tests. EMG variables and TCMS were analyzed with multiple one-way MANOVAs.

Results

Males had 13% greater isometric hip flexor (males = 5.9 ± 1.3, females = 5.2 ± .7 N/kg; t = 2.3, p = .030) and 15% greater external rotator (males = 5.3 ± 1.3, females = 4.5 ± .6 N/kg; t = 2.4, p = .020) strength than females. Females had 21% greater adductor longus EMG preparatory area (females = 6.7 ± 2.2, males = 5.3 ± 2.0; F = 4.5, p = .040), whereas males demonstrated 31% higher gluteus medius/adductor longus EMG preparatory muscle co-activation area ratio (females = 1.1 ± 0.5, males = 1.6 ± .7; F = 6.7, p = .010). No significant gender differences existed in reactive EMG or TCMS.

Discussion

Center of mass stabilization in landing and deceleration is gained through optimal alignment of lower extremity joint segments and equalization of forces, requiring joint moments at the hip, knee, and ankle. Larger joint moments created with increased postural sway reflect a longer time to center of mass stabilization, requiring greater muscle activation to achieve postural stability. This may be metabolically costly, leading to earlier onset of muscle fatigue, breakdown in landing technique, and increased risk of non-contact injury. Although possibly attributed to anatomical differences in pelvic width, greater adductor longus preparatory activity found in females may pre-align the hip in adduction, which with higher ground reaction forces would result in increased knee valgum. Greater gluteus medius/adductor longus co-activation in males, with greater gluteus medius pre-activation, may reflect a more efficient landing strategy and optimal alignment of lower extremity segments in preparation for landing.

Conclusions

Despite gender differences in hip neuromuscular control strategies in preparation for landing, males and females were similar in achieving dynamic stability after ground contact. The extent to which this occurs on more demanding functional tasks is unclear and may be important in explaining gender differences in acute non-contact knee injury risk.

Figure 1. Two-legged standing broad-jump to one-legged landing.

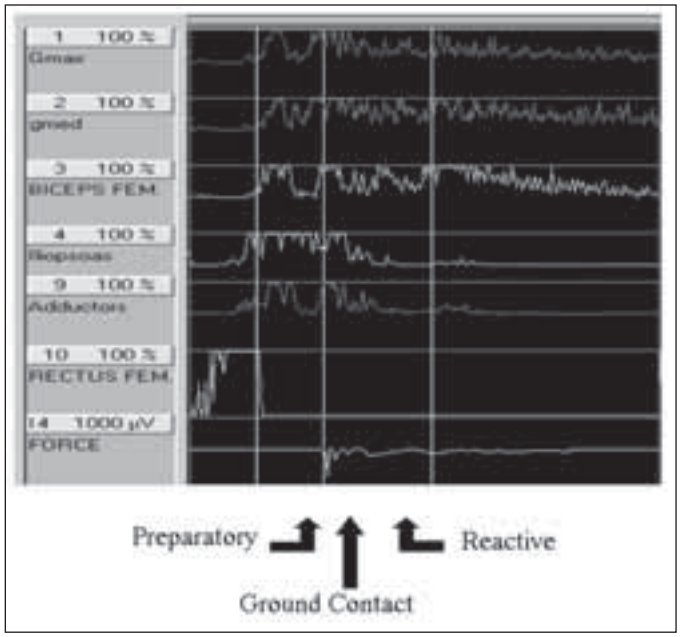


Figure 2. EMG

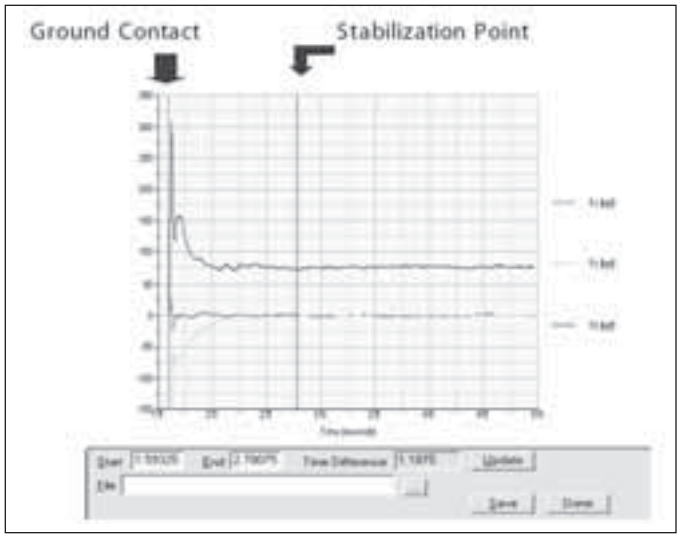


Figure 3. TCMS

Abstract

Augmented Low-Dye Arch Taping Effects on Muscle Activity and Ground Reaction Forces in People with Pes Planus

KILY B. WALL, MS, ATC, KATHLEEN A. SWANIK, PHD, ATC,
CHARLES B. SWANIK, PHD, ATC, DAVID J. STEARNE, PHD, ATC

Department of Kinesiology, Temple University, Philadelphia, PA

Purpose

Arch taping is a common treatment for individuals with pes planus. However, limited data exists on its impact on muscle activation and force dissipation. Therefore, the purpose of this study is to evaluate muscle recruitment strategies and ground reaction forces (GRF) in people with flexible pes planus (FPP) using an augmented low-Dye arch taping technique (ALDTT) while performing functional tasks.

Methods

A two group pre- and post-test non-equivalent group design was used. Twenty-two (11 males, 11 females, 20.27 ± 1.61 years of age) people with a vertical navicular drop ≥10 mm volunteered for this study. Subjects were divided into groups based on shin pain, control (no pain) and experimental groups (pain). Independent variables were tape and functional tasks (backpedal (BP), cutting (CUT), drop jump (DJ), and hopping (HOP)). The dependent variables included surface EMG (anterior tibialis, peroneus longus, and soleus) which measured time to peak, average area, and average peak following ground contact. GRFs measured included peak vertical force (Fz), range of force in medial-lateral (Fx), anterior-posterior (Fy) directions, center of pressure displacement area (CPDA) and velocity (CPDV). Visual analog pain scale (VAP) was also used. Tests were counterbalanced and order was randomized. Statistical tests were performed using SPSS 12.0. A 2 (tape) x 2 (symptoms) MANOVA with repeated measures on tape determined differences in EMG and GRF's between the two conditions in all four tasks (BP, CUT, HOP, DJ). A paired sample t-test assessed differences in CPDA, CPDV, and VAP between the two conditions in all four tasks. P = 0.05 determined significance.

Results

MANOVAs identified significantly lower peak soleus and peroneus longus muscle activity in all four tasks, taped vs. un-taped (Soleus: BP ($p = 0.015$), CUT ($p = 0.000$), DJ ($p = 0.001$, HOP ($p = 0.001$); peroneus longus = BP ($p = 0.016$, CUT ($p = 0.003$), DJ ($p = 0.000$), HOP ($p = 0.001$). Average area EMG increased for the anterior tibialis during the DJ ($p = 0.03$) while taped. GRF revealed significance for the symptomatic group: decreased time to peak Fz while CUT un-taped ($p = 0.04$), increased time to peak (VGRF) for the DJ taped ($p = 0.024$), increased Fx while CUT taped ($p = 0.011$) and un-taped ($p = 0.036$). Pain significantly decreased in both groups while taped during HOP ($p = 0.026$) and CUT ($p = 0.025$).

Conclusions

ALDTT may provide support to the subtalar joint offering a more efficient mechanism of force dissipation, thereby decreasing associated shin pain.

Abstract

Transient Electric Changes Immediately After Surgical Trauma

Jeffrey B. Driban, MEd, ATC, CSCS,[1] C. Buz Swanik, PhD, ATC,[3]
Kellie C. Huxel, PhD, ATC,[4] Easwaran Balasubramanian, MD[2]

[1]*Department of Kinesiology,* [2]*Department of Orthopaedic Surgery, Temple University, Philadelphia, PA,*
[3]*University of Delaware, Newark, DE,* [4]*Indiana State University, Terre Haute, IN*

Purpose

Electric stimulation is frequently used to promote soft tissue healing, although we do not have a complete understanding of the tissue's electromagnetic properties. The purpose of this study was to measure the transient electric changes in skin and muscle tissue immediately after surgical trauma.

Methods

A one-group time series study was performed in a climate-controlled operating room in a public urban hospital. Eleven participants (8 females, 3 males) with a mean age of 65.18 ± 11.36 years underwent an elective total hip arthroplasty. An incision approximately 10 cm distal to the posterior superior iliac spine was made, extending distally over the greater trochanter and along the lateral limb. The incision was completed, identifying two layers: (1) skin and subcutaneous fat and (2) muscle tissue. Three measurement sessions were performed with an electrometer before and after a skin incision and after a muscle incision (Figure 1). Potential differences and current intensity were measured immediately after acute trauma to determine the transient electric changes associated with soft tissue injury.

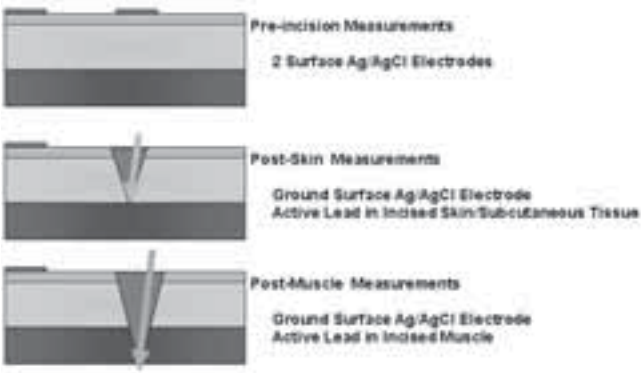


Figure 1

Results

The electric potentials were significantly more negative after the skin incision (P = .036) and skin plus muscle incision (P = .008; preincision = 0.001 ± 0.015 V, skin incision = –0.127 ± 0.134 V, skin plus muscle incision = –0.192 ± 0.153V; Figure 2). Current intensity changed significantly after the skin plus muscle incision (P = .008; preincision = 0.046 ± 0.112 pA, skin incision = –0.803 ± 0.904 pA, skin plus muscle incision = –1.708 ± 1.302 pA; Figure 3).

Conclusions

Soft tissue trauma generated negative transient electric changes.

Key Points

- Previous authors' examinations of the transient electric properties of acutely injured tissue have led to the use of electromagnetic stimulation to promote healing in chronic skin ulcers and nonunion fractures.
- Surgical trauma induced changes in the electric properties of soft tissue.
- New therapeutic protocols that are based on electric changes in traumatized soft tissue may optimize healing in surgical incisions and muscle injury.
- Individualized therapeutic protocols may be needed to account for each patient's unique inflammatory response and structural distinctions.

Previously published in *Journal of Athletic Training* 2007;42(4):524–9.

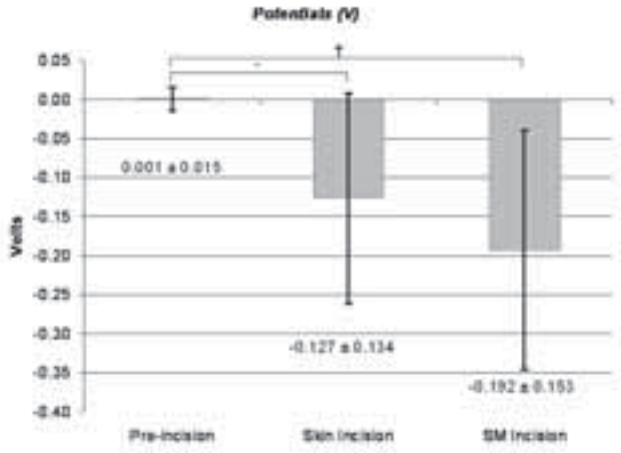


Figure 2

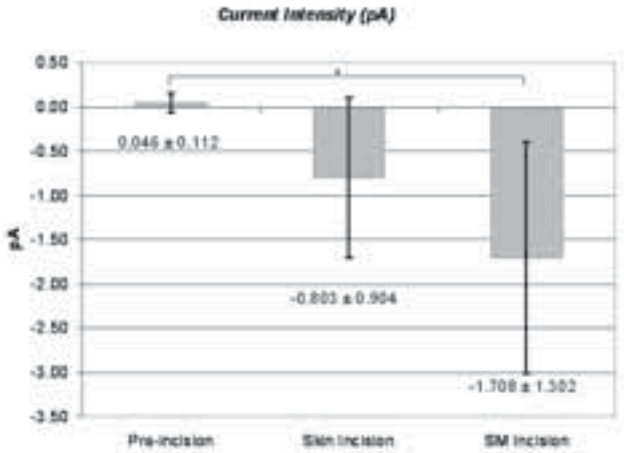


Figure 3

Abstract

Neuromuscular and Psychological Influences on Range of Motion Recovery in Anterior Cruciate Ligament Reconstruction Rehabilitation Patients

Kathy P. Hemsley, PhD,[1] ATC, Michael R. Sitler, EdD,[1] ATC, Ray A. Moyer, MD,[2] Carol A. Oatis, PhD, PT,[3] Ryan T. Tierney, PhD,[1] ATC, Zebulon V. Kendrick, PhD[1]

[1]*Department of Kinesiology,* [2]*Department of Orthopaedic Surgery, Temple University, Philadelphia, PA,* [3]*Arcadia University, Glenside, PA*

Purpose

Postoperative knee stiffness following anterior cruciate ligament reconstruction (ACLR) can contribute to an unnecessarily prolonged rehabilitation course. Pain-associated reflexive muscle guarding has been observed in ACLR cases inhibited in their range of motion (ROM) recovery.

The purpose of this study is to determine if differences existed in the neuromuscular stretch reflex and psychological factors of pain perception and anxiety between postoperative ACLR patient groups of a protracted and normal course of ROM recovery.

Methods

Design: Cross-sectional sixth-week postoperative design.
Setting: Biokinetics Research Laboratory.
Patients or Other Participants: 44 volunteer participants (age, 25 ± 4.1 years; gender, 26 males, 18 females) consisting of ACLR patients and noninjured controls. The ACLR participants (same surgeon and rehabilitation protocol) were categorized into a slow recovery group (SRG: >6 weeks to recover 0–125° knee flexion [n = 10]) and a normal recovery group (NRG: <6 weeks to recover 0–125° knee flexion [n = 12]). The control group participants (n = 22) were age, gender and athletic activity level-matched to the surgical participants.
Interventions: Neuromuscular testing consisted of 2-D video kinematics of the Wartenberg Pendulum Test determining lower limb stiffness indices (Figure 1), and electromyography-monitored patellar tendon tap reflex responses (Figure 2). Psychological and health status assessments consisted of the State-Trait Anxiety Inventory and SF-36™ Health Survey.
Main Outcome Measures: Lower limb stiffness and damping coefficients, neuromuscular response (reflex latency, normalized patellar tendon reflex response), pain perception, anxiety scores, and SF-36™ indices. Statistical analyses consisted of 3 (group) x 2 (leg) analysis of variance (ANOVA) and 1 x 3 group ANOVA with significance set at $p \leq .05$.

Results

Stiffness and damping coefficients, neuromuscular reflex profiles, pain, anxiety and SF-36™ indices were not significantly different between the surgical groups. The SRG and NRG had significantly greater pain levels (27%, 2.67 ± 2.27; $P < .01$) and (15%, 1.49 ± 1.15; $P < .01$), respectively, than the control group. SF-36TM indices were significantly lower for the SRG (18-46%, 546.55 ± 94.70; $P < .01$) and NRG (19–46%, 577.57 ± 125.58; $P < .01$) than the control group for total score, function, physical, social, and emotional subscales. The SRG (14%) and NRG (17%) exhibited significantly less damping (.6075 ± .4667, .4392 ± .1563; $P = .049$, respectively), than the control group.

Conclusions

Neuromuscular reflex responses, pain, and anxiety are not distinguishing factors for ROM recovery between the SRG and NRG at the 6th postoperative interval. Pain and decreased SF-36™ indices are clinically relevant factors distinguishing and affecting postoperative ROM recovery rate. Interventions to control pain should be considered to facilitate ROM recovery in ACLR patients and avert development of arthrofibrosis delaying return to athletic activity.

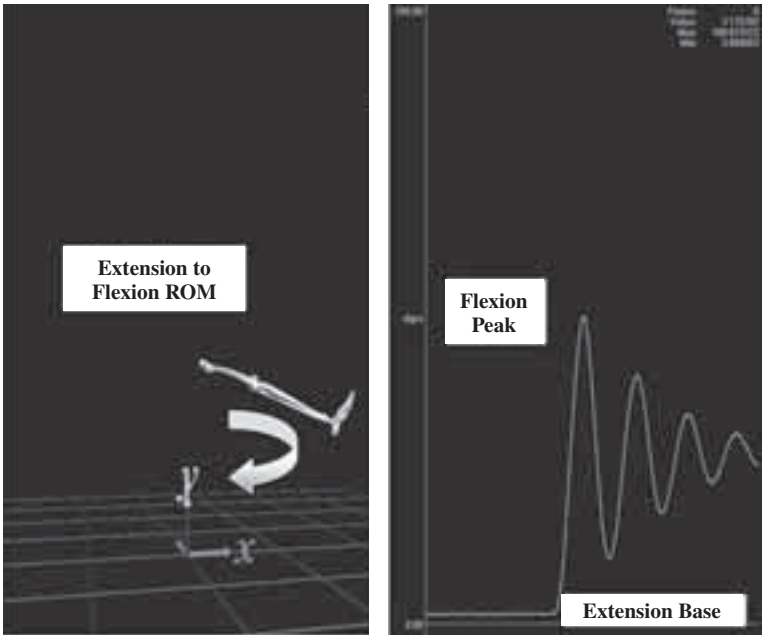


Figure 1. Damped natural frequency of lower leg osscilation in the sagittal plane.

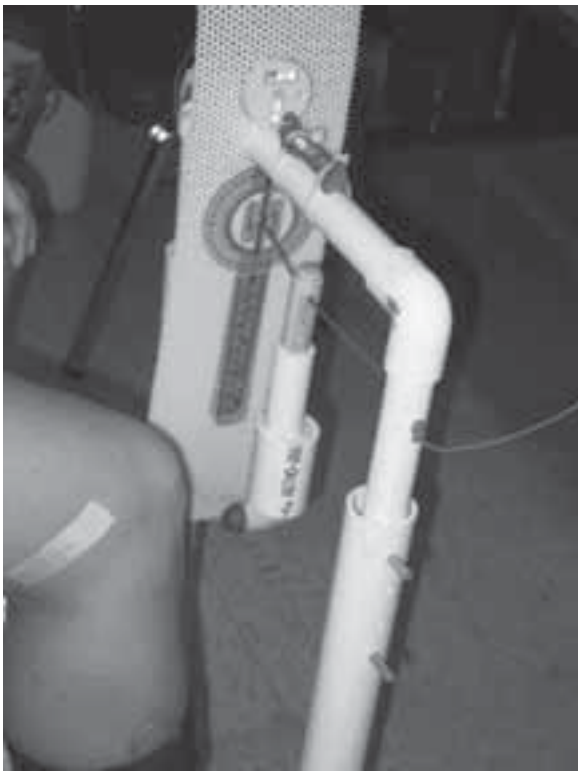


Figure 2. Patellar tendon tap reflex testing apparatus.

Reprint

Inflammatory Biomarkers Increase with Severity of Upper Extremity Overuse Disorders

Stephen J. Carp,[1] Mary F. Barbe,[2, 3] Kathryn A. Winter,[4] Mamta Amin,[2] Ann E. Barr[2]

[1]*Department of Physical Medicine, Chestnut Hill Health System, Philadelphia, PA,*
[2]*Department of Physical Therapy, College of Health Professions, Temple University, Philadelphia, PA,*
[3]*Department of Anatomy and Cell Biology, School of Medicine, Temple University, Philadelphia, PA,*
[4]*American College of Radiology, Clinical Research Office, Philadelphia, PA*

Abstract

Musculoskeletal disorders (MSDs) from overuse are common occupational health problems that cause pain, functional loss, and loss of work time. Our goal was to determine if a relationship exists between the severity of early onset overuse-related MSDs of the upper extremity and serum levels of interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP). Twenty-two subjects affected with upper extremity MSDs due to overuse for no longer that 12 weeks were stratified according to the severity of upper extremity signs and symptoms as determined by an upper body musculoskeletal assessment (UBMA). Nine asymptomatic subjects also participated. Serum cytokines were analyzed using enzyme linked immunosorbent assays (ELISA), and CRP was analyzed using laser nephelometry technique. CRP was strongly correlated, and TNFα, IL-1β and IL-6 were moderately correlated with UBMA scores. Only CRP and TNFα were significantly associated with UBMA scores in an ordinal logistic regression analysis in which age and body mass index (BMI) were covariates. These results are of clinical importance as they suggest that early onset overuse-related MSDs may have an inflammatory component. The possibility of using a combination of serum biomarkers to follow the progression of overuse-related MSDs or their response to therapeutic intervention may be of interest to clinical practitioners and should be the focus of future research.

Acknowledgments

This work was supported by Temple University. The authors would like to thank Susan Michlovitz, PT, PhD, CHT and Fayez Safadi, PhD for their advice and editorial assistance.

Reprinted with permission from *Clinical Science* (2007) 112, 305–314.

Abbreviations Used

BMI: Body mass index
CRP: C-reactive protein
ELISA: Enzyme Linked-Immuno-Sorbent Assay
IL-1β: Interleukin-1 beta
IL-6: Interleukin-6
MSDs: Musculoskeletal disorders
NSAIDs: Non-steroidal anti-inflammatory drugs
TNFα: Tumor necrosis factor alpha
UBMA: Upper body musculoskeletal assessment

Introduction

According to the most recent US Department of Labor survey of occupational injuries and illnesses, which reports on US private industry injury and illness records from 2004, musculoskeletal disorders (MSDs) accounted for 402,700 (32%) of the injuries and illnesses with days away from work.[1] Service industries accounted for 69% of all lost work day MSDs, and goods producing industries accounted for 31% of all MSD cases. Upper extremity MSDs have a relatively high impact on number of days away from work. For example, carpal tunnel syndrome is associated with the highest number of lost work days (median of 28 days), and injuries to the shoulder and wrist accounted for median lost work days of 17 and 14, respectively. In addition, exposure to repetitive motion, such as grasping tools, scanning groceries, and typing, resulted in the longest absences from work by exposure type (median of 20 days).

Despite epidemiological evidence linking the onset and severity of MSDs to repetitive and forceful tasks.[2, 3] there is still much to learn about the underlying pathophysiology of these disorders. Previously, we conducted a series of studies using a rat model to explore the early onset of overuse MSDs in which we found motor behavioral and physiological tissue changes similar to that seen in humans with overuse MSDs.[4–7] We have shown a dose-dependent relationship between reach rate (i.e., level of overuse exposure) and the concentrations of the pro-inflammatory cytokines interleukin-1 alpha (IL-1α) and IL-1β in serum.[4, 5] This body of work leads us to hypothesize that there is a relationship between severity of early onset upper extremity MSDs due

to overuse and the serum concentration of inflammatory markers, such as pro-inflammatory cytokines.

The cytokines IL-1, tumor necrosis factor alpha (TNFα) and IL-6 are intercellular signaling polypeptides produced by most injured cells as well as activated immune cells, including activated monocytes and macrophages.[6, 8] Cytokines are the chief stimulators of acute phase response proteins, and contribute to the development and remediation of signs and symptoms of acute and chronic inflammation, such as the recruitment of immune cells. IL-1 and TNFα can potently stimulate immune and stromal cell production of other cytokines and chemokines as well as most mechanisms of inflammation, including phagocyte proliferation and activation, adhesion and angiogenesis.[8] IL-6, a pleiotropic cytokine, has many pro-inflammatory effects that overlap those of IL-1 and TNFα. For example, IL-6 induces all positive acute phase response proteins.[9] IL-6 also increases in response to exercise independent of muscle damage.[10] Interstitial muscle and peritendon IL-6 production and subsequent release into the blood stream is relative to the intensity and duration of the exercise and occurs as a result of muscle glycogen depletion.[10] The circulating IL-6 then acts in a hormone-like fashion to regulate lipolysis and fat oxidation.[11] IL-1β and TNFα are not influenced by glycogen content in muscle, and thus are not elevated in serum during exercise unless tissue damage has occurred.[11]

The acute phase response is a general response designed to aid tissue repair and facilitate a return to physiological homeostasis. C-reactive protein (CRP) is a sensitive acute phase reactant produced by hepatocytes in the liver.[12, 16] CRP is a prototypic inflammatory marker of underlying low grade inflammation[12, 13] that is beneficial in identifying individuals with unstable angina pectoris underlying coronary artery disease,[14] or risk of future stroke.[15, 16] CRP is also elevated in smokers, elderly at risk for mortality, and patients with metabolic disease and diabetes.[17] Although controversial, there is emerging evidence that CRP is not only a marker of the acute phase response but may also be causal in the pathogenesis of inflammatory disease.[17, 18]

Kramer et al.[19] developed a tool to quantify the severity of work-related MSDs known as the Upper Body Musculoskeletal Assessment Instrument (UBMA). The UBMA takes a regional approach to diagnosis using clinically common tests resulting in a single composite outcome score that quantifies severity of work-related MSDs irrespective of specific diagnosis and may be useful in clinical diagnosis and evaluation of progress toward remediation. Test-retest reliability of the UBMA has been shown to be excellent (ICC = 0.88 for side of workplace equipment use and ICC = 0.94 for side opposite equipment use) among patients with upper extremity MSDs due to overuse.[19] In addition, the UBMA was shown to distinguish between a group of healthy controls and a group of workers with MSDs for both the side of equipment use and the side opposite equipment use ($p < 0.001$).[19]

In this study, we have utilized the UBMA in combination with biochemical assays of human serum to determine if a relationship exists between the severity of early onset overuse MSDs of the upper extremity and circulating inflammatory mediators and markers. Twenty-two subjects affected with upper extremity MSDs due to overuse for no longer than 12 weeks and 9 healthy, asymptomatic subjects participated. Serum was collected and examined for the presence of IL-1β, IL-6, TNFα, and CRP. We found that each of these proteins was progressively elevated with increasing UBMA score. However, only CRP and TNFα were significantly associated with UBMA score in an ordinal logistic regression model.

Materials and Methods

Subjects

Subjects were recruited from an outpatient physical therapy clinic, Chestnut Hill HealthCare facilities in Philadelphia, Pennsylvania, for participation in this study. Both the Temple University Institutional Review Board and Chestnut Hill Hospital Institutional Review Board approved all procedures. The research was carried out in accordance with the Declaration of Helsinki (2000) in the World Medical Association. All subjects signed an informed consent after full explanation of the purpose, nature and risk of all procedures. Individuals with a history of upper extremity MSDs due to overuse of no longer than 12 weeks duration were included in the study. A standardized demographic questionnaire covering medical history and medication use was administered. Exclusion criteria included a history of inflammatory disease (e.g., lupus, rheumatoid arthritis, diabetes, non-medically controlled hypertension), cancer, known coronary artery disease, disease processes that required ongoing treatment with steroids or non-steroidal anti-inflammatory drugs (NSAIDs), and cigarette smoking. Subjects were also excluded if they were medically unable or unwilling to refrain from taking NSAIDs or full dose aspirin for a period of 7 days. Individuals with a history of hypertension were included if the hypertension was currently controlled with medication. The study's demographic questionnaire included characteristics such as age, gender and race. Information was obtained related to the subject's referring diagnosis, occupation and/or primary activity related to the development of MSD. Body mass index (BMI) was calculated as weight (in kg) divided by the square of height (in m).

Subjects were examined by the same physical therapist using the UBMA as described by Kramer et al.[19] Twenty-two symptomatic subjects were recruited using a stratified, non-random sampling procedure where the strata were predefined UBMA score ranges (50–74, 75–99, and ≥100; n = 6–9 subjects per stratum). This sampling procedure was undertaken to obtain a full range of UBMA scores. Nine healthy, asymptomatic subjects were also included, and their UBMA scores were all less than 50.

Biochemical Analysis of Serum

Subjects were asked to refrain from performing strenuous exercise and taking NSAIDs or full dose (325 mg) aspirin for 7 days prior to the drawing of blood samples. Subjects taking low dose aspirin (81 mg/day) were included in this study. Venous blood samples were drawn from all subjects between 7 a.m. and 12 noon, and were collected into sterile Enzyme Catalyzed Therapeutic Activation (ECTA) tubes (5×10^{-3} mol/l; Labco, Califon, NJ) containing aprotinin (bovine lung 15–30 U/ml; Sigma (St. Louis, MO) at 0.67 U/ml. Serum was immediately separated from cells and platelets by centrifugation at 400 g for 7 minutes and then at 10,000 g for 7 minutes at 4°C. Following removal of appropriate quantities of serum for C-reactive protein (CRP) analysis, the aqueous phase was aspirated and stored in 150 microliter aliquots at –80°C until assayed as described below. Aliquots were assayed in batches to avoid any thawing and refreezing.

CRP was measured by a modification of the laser nephelometry technique (Berhing Diagnostics, GMGH, Deerfield, Illinois) according to standard protocols by the Chestnut Hill Hospital Pathology Lab. The CRP assay was standardized according to the World Health Organization First International Reference Standard. Data are expressed in mg/dL to be consistent with conventional units of reporting in the clinical literature.

For analysis of cytokines, serum samples were allowed to thaw on ice. Commercially available Enzyme Linked-Immuno-Sorbent Assay (ELISA) kits (OptEIA ELISA kits for human serum; catalog numbers 55911, 550799, 5550610, respectively; BD Biosciences, San Diego, CA) with high sensitivity for serum cytokine levels were used to determine the circulating levels of the three cytokines, IL-1β, IL-6, and TNFα. Each sample was run in duplicate for ELISA assays as a measure to control pipetting error. A mean was calculated from the duplicate values for further analysis. Data are expressed in pg/ml serum to be consistent with conventional units of reporting in the clinical literature.

Statistical Analysis

A comparison between UBMA scores for the asymptomatic and symptomatic subjects was performed using a Mann-Whitney U test. In addition, the number of single and multiple site impairments in symptomatic subjects was compared to that in asymptomatic subjects using a Chi square test. Comparisons of BMI and age between symptomatic and asymptomatic subjects were performed using independent samples t-tests. Spearman's rank correlation tests were used to determine correlations between each inflammatory biomarker and UBMA score. Ordinal logistic regression analysis with backward elimination was used to determine which combination of the inflammatory biomarkers, age and BMI were associated with UBMA score. SAS (SAS Institute, Inc., Cary, NC) was used for the statistical analyses. P-values of less than 0.05 were considered significant for all analyses.

Results

General characteristics of the subjects, existence of medically controlled hypertension, occupation and/or primary activity related to MSD, are given in Table 1, as are the UBMA scores. Table 2 summarizes the referring diagnoses, symptom duration and medications used during the time of the study for each subject. All of the referring diagnoses involved disorders of the upper extremity. The average duration of symptoms was 51.7 ± 18.9 (mean ± SD) days with a range from 17 to 76 days. Independent samples t-tests showed no significant differences between the asymptomatic and symptomatic subjects with respect to age ($p = 0.23$) and BMI ($p = 0.65$). A Mann-Whitney U test showed that UBMA score was significantly higher in the symptomatic group as compared to the asymptomatic group ($p < 0.0001$). Table 3 summarizes the UBMA results describing the number and type of impairments. The frequency of single site impairments (i.e., those related to a single anatomical region) was greater in symptomatic than in asymptomatic subjects (7 and 53, respectively), as was the frequency of multiple site impairments (i.e., those related to multiple anatomical regions; 1 and 28, respectively). Chi square analysis confirmed this difference between symptomatic and asymptomatic groups in single and multiple site impairments ($\chi^2 = 348$; $.001\chi^2(1) = 10.83$).

Spearman's rank correlation tests showed that all of the biomarkers were positively correlated with UBMA score. As shown in Figure 1, CRP was the most highly correlated with a Spearman's rank correlation coefficient of $r_s = 0.81$ ($p < 0.0001$). IL-1β was a moderately correlated biomarker with a Spearman's rank correlation coefficient of $r_s = 0.70$ ($p < 0.0001$), as were TNFα ($rs = 0.66$; $p < 0.0001$) and IL-6 ($r_s = 0.52$; $p = 0.003$).

Mean values for the serum levels of each biomarker are shown in Table 4 and reflect the correlational findings of increasing biomarker level with increasing UBMA score. Ordinal logistic regression analysis using the cut points for UBMA score indicated in Table 4 showed that CRP ($p = 0.0003$) and TNFα ($p = 0.0007$) were significantly associated with an increased UBMA score (Table 5). IL-1β and IL-6 were removed from the model with p values of 0.09 and 0.48, respectively. The covariates age ($p = 0.16$) and BMI ($p = 0.62$) were also removed from the model.

Discussion

Overall, there was a positive relationship between MSD severity, as reflected by UBMA score, and cytokine and CRP concentrations. All of the markers were positively correlated with UBMA: CRP was strongly correlated, and IL-1β, TNFα and IL-6 were moderately correlated. However, only CRP and TNFα were significantly associated with UBMA score in an ordinal logistic regression model. These results are consistent with the progressive increase in the levels of these markers with increasing severity of UBMA score.

Table 1. Demographic Characteristics of Subjects Ranked by Upper Body Musculoskeletal Assessment (UBMA) Score.
Means and standard deviations are shown for age and body mass index (BMI). Means and mean ranks, as determined for the Mann-Whitney U test, are shown for UBMA score.

UBMA Score	Gender	Age	Race/hypertension	BMI (kg/m^2)	Occupation/Primary Activity Related to MSD
Asymptomatic Subjects					
10	F[a]	47	Caucasian	19.2	Nurse
11	F[a]	49	Caucasian	23.0	Biomedical Engineer
12	M	46	Caucasian	22.0	Maintenance Engineer
16	M	29	Caucasian	24.6	Physical Therapist
22	F	37	Caucasian	20.3	Clerk
30	F	19	Caucasian	16.8	Administrative Assistant
31	M	30	Caucasian	25.2	Clerk
31	F[a]	46	Caucasian	24.0	Biomedical Engineer
41	F[a]	48	African-American	29.3	Hospital Administrator
39.0 (Mean)		39.0 (Mean)		22.7 (Mean)	
5.0 (Mean rank)		10.8 (SD)		3.7 (SD)	
Symptomatic Subjects					
50	M	29	Caucasian	24.4	Nurse
51	F	28	Caucasian	20.6	Engineer
52	F[a]	69	Caucasian	20.1	Gardener, Potter
56	F[b]	26	Caucasian	16.9	Recreation Therapist
56	M	33	Caucasian	26.2	Clerk
59	F	26	Caucasian	25.0	Nurse
66	M	42	Caucasian	23.5	Stockroom Clerk
66	F	34	Hispanic	20.4	Nurse (retired 1 month)
78	M	25	Caucasian	21.0	Engineer
78	F	31	Caucasian	27.0	Cardiologist
83	F	39	Caucasian	23.4	Engineer
84	M	73	Caucasian	27.3	Gardener, House Painter
86	F	39	Caucasian	22.1	Teacher
88	M	29	Caucasian	24.9	Cable TV Installer
90	M	49	Caucasian	24.0	Laboratory Technician
91	F[a]	62	Caucasian	21.1	Computer Programmer
102	M	66	Caucasian	23.5	Woodworker
105	M	54	Caucasian	19.7	Manager
106	M	74	African-American	26.9	Artist (painter)
109	M	57	Caucasian	19.1	Consultant
119	F[a]	56	Caucasian	32.6	Manager
124	F[a]	54	Caucasian	24.0	Cook
81.6 (Mean)		45.2 (Mean)		23.4 (Mean)	
20.5 (Mean rank)*		16.7 (SD)		3.5 (SD)	

[a]Post-menopausal subject; [b]subject menstruating at the time of serum collection; [c]History of hypertension that is currently controlled medically.
*Significantly different from asymptomatic subjects by Mann-Whitney U test ($p < 0.0001$).

The results from the UBMA showed the presence of local signs of pain, tenderness, peripheral nerve irritation, weakness and limited motion that progressively increased in number with increasing serum CRP, IL-1β and TNFα levels. The number of cases with involvement of multiple anatomical sites also increased with increased MSD severity and increased serum CRP, IL-1β and TNFα levels. These results are similar to those of Ravaglia et al.[20] showing that at least CRP has a strong association with functional impairment. These results are also similar to those from an earlier study of IL-1β using a rat model of MSD developed in our laboratory.[4, 5] It seems intuitive that the more severe the MSD, the more sites are injured, the larger the acute phase response and thus the larger the concentration of serum inflammatory mediators and markers. Therefore, we suggest that the systemic inflammatory response is associated with local signs and symptoms of inflammation in humans as in our rat model. It is likely that the systemic response is initiated by a local response and is proportionally amplified in the presence of greater tissue injury and inflammation (i.e., greater number of physical signs, symptoms and impairments). The increase in the number of affected anatomical sites may be either a cause or an effect of the systemic inflammatory response.

In contrast to IL-1 and TNFα, circulating IL-6 has a more complex relationship with MSD severity in this study. The pleiotropic effects of IL-6 may help explain these results. IL-6 is a tightly regulated cytokine that is not normally detected in serum unless there is trauma, infection, cellular/tissue stress, or during or following muscle glycogen-depleting exercise intensities.[10, 11, 21] In the case of infection or inflammation, IL-6 is an early cytokine responder.[21, 22]

Table 2. Referring Diagnoses, Symptom Duration and Medication Use Ranked by Upper Body Musculoskeletal Assessment (UBMA) Score

UBMA Score	Referring Diagnosis	Symptom Duration (Days)	Medications
Asymptomatic Subjects			
10	N/A	N/A	
11	N/A	N/A	HCTZ
12	N/A	N/A	Flonase
16	N/A	N/A	
22	N/A	N/A	Flonase
30	N/A	N/A	Mvi
31	N/A	N/A	
31	N/A	N/A	Tylenol
41	N/A	N/A	Mvi
Symptomatic Subjects			
50	Median neuropathy	61	Atenelol
51	Lateral epicondylitis	52	
52	Wrist tendonitis	18	Tylenol, Pravachol[a]
56	Wrist sprain	30	
56	Wrist strain	45	Motrin
59	Myalgia	33	
66	Overuse syndrome	66	
66	Wrist extensor strain	61	Birth Control Pills
78	Rotator cuff tendonitis, wrist strain	66	
78	Lateral epicondylitis	72	Birth Control Pills
83	Carpal tunnel syndrome	29	Birth Control Pills
84	Early compartmental syndrome	17	Low Dose Aspirin, Mvi, Plavix
86	Overuse syndrome forearm	32	Tylenol, Neurontin
88	Tendonitis	72	
90	Tendonitis	48	Tylenol PM, Neurontin
91	Carpal tunnel syndrome	55	Prilosec
102	Carpal tunnel syndrome	64	
105	Cervical strain, pronator teres syndrome	71	Low Dose Aspirin, Pravachol[a]
106	Bicipital tendonitis, hand edema	68	Mvi, Lopressor, Dilantin
109	Bicipital tendonitis	34	
119	Wrist tendonitis	67	Zocor[a]
124	Carpal tunnel syndrome	76	Tylenol, Pravachol[a]
		51.7 (mean)	
		18.9 (SD)	

HCTZ = hydrochlorothiazide; Mvi = multivitamins; N/A = not applicable.
[a]Indicates a statin medication.

Table 3. Impairments Identified by Upper Body Musculoskeletal Assessment (UBMA) in Asymptomatic and MSD Groups

Impairment	# Single Site Impairments	# Multiple Site Impairments
Asymptomatic Subjects		
Resisted MMT	0	0
PROM	1	0
Trigger Point	5	1
Median Tinel	1	N/A
Finkelstein	0	N/A
Phalen	0	N/A
Adson	0	N/A
Grasp/Pinch	0	N/A
Total	7	1
Symptomatic Subjects		
Resisted MMT	10	9
PROM	7	10
Trigger Point	10	17
Median Tinel	6	N/A
Finkelstein	4	N/A
Phalen	7	N/A
Adson	3	N/A
Grasp/Pinch	15	N/A
Total	53*	28*

N/A = not applicable because none of these tests are administered to multiple sites.
MMT = manual muscle test. PROM = passive range of motion.
*Significantly higher observed frequency than expected from the frequency in asymptomatic subjects as determined by χ^2 analysis ($p < 0.001$).

Pro-inflammatory effects of IL-6 include induction of cell growth and proliferation, inflammation, and acute-phase responses.[22, 23] It also appears to have anti-inflammatory actions such as inducing increases in circulating levels of IL-1 receptor antagonist and soluble TNF receptor.[22, 24] These activities would have a potent anti-inflammatory effect by suppressing the actions of circulating IL-1 and TNFα. We would expect the IL-6 concentrations in the serum of our subjects to fluctuate depending upon whether IL-6 is inducing pro- or anti-inflammatory effects, and would further hypothesize that symptomatic subjects less severely affected (i.e., those with UBMA scores in the 50–75 range) would benefit the most from the anti-inflammatory functions of IL-6, such as attenuating IL-1β and the highly cytotoxic TNFα. Indeed, in our subjects, serum levels of TNFα are within range of control values at UBMA scores between 50 and 75 (Figure 1C), as are IL-1β levels in 3 of 8 subjects (Figure 1B). Among more severely affected subjects (i.e., those with UBMA scores above 100), IL-6 may augment the inflammatory response, or it may be unable to downregulate the production of other proinflammatory cytokines.

Our serum results differ from those in a study by Freeland et al.[25] in which serum and tenosynovial tissues were examined in 41 patients with idiopathic carpal tunnel syndrome (most with abnormal nerve conduction velocity changes). Serum was collected 1 week prior to carpal tunnel release surgery, while tendosynovial tissue was collected at the time of surgery. Their findings of increased serum malondialdehyde, a marker of cell injury resulting from reperfusion, an absence of serum IL-1 and IL-6, as well as increased malondialdehyde, prostaglandin E2 and IL-6 in the tendosynovial tissues, led them to hypothesize that idiopathic carpal tunnel syndrome has a non-inflammatory ischemia-reperfusion etiology that results in fibrosis of carpal tunnel tissues. We also found fibrosis of carpal tunnel tissues in our rat model between 9 and 12 weeks, a few weeks after the onset of the inflammatory response.[7] The fibrotic carpal tunnel changes were accompanied by significant declines in median nerve

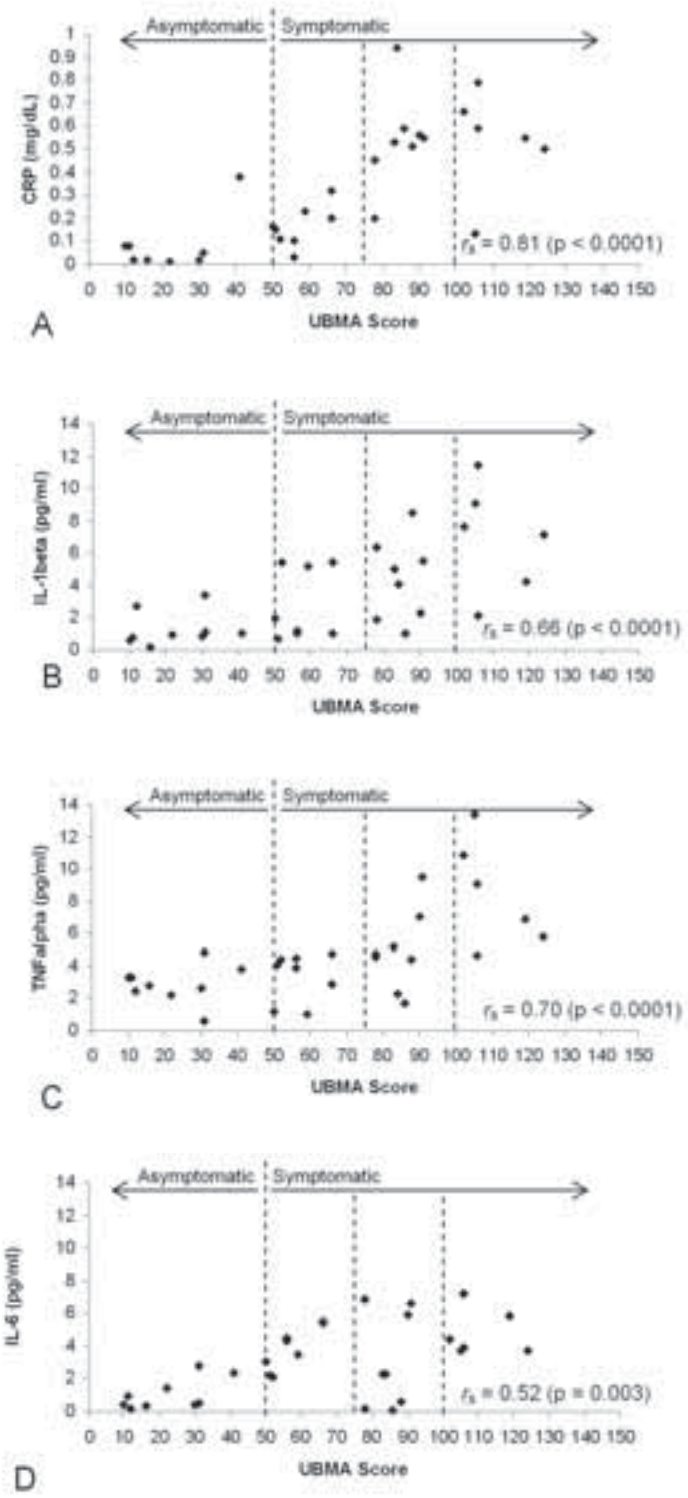


Figure 1. Inflammatory biomarker concentrations versus upper body musculoskeletal assessment (UBMA) scores for all symptomatic (n = 22) and asymptomatic (n = 9) subjects showing Spearman's rank correlation coefficients (r_s). **(A)** C-reactive protein (CRP); **(B)** interleukin-1β (IL-1Beta); **(C)** tumor necrosis factor α (TNF alpha); and **(D)** interleukin-6 (IL-6). Vertical dashed lines show cut points used in ordinal logistic regression. Horizontal arrows indicate ranges of scores for asymptomatic (left arrow) and symptomatic (right arrow) subjects.

Table 4. Summary of Mean (SD) Inflammatory Marker Concentrations in Serum for the Asymptomatic and Symptomatic Groups Calculated According the Cut Points Used in the Ordinal Logistic Regression Analysis.
CRP is expressed in mg/dL, and TNFα, IL-1β and IL-6 are expressed in pg/ml.

UBMA Score Range	CRP	TNFa	IL-1b	IL-6
0–49 (asymptomatic)	0.08 (0.12)	2.87 (1.18)	1.29 (1.04)	1.05 (0.94)
50–74	0.16 (0.09)	3.35 (1.49)	2.73 (2.18)	3.82 (1.32)
75–99	0.54 (0.20)	4.93 (2.49)	4.33 (2.50)	3.11 (2.93)
100–150	0.54 (0.22)	8.45 (3.32)	6.95 (3.35)	4.80 (1.42)

CRP = C-reactive protein, IL-1 = interleukin, SD = standard deviation, UBMA = upper body musculoskeletal assessment.

Table 5. Summary of Final Step in the Backward Ordinal Logistic Regression Model Showing the Significant Variables, C-reactive Protein (CRP) and Tumor Necrosis Factor Alpha (TNFα)

Variable Name	OR	CI	p
CRP	>999.9	111.8–>999.9	0.0003
TNFα	2.2	1.4–3.4	0.0007

OR = odds ratio; CI = 95% confidence interval.

conduction velocity. Recent and as yet unpublished results from our rat model indicate that the serum cytokine levels return to normal after the changeover to a fibrotic tissue state. We hypothesize that our observed serum inflammatory responses in both this current human study and in our previous rat studies are signs of early onset of MSDs and are not indicative of later stages of MSDs. We would also like to note that this current study is not entirely comparable to Freeland's study. We had only 4 patients diagnosed with carpal tunnel syndrome in this study. The remainder of our symptomatic subjects had musculoskeletal overuse diagnoses. Further experimentation is needed to determine if the involvement of musculoskeletal tissues instead of or in addition to nerve tissue is necessary for an increase in serum cytokines.

There are many patient characteristics in addition to the presence of MSD that may affect the serum concentrations of these inflammatory biomarkers. While intense and prolonged exercise elevates IL-6 due to exercise-induced glycogen depletion,[10, 11] repetitive low intensity exercise does not appear to contribute to elevated serum IL-6 levels.[26] In a study using microdialysis catheters to measure IL-6 levels in the trapezius following 20 minutes of repetitive low-force exercise, interstitial muscle levels of IL-6 were elevated but not serum levels.[26] Conversely, in another study by Chan et al.,[11] serum levels of IL-6 increased significantly after 2.5 hours of high intensity, glycogen-depleting exercise. Circulating levels of IL-6 have been shown to remain increased

for 48 hours after prolonged exercise.[27] Therefore, our subjects were asked to refrain from vigorous exercise for 7 days before having their blood drawn. While we did not ask them to refrain from light intensity exercise, it is unlikely that our measures were affected by low intensity physical activity, as suggested by Rosendal et al.[26]

The more severely affected symptomatic subjects show similar CRP levels as elderly subjects[28] and patients with non-medically controlled angina,[14] but greater than smokers.[15] Hypertension, obesity and high coffee intake contribute to levels of serum CRP and TNFα that are similar to those seen in our more severely affected subjects, and to serum levels of IL-6 seen in all of our symptomatic subjects.[29–31] The IL-6 levels in our MSD subjects are also similar to the very elderly, aged smokers, and aged patients with significantly reduced functional status,[32] although considerably higher than levels found by Hager et al.[9] in elderly subjects. All of our subjects had CRP and serum cytokine levels that were considerably lower than those seen in studies examining patients with severe trauma with risk for mortality, cardiogenic shock and sepsis.[33–35, 49]

Obesity is associated with an increase in serum CRP, TNFα and IL-6.[30, 36] In our study, the mean BMIs for the asymptomatic and MSD groups were below the threshold for obesity of 30 kg/m^2 defined by the American Heart Association (Table 1; americanheart.org). Only one of our symptomatic subjects would be considered obese. Therefore, BMI was not a significant covariate in our regression model, although a sample with a larger number of obese individuals might give a different result.

Medications may affect serum levels of inflammatory mediators. Statin medications have been shown to reduce serum levels of IL-1β[37] and CRP,[37, 38] but not TNFα.[39] Low dose aspirin has been shown to reduce IL-1β, but not CRP.[37] We did not exclude subjects who were prescribed and taking low dose aspirin (81 mg/day) and statin drugs. Four of our symptomatic subjects were prescribed statin therapy or low dose aspirin (Table 2). Since statins and aspirin tend to lower CRP and pro-inflammatory cytokine levels, their ingestion by any of our subjects would lower the concentration of the biomarkers, thereby diluting our main effects and, therefore, at least not falsely supporting our hypothesis.

Hormonal factors also affect the production of inflammatory mediators, and may help explain the increased susceptibility of women to overuse MSDs. Estrogens exacerbate inflammation making women more vulnerable to chronic inflammatory disorders.[40] Lack of estrogen, through naturally occurring or medically induced menopause, is associated with systemic increases in IL-6, and localized tissue increases in IL-1, IL-6 and TNFα.[41–43] In addition, the use of hormone replacement therapy might be associated with an enhanced thrombotic tendency.[44, 45] The evidence is equivocal about the relationship between pro-inflammatory cytokines and estrogen. We are uncertain as to the effect of not stratifying our female subjects by their hormonal status other than recording whether the subject was post menopausal or menstruating at the time of serum collection. Four of the 9 asymptomatic subjects were postmenopausal, whereas 5 of the 22 symptomatic subjects were postmenopausal or menstruating at the time of serum collection. The effect of this small number of subjects would tend to dilute our main effects, thus not falsely supporting our hypothesis.

The effect of aging on CRP and cytokine production has also been studied extensively. Roubenoff et al.[46] found that serum concentrations of IL-6, CRP and IL-1 receptor antagonist, but not IL-1β or TNFα, were increased in elderly subjects (mean age 79 years) compared to younger control subjects (mean age 39 years). In addition, the increased concentration of IL-6 was correlated with an increased serum concentration of CRP. The authors postulated a dysregulation of IL-6, CRP and IL-1 receptor antagonist with aging. However, since findings by Macy et al.[12] and Chrysohoou et al.[29] indicate a weak or absent association of CRP with age, perhaps the elevation of CRP in the elderly population studied by Roubenoff was due to inflammatory comorbidities, which were not reported. On the other hand, in a large study of community-dwelling elderly (aged 65 and older) by Cohen et al.,[32] elevation of IL-6 was correlated strongly with age independent of several selected disease states and disorders of aging. Similar results of increased proinflammatory cytokine activity after menopause have been found in numerous studies.[32, 47, 48] In our study, even though the mean age of our symptomatic subjects was higher than that of our asymptomatic subjects, the difference was not statistically significant. Despite there being 4 individuals among our symptomatic subjects greater than 65 years of age (Table 1), age was not found to be a significant covariate in the ordinal logistic regression model. While inclusion of a larger number of aged subjects might change this finding, the age group included in this study is certainly representative of working-age adults, which is a group greatly affected by overuse MSDs.[1–3]

Cardiovascular problems such as severe unstable angina,[14] underlying coronary artery disease, hypertension, and risk of future stroke[15, 16] are well known to result in elevation of CRP. CRP and proinflammatory cytokines have been shown to be among the first responders in many inflammatory and/or infectious conditions. For example, Fida et al.[49] evaluated the utility of using serum levels of IL-1α, IL-6, TNFα and CRP in differentiating sepsis from meningitis in children. They found that optimal cut-off points (i.e., the points that allow detection of as many true positive and as few false positive results as possible) were 0.70 mg/dL for CRP, 12.07 pg/ml for IL-1α, 5.43 pg/ml for IL-6, and 27.35 pg/ml for TNFα. Liuzzo et al.[50] evaluated the prognostic value of CRP in adults with unstable angina. Using a cut-off point for CRP of 0.3 mg/dL as a marker for subsequent cardiac events or the need for urgent angioplasty, they found a sensitivity of 90% and a specificity of 82%. Our findings also suggest a relationship between the severity of MSD and the plasma

concentrations of CRP and the proinflammatory cytokines. Although serum concentrations among our subjects are below the cut-off points for severe conditions, such as sepsis, they are comparable to those for cardiac disease risk. If CRP is a mediator of future cardiac events, as some recent hypotheses in the literature suggest, then the elevated CRP levels induced by overuse leading to MSDs could contribute to future cardiac problems if left unchecked. Clearly, the clinical use of these measures in determining the specific cause of an inflammatory disease process has limitations and it is necessary to control for potentially confounding factors when using CRP and proinflammatory cytokines as disease markers. However, their usefulness in identifying an underlying inflammatory component may add significantly to the understanding of a disease process, and these biomarkers may prove useful in determining the exacerbation or remission of the inflammatory response in MSDs such as might occur with chronic risk factor exposure or clinical intervention.

Conclusion

Several key points are supported by these findings. First, early onset MSDs due to overuse are associated with a systemic inflammatory response as demonstrated by a direct positive relationship between serum concentrations of key markers of inflammation and symptom severity in subjects with early onset MSDs. Second, increases in serum biomarkers are associated with an increase in the number of local signs of pain, tenderness, peripheral nerve irritation, weakness and limited motion as well as the involvement of multiple anatomical sites among these subjects. Recent work in our animal model of repetitive motion injury shows that local tissue injury and inflammatory responses are linked to a systemic release of proinflammatory cytokines. Therefore, the results of the present study indicate that the inflammatory markers reflect an underlying low grade inflammatory process induced by overuse. Third, the magnitude of the systemic serum response in the patients with more severe MSD signs and symptoms is of the same order as several low grade chronic inflammatory conditions known to produce elevated serum pro-inflammatory biomarkers, although not as high as major organ trauma, serious infections or inflammatory diseases. Therefore, in any study that monitors the serum levels of pro-inflammatory cytokines and CRP, care must be taken to control for other confounding characteristics, diseases and injuries. Based on our results, MSDs should be counted among these confounding variables. Fourth, while the non-specificity of the serum cytokine and CRP response presents limitations to the use of these markers in the diagnosis of specific overuse MSD conditions, the potential use of multiple serum inflammatory marker levels as indicators of the exacerbation and resolution of MSDs in combination with the UBMA instrument or a similar assessment tool is compelling, may be of interest to clinical practitioners and should be the focus of future research.

References

1. Bureau of Labor Statistics: Lost-worktime injuries and illnesses: characteristics and resulting days away from work, 2004, United States Department of Labor News USDL 05-2312, December 13, 2005.
2. Bernard B, Fine L, eds. (1997) Musculoskeletal Disorders and Workplace Factors. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health. DHHS (NIOSH) Publication #97–141.
3. National Research Council and Institute of Medicine. (2001) Musculoskeletal Disorders and the Workplace, Washington, DC, 2001, National Academy Press.
4. Barbe, M.F., Barr, A.E., Gorzelany, I., Amin, M., Gaughan, J.P., Safadi, F.F. (2003) Chronic repetitive reaching and grasping results in decreased motor performance and widespread tissue responses in a rat model of MSD. *J. Orthop. Res.* 21,167–176.
5. Barr, A.E., Amin, M., Barbe, M.F. (2002) Dose response relationship between reach repetition and indicators of inflammation and movement dysfunction in a rat model of work-related musculoskeletal disorder. Proceedings of the Human Factors and Ergonomics Society; 46th Annual Meeting, 1486–1490.
6. Al-Shatti, T., Barr, A.E., Safadi, F., Amin, M., Barbe, M.F. (2005) Increase in pro- and anti-inflammatory cytokines in median nerves in a rat model of repetitive motion injury. *J Neuroimmunol.* 167, 13–22.
7. Clark, B.D., Al-Shatti, T.A., Barr, A.E., Amin, M., Barbe, M.F. (2004) Performance of a high-repetition, high-force task induces carpal tunnel syndrome in rats. *J. Orthop. Sports Phys. Ther.* 34, 244–253.
8. Ruminy, P., Gangneux, C., Claeyssens, S., Scotte, M., Daveau, M., Salier, J.P. (2001) Gene transcription in hepatocytes during the acute phase of a systemic inflammation: from transcription factors to target organ. *Inflamm. Res.* 50, 383–390.
9. Hager, K., Machein, U., Krieger, S., Platt, D., Seefried, G., Bauer, J. (1994) Interleukin-6 and selected plasma proteins in healthy persons of different ages. *Neurobiol. Aging.* 15, 771–772.
10. Pedersen, B.K., Steensberg, A., Schjerling, P. (2001) Muscle-derived interleukin-6: possible biological effects. *J. Physiol.* 526; 329–337.
11. Chan, M.H., Carey, A.L., Watt, M.J., Febbraio, M.A. (2004). Cytokine gene expression in human skeletal muscle during concentric contraction: evidence that IL-8, like IL-6, is influenced by glycogen availability. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 287, R322–R327.
12. Macy, E.M., Hayes, T.E., Tracy, R.P. (1997) Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin. Chem.* 43, 52–58.
13. Jialal, I., Devaraj S. (2001) Inflammation and atherosclerosis: the value of the high-sensitivity C-reactive protein assay as a risk marker. *Am. J. Clin. Pathol.* 116 Suppl, S108–115.
14. Liuzzo, G., Biasucci, L.M., Gallimore, J.R., Grillo, R.L., Rebuzzi, A.G., Pepys, M.B., Maseri, A. (1994) The prognostic value of C-reactive protein and serum amyloid a protein in severe unstable angina. *N. Engl. J. Med.* 331, 417–424.
15. Ridker, P.M., Cushman, M., Stampfer, M.J., Tracy, R.P., Hennekens, C.H. (1997) Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N. Engl. J. Med.* 336, 973–979.
16. Beckman, J.A., Preis, O., Ridker, P.M., Gerhard-Herman, M. (2005) Comparison of usefulness of inflammatory markers in patients with versus without peripheral arterial disease in predicting adverse cardiovascular outcomes (myocardial infarction, stroke, and death). *Am. J. Cardiol.* 96, 1374–1378.
17. Nijmeijer, R., Lagrand, W.K., Visser, C.A., Meijer, C.J., Niessen, H.W., Hack, C.E.. (2001) CRP, a major culprit in complement-mediated tissue damage in acute myocardial infarction? *Int. Immunopharmacol.* 1, 403–414.
18. Lagrand, W.K., Visser, C.A., Hermens, W.T., Niessen, H.W., Verheugt, F.W., Wolbink, G.J., Hack, C.E. (1999) C-reactive protein as a cardiovascular risk factor: more than an epiphenomenon? *Circulation* 100, 96–102.
19. Kramer, J.F., Potter, P., Harburn, K.L., Speechley, M., Rollman, G.B. (2001) An upper body musculoskeletal assessment instrument for patients with work-related musculoskeletal disorders: a pilot study. *J. Hand Ther.* 14, 115–121.

20. Ravaglia, G., Forti, P., Maioli, F., Brunetti, N., Martelli, M., Talerico, T., Bastagli, L., Muscari, A., Mariani, E. (2004) Peripheral blood markers of inflammation and functional impairment in elderly community-dwellers. *Exp. Gerontol.* 39, 1415–1422.
21. Ershler, W.B., Keller, E.T. (2000) Age-associated increased interleukin-6 gene expression, late-life diseases, and frailty. *Annu. Rev. Med.* 51, 245–270.
22. Biffl, W.L., Moore, E.E., Moore, F.A., Peterson, V.M. (1996) Interleukin-6 in the injured patient. Marker of injury or mediator of inflammation? *Ann. Surg.* 224, 647–664.
23. Akira, S., Taga, T., Kishimoto, T. (1993) Interleukin-6 in biology and medicine. *Adv. Immunol.* 54, 1–78.
24. Tilg, H., Trehu, E., Atkins, M.B., Dinarello, C.A., Mier, J.W. (1994) Interleukin-6 as an anti-inflammatory cytokine: induction of circulating IL-1 receptor antagonist and soluble tumor necrosis factor receptor p55. *Blood.* 83, 113–118.
25. Freeland, A.E., Tucci, M.A., Barbieri, R.A., Angel, M.F., Nick, T.G. (2002) Biochemical evaluation of serum and flexor tenosynovium in carpal tunnel syndrome. *Microsurgery* 22,378–385.
26. Rosendal, L., Sogaard, K., Kjaer, M., Sjogaard, G., Langberg, H., Kristiansen, J. (2005) Increase in interstitial interleukin-6 of human skeletal muscle with repetitive low-force exercise. *J. Appl. Physiol.* 98, 477–481.
27. Langberg, H., Olesen, J.L., Gemmer, C., Kjaer, M. (2002). Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. *J. Physiol.* 542, 985–990.
28. Ballou, S.P., Lozanski, F.B., Hodder, S., Rzewnicki, D.L., Mion, L.C., Sipe, J.D., Ford, AB, Kushner I. (1996) Quantitative and qualitative alterations of acute-phase proteins in healthy elderly persons. *Age Ageing.* 25, 224–230.
29. Chrysohoou, C., Pitsavos, C., Panagiotakos, D.B., Skoumas, J., Stefanadis, C. (2004) Association between prehypertension status and inflammatory markers related to atherosclerotic disease: The ATTICA Study. *Am. J. Hypertens.* 17, 568–573.
30. Panagiotakos, D.B., Pitsavos, C., Yannakoulia, M., Chrysohoou, C., Stefanadis, C. (2005) The implication of obesity and central fat on markers of chronic inflammation: The ATTICA study. *Atherosclerosis.* 183, 308–15.
31. Zampelas, A., Panagiotakos, D.B., Pitsavos, C., Chrysohoou, C., Stefanadis, C. (2004) Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am. J. Clin. Nutr.* 80, 862–867.
32. Cohen, H.J., Pieper, C.F., Harris, T., Rao, K.M., Currie, M.S. (1997) The association of plasma IL-6 levels with functional disability in community-dwelling elderly. *J. Gerontol. A. Biol. Sci. Med. Sci.* 52, M201–208.
33. de Werra, I., Jaccard, C., Corradin S.B., Chiolero, R., Yersin, B., Gallati, H., Assicot, M., Bohuon, C., Baumgartner, J.D., Glauser, M.P., Heumann, D. (1997) Cytokines, nitrite/nitrate, soluble tumor necrosis factor receptors, and procalcitonin concentrations: comparisons in patients with septic shock, cardiogenic shock, and bacterial pneumonia. *Crit. Care. Med.* 25, 607–613.
34. Strecker, W., Gebhard, F., Perl, M., Rager, J., Buttenschon, K., Kinzl, L., Beck, A. (2003) Biochemical characterization of individual injury pattern and injury severity. *Injury.* 34, 879–887.
35. Plank, L.D., Hill, G.L. (2000) Sequential metabolic changes following induction of systemic inflammatory response in patients with severe sepsis or major blunt trauma. *World J. Surg.* 24, 630–8.
36. Ziccardi, P., Nappo, F., Giugliano, G., Esposito, K., Marfella, R., Cioffi, M., D'Andrea, F., Molinari, A.M., Giugliano, D. (2002) Reduction of inflammatory cytokine concentrations and improvement of endothelial function in obese women after weight loss over one year. *Circulation.* 105, 9075–9076.
37. Ferroni, P., Martini, F., Cardarello, C.M., Gazzaniga, P.P., Davi ,G., Basili, S. (2003) Enhanced interleukin-1beta in hypercholesterolemia: effects of simvastatin and low-dose aspirin. *Circulation.* 108, 1673–1675.
38. Ansell, B.J., Watson, K.E., Weiss, R.E., Fonarow, G.C. (2003) HsCRP and HDL effects of statins trial (CHEST): rapid effect of statin therapy on C-reactive protein and high-density lipoprotein levels: A clinical investigation. *Heart. Dis.* 5, 2–7.
39. Zubelewicz-Szkodzinska, B., Szkodzinski, J., Danikiewicz, A., Romanowski, W., Blazelonis, A., Muc-Wierzgon, M., Pietka-Rzycka, A., Muryn, Z. (2003) Effects of simvastatin on pro-inflammatory cytokines in patients with hypercholesteremia. *Kardiol. Pol.* 59, 465–474.
40. Flake, N.M., Bonebreak DB., Gold M.S. (2005) Estrogen and Inflammation Increase the Excitability of Rat Temporomandibular Joint Afferent Neurons. *J. Neurophysiol.* 93, 1585–1597.
41. Pacifici, R, Rifas, L., Teitelbaum, S., Slatopolsky, E., McCracken, R., Bergfeld, M., Lee, W., Avioli, L.V., Peck, W.A. (1987) Spontaneous release of interleukin 1 from human blood monocytes reflects bone formation in idiopathic osteoporosis. *Proc. Natl. Acad. Sci. U.S.A.* 84, 4616–4620.
42. Ralston, S.H. (1994) Analysis of gene expression in human bone biopsies by polymerase chain reaction: evidence for enhanced cytokine expression in postmenopausal osteoporosis. *J. Bone Miner. Res.* 9, 883–890.
43. Seck, T., Diel, I., Bismar, H., Ziegler, R., Pfeilschifter, J. (2002) Expression of interleukin-6 (IL-6) and IL-6 receptor mRNA in human bone samples from pre- and postmenopausal women. *Bone.* 30, 217–222.
44. Leng, X.H., Zhang, W., Nieswandt, B., Bray, P.F. (2005) Effects of estrogen replacement therapies on mouse platelet function and glycoprotein VI levels. *Circ. Res.* 97, 415–7.
45. Yildirir, A., Aybar, F., Tokgozoglu, L., Yarali, H., Kabakci, G., Bukulmez, O., Sinici, I., Oto, A. (2002) Effects of hormone replacement therapy on plasma homocysteine and C-reactive protein levels. *Gynecol. Obstet. Invest.* 53, 54–58.
46. Roubenoff, R., Harris, T.B., Abad, L.W., Wilson, P.W., Dallal, G.E., Dinarello, C.A. (1998) Monocyte cytokine production in an elderly population: effect of age and inflammation. *J. Gerontol. A. Biol. Sci. Med. Sci.* 53, M20–26.
47. Giuliani, N., Sansoni, P., Girasole, G., Vescovini, R., Passeri, G., Passeri, M., Pedrazzoni, M. (2001) Serum interleukin-6, soluble interleukin-6 receptor and soluble gp130 exhibit different patterns of age- and menopause-related changes. *Exp. Gerontol.* 36, 547–557.
48. Pfeilschifter, J., Koditz, R., Pfohl, M., Schatz, H. (2002) Changes in proinflammatory cytokine activity after menopause. *Endocr. Rev.* 23, 90–119.
49. Fida, N.M., Al-Mughales, J., Farouq, M. (2006) Interleukin-1a, interleukin-6 and tumor necrosis factor-a levels in children with sepsis and meningitis. *Ped Internat.* 48, 118–124.
50. Liuzzo, G., Biasucci, L.M., Gallimore, J.R., Gillo, R.L., Rbuzzi, A.G., Pepys, M.B., Maseri, A. (1994) The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N. Engl. J. Med.* 331, 417–424.

Reprint

de Quervain Tenosynovitis of the Wrist

Asif Ilyas, MD, Michael Ast, MD, Alyssa A. Schaffer, MD, Joseph Thoder, MD

Department of Orthopaedic Surgery, Temple University, Philadelphia, PA

Abstract

de Quervain disease, or stenosing tenosynovitis of the first dorsal compartment of the wrist, is a common wrist pathology. Pain results from resisted gliding of the abductor pollicis longus and the extensor pollicis brevis tendons in the fibro-osseus canal. de Quervain tenosynovitis of the wrist is more common in women than men. Diagnosis may be made on physical examination. Radiographs are helpful in ruling out offending bony pathology. Nonsurgical management, consisting of corticosteroid injections and supportive thumb spica splinting, is usually successful. In resistant cases, surgical release of the first dorsal compartment is done, taking care to protect the radial sensory nerve and identify all accessory compartments. Repair of the extensor retinaculum by step-cut lengthening or other techniques is rarely required.

de Quervain disease is a stenosing tenosynovitis of the first dorsal compartment of the wrist. It often presents with a gradual onset of pain that may be exacerbated by grasping, thumb abduction, and ulnar deviation of the wrist. The etiology is thought to be secondary to repetitive or sustained tension on the tendons of the first dorsal compartment. This tension produces a fibroblastic response, resulting in thickening and swelling of the compartment and discomfort with use of the hand and wrist.

Fritz de Quervain,[1] a Swiss physician, is credited with describing the condition when he presented a case series in 1895. In 1930, Finkelstein[2] presented 24 cases, provided a detailed review of the literature and results of animal studies, and described a physical examination test. Patterson[3] first dubbed the condition de Quervain disease in 1936. Multiple names have been attributed to de Quervain disease, including stenosing tenosynovitis, stenosing tendinitis, peritendinitis, styloid tenovaginitis, and stenosing tendovaginitis (as used by de Quervain). These terms are misleading, however, because they imply merely inflammation of the tendon, whereas de Quervain disease represents an attritional and degenerative process of the compartment.[4, 5]

No long-termepidemiologic study has been done of the prevalence of de Quervain disease, but it is known to be relatively common. Case series suggest that it affects women up to six times more often than men and is associated with the dominant hand during middle age.[1–3, 6–8] Historically, overexertion from household duties was the most common reported cause. Occupations requiring repetitive typing, lifting, and manipulation have been considered risk factors, as well. Ranney et al.[9] studied female workers in highly repetitive jobs and showed de Quervain disease to be the most prevalent tendon disorder of the wrist. Pregnant and lactating women represent an increasing cohort of patients with new-onset, self-limited de Quervain disease.[10–13]

Anatomy

Knowledge of the anatomy of the dorsal compartments of the wrist is central to understanding the pathophysiology of de Quervain disease. Many of the muscles that produce finger motion exist outside the hand (extrinsic muscles) and are opposed by muscles within the hand (intrinsic muscles). The extrinsic muscles exert their force by transmitting tension via tendons traveling through unyielding fibro-osseous tunnels on the radius. Six fibro-osseous tunnels representing the dorsal compartments on the distal radius surround the extensor tendons and function to prevent bowstringing of the extensor tendons. Each compartment is lined with a synovial sheath membrane.

The first dorsal compartment is approximately 2 cm long and is located over the radial styloid proximal to the radiocarpal joint. The abductor pollicis longus (APL) and the extensor pollicis brevis (EPB) tendons pass through this compartment (Figure 1). The APL originates on the distal third of the radius and has multiple slips (2 to 4), with variable insertions on the base of the thumb metacarpal and trapezium. The primary function of the APL is to abduct the thumb and assist with radial deviation of the wrist. The EPB originates on the dorsal surface of the radius and the interosseous membrane and inserts on the base of the proximal phalanx of the thumb. The EPB functions to extend the metacarpophalangeal joint and to weakly abduct the thumb.

Pathophysiology

Stenosing tenosynovitis of the first dorsal compartment is caused by attritional forces secondary to friction; the attritional forces produce swelling and thickening of the exten-

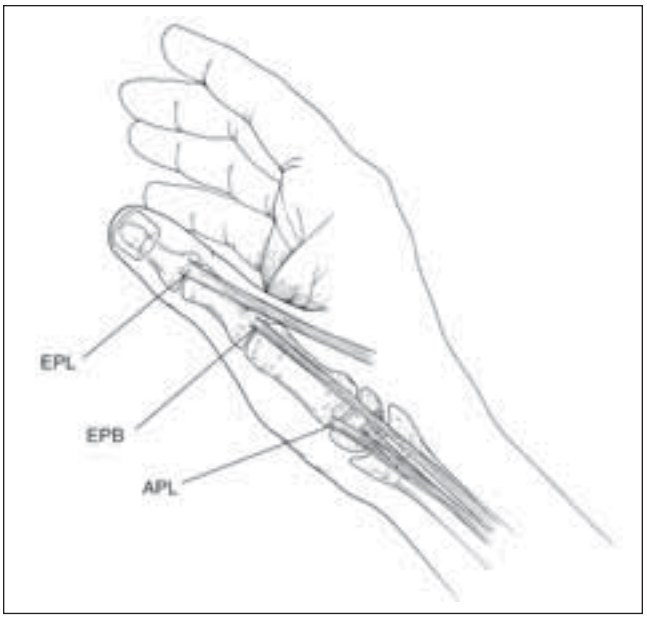


Figure 1. Anatomy of the first dorsal compartment demonstrating the insertion of the abductor pollicis longus (APL), extensor pollicis brevis (EPB), and extensor pollicis longus (EPL) tendons.

sor retinaculum covering the first dorsal compartment. The functional impairment is secondary to resisted gliding of the APL and the EPB within the narrowed fibro-osseous canal, resulting in pain and decreased motion.[14]

The histopathology of de Quervain disease generally does not involve inflammation but is related instead to thickening of the extensor tendons and surrounding extensor retinaculum. Clarke et al.[5] examined the microanatomic findings of the tendon sheaths and synovium of symptomatic patients; these authors found thickening of the tendon sheaths to be up to five times that of control subjects because of deposition of dense fibrous tissue, increased vascularity of the tendon sheaths, and accumulation of mucopolysaccharides, which are indicators of myxoid degeneration. Notably, the synovial linings were preserved and were histologically normal. The authors postulated that these changes, as opposed to the common histologic changes seen in chronic inflammation, may indicate that de Quervain disease is a result of an intrinsic degenerative mechanism rather than an inflammatory one, as is often described.[5]

Several theories exist regarding the cause of de Quervain disease. Possible etiologies include trauma, increased frictional forces, anatomic abnormality, biomechanical compression, repetitive microtrauma, inflammatory disease, and increased volume states, such as occurs during pregnancy.[1–13, 15, 16] All of these processes have the ability to create the environment necessary to develop a stenosing tenosynovitis of the first dorsal compartment.

Several studies have identified anatomic variations of the first dorsal compartment.[15–17] Variations include septation of the first dorsal compartment and the presence of multiple slips of the APL and, occasionally, of the EPB tendon. Bahm et al.[18] found division of the first dorsal compartment by an additional septum in 60% of patients with symptomatic de Quervain disease; the APL consisted of multiple tendons in 76%. In a cadaveric study, Shiraishi and Matsumura[19] noted variation in the number of tendons, including up to seven slips of the APL and up to three of the EPB. Aktan et al.[20] examined the wrists of patients with de Quervain disease and found that the number of tendons present in the first compartment differed from the accepted standard in 82% of patients; 46% of the compartments were septated.

These anatomic variations may have an effect on the underlying pathophysiology of de Quervain tenosynovitis. Kutsumi et al.[14] examined 15 cadaveric wrists with and without septation of the first dorsal compartment and measured the gliding resistance of the APL and the EPB tendons in several wrist positions, including flexion, extension, abduction, and adduction. The authors found that the presence of septation and wrist position (eg, 30° of ulnar deviation, as in the Finkelstein test) affected the gliding resistance of the EPB tendon. These anatomic variations may predispose a patient to de Quervain disease. The patient with such a predisposition may respond poorly to nonsurgical treatment.

Diagnosis

The clinical presentation of de Quervain tenosynovitis is fairly consistent. It most commonly presents with a gradual onset of pain localized along the radial side of the wrist, with an exacerbation of symptoms caused by grasping and raising objects with the wrist in neutral rotation. The differential diagnosis includes intersection syndrome, radial styloid fracture, scaphoid fracture, instability or basilar arthritis of the thumb, and radial neuritis.

Basilar arthritis of the thumb (arthritis of the trapeziometacarpal or scaphotrapezial joints) should be differentiated from de Quervain disease. Because of similar demographics, these two entities commonly coexist. Arthritic symptoms are elicited with palpation of the basal joint of the thumb and with painful axial compression and circumduction of the thumb. Intersection syndrome results from tendinopathy between the APL and common wrist extensor tendons. The patient presents with focal tenderness and crepitus 4 to 5 cm proximal to the wrist joint, centered dorsally over the second dorsal compartment. Although pain and crepitus are the most common presenting symptoms of intersection syndrome, some patients also report stiffness or neuralgia.

With de Quervain disease, the location of tenderness is more specific to the first extensor compartment over the radial styloid, with possible radiation of pain to the forearm and distally to the thumb. The patient also may report an increase in pain with repetitive motion of the thumb that is improved with rest or immobilization. In addition, uncommon but well-recognized presentations include extensor triggering or locking of the thumb as well as dorsal ganglion

cyst formation.[21–23]

The Finkelstein test is the classic maneuver for diagnosis and is considered pathognomonic for de Quervain disease.[2, 24] It is performed by grasping the patient's thumb and quickly deviating the hand and wrist ulnarly. A positive test reproduces the pain. However, the examiner must be mindful that the patient may not be able to differentiate the pain of tenosynovitis focused at the radial styloid from that of basilar arthritis of the thumb.

An alternative to the Finkelstein test is the Eichoff maneuver. This test is performed by having the patient clench his or her thumb in a fist, followed by brisk deviation of the wrist ulnarly.[24] The Eichoff maneuver has been confused with the Finkelstein test, which has led many to consider the Eichoff maneuver and Finkelstein test to be the same.[25] Although sensitive, the specificity of the Finkelstein test may be called into question because of its propensity to provoke pain in asymptomatic patients and those with underlying arthritis.

Brunelli[26] proposed a test involving strong abduction of the thumb with the wrist in radial deviation. The author proposed that his test was more effective than the Finkelstein test because it provoked tendon irritation of the first dorsal compartment against their pulleys.

Imaging Studies

de Quervain disease is diagnosed clinically; no imaging studies are required. Wrist imaging is required only in the presence of associated processes that may need to be evaluated, such as previous distal radius or scaphoid fracture, arthritis of the thumb, and instability of the wrist. Occasionally, radiographs may identify bony changes on the radial styloid, such as spurring or lesions that may directly irritate the first dorsal compartment.[27] Several authors have recommended other imaging modalities, including magnetic resonance imaging, ultrasound, and bone scanning, and have demonstrated findings that may support the diagnosis of de Quervain disease.[28–31] However, routine use of radiographs and advanced imaging is not required when the presentation is clear.

Treatment

Nonsurgical

Nonsurgical treatment should be the first course of action for de Quervain disease. The patient presenting with mild to moderate pain that does not limit activities of daily living should be treated with rest, splinting, nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroid injection of the first dorsal compartment. Splinting is an effective method for resting the APL and EPB tendons by immobilizing the thumb and wrist in a single position and reducing or preventing the friction that may exacerbate swelling and pain. Custom or prefabricated splints should be forearm-based; one such splint is a radial thumb spica extension that holds the wrist in neutral and the thumb in 30° of flexion and 30° of abduction. Although symptoms may improve with splinting, on removal of the splint, symptoms quickly return in some patients when the inciting activity is resumed.[27]

Corticosteroid injection into the first dorsal compartment is perhaps the most common and effective treatment of de Quervain disease. Many patients experience complete relief of symptoms with a single corticosteroid injection.[7, 8, 32] Richie and Briner[33] performed a pooled quantitative literature evaluation to determine the reported cure rate of corticosteroid injection for de Quervain disease; they reported that 83% of patients had complete relief with injection alone. Failure of response to corticosteroid injection has been attributed to poor technique and anatomic variations within the first dorsal compartment.

In their series of 63 patients, Harvey et al.[7] found that 82% had relief of pain after one or two corticosteroid injections. Of the 11 patients who did not have complete pain relief and went on to surgery, 10 had a separate compartment for the EPB. Zingas et al.[34] studied injection accuracy and found that the needle was accurately placed into the first dorsal compartment in 84% of patients. However, the EPB tunnel was missed in 68% of patients, either because it was too small or was in a separate compartment, thus compromising the overall outcome. Similarly, Witt et al.[35] found that 79% of patients who were resistant to corticosteroid injection had a separate compartment for the EPB tendon at the time of surgery.

Corticosteroid injection for de Quervain disease consists of 1mL of corticosteroid with 0.5 to 1 mL of a local anesthetic. Success has been reported with a variety of corticosteroids (eg, betamethasone, triamcinolone, dexamethasone, methylprednisolone) combined with any of several local anesthetics (eg, bupivacaine, lidocaine).[7, 8, 13, 34–36] We prefer a water-soluble preparation; insoluble preparations have been associated with more local complications.[37] As such, we administer 5 mg of dexamethasone and 1 mL of 1% lidocaine.

With the wrist in neutral radioulnar deviation, a rolled-up towel is placed under the wrist to position it in slight ulnar deviation (Figure 2). The injection site is prepped sterile. The course of the APL and EPB tendons along the radial styloid is palpated, and the borders of the first dorsal compartment are straddled with the examiner's opposite thumb and index finger. A 25-gauge needle is introduced into the tendon sheath at the level of the styloid, parallel to the tendons. Resistance indicates that the needle is likely in the tendon. The needle is carefully backed out while maintaining pressure on the plunger of the syringe. The injectable medication should flow smoothly and easily, with both visual and palpable inflation of the compartment.

Before injection, the patient must be informed that subdermal atrophy and hypopigmentation may occur at the injection site, particularly in the darker-skinned patient. Avoid injecting directly into the tendon. This carries the risk of weakening the tendon and causing tendon rupture. Adverse

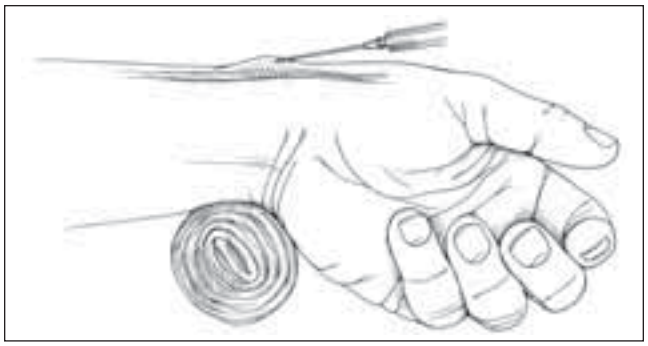


Figure 2. Injection of the first dorsal compartment with the wrist in neutral rotation and gentle ulnar deviation over a rolled-up towel. A 25-gauge needle is introduced into the tendon sheath at the level of the radial styloid and parallel to the tendons. The medication should flow smoothly and should both visually and palpably inflate the compartment.

reactions to corticosteroid injection are generally minor and self-limited; they include pain, neuritis, fat necrosis, and postinjection flare.[33, 36–38] Additionally, local infection and tendon rupture, although unusual, may occur.

Richie and Briner[33] performed a quantitative literature evaluation of studies of comparative treatment modalities for de Quervain disease. Of the 495 wrists studied, there was an 83% success rate for corticosteroid injection alone. Surprisingly, the success rate with injection and splinting together was just 61%. Splinting alone had a success rate of 14%. NSAIDs and rest yielded a 0% success rate. The efficacy of NSAIDs has been studied further; they were found to provide no benefit when used to supplement corticosteroid injection.[38]

Our initial preferred treatment is corticosteroid injection with dexamethasone and lidocaine. Subsequently, tendon gliding and stretching exercises are taught. We also prescribe a forearm-based thumb spica splint in the patient with persistent or severe symptoms. An additional injection may be offered after a 4- to 8-week interval for the patient who has experienced some improvement with the initial injection but who continues to report discomfort. When pain does not resolve after two corticosteroid injections and 6 months of nonsurgical management, and when other pathologies have been ruled out, then surgical release of the first dorsal compartment is recommended.

Surgical

Surgical treatment is based on release of the fibro-osseous roof of the first dorsal compartment and decompressing the stenosed APL and EPB tendons. Fundamental to surgical intervention is protection of the radial sensory nerve and complete decompression of the first dorsal compartment, including release of additional tendinous slips and compartments. In several series, the reported incidence of separate compartments at surgery is higher than that seen in anatomic specimens.[7, 8, 35, 39] In particular, the potential for septation of the EPB compartment increases the chance that nonsurgical treatment will fail; surgical decompression may be compromised if the condition is not identified.[7, 34, 35] Surgical treatment should be approached with the mindset that anatomic variations of the compartment are the rule rather than the exception. Injury to the radial sensory nerve and failure to recognize variations in the first dorsal compartment may result in continued pain and treatment failure.[39–41]

Our preferred technique is to perform the surgery under local anesthesia, with or without intravenous sedation, and tourniquet control. Although multiple incisions (eg, transverse, longitudinal, oblique) may be used to provide excellent exposure of the first dorsal compartment, we employ a chevron-style incision because we believe it aids in visualization of the radial sensory nerve, avoids tendon injury, and enhances wound healing (Figure 3A). Once the skin incision is made, blunt dissection is used to identify and protect the radial sensory nerve. Sharp dissection with a scalpel through the subcutaneous tissue may injure branches of the nerve and should be avoided. One to three branches of the radial sensory nerve are identified and protected with blunt retractors (Figure 3B).

Dissection is then carried down to the first dorsal compartment. The retinaculum of the first dorsal compartment is completely incised with a scalpel in line with the APL and EPB tendons. Burton and Littler[42] recommend releasing the sheath along its dorsal margin, thus leaving the volar flap intact to prevent subluxation of the tendons (Figure 3C). The tendons are examined, and the compartment is diligently explored. The APL tendon is larger and is routinely composed of two or more distinct tendons. The EPB tendon is smaller, dorsal, and often lies in a separate compartment.[7, 34, 35]

Although complete excision of the extensor sheath is avoided, any intra-compartmental septae should be released and excised. Tendons may be carefully tensioned using atraumatic technique to simulate their function, aid in their identification, and confirm decompression. Active and free thumb abduction and extension then can be performed on the awake patient. Next, any loose tenosynovial tissue on the tendon is débrided. After confirming that the compartment is completely released, the tourniquet is released, and hemostasis is achieved.

We do not approximate the edges of the released extensor retinaculum. Step-cut lengthening is rarely required; we do not recommend a step-cut release with repair of the retinaculum. The skin incision is closed using single interrupted 4-0 nylon sutures. Postoperatively, a plaster thumb spica splint is applied to aid in pain control and wound healing. The splint and sutures are removed 10 to 14 days postoperatively, and the patient is allowed to resume normal activities as tolerated. Physical and occupational therapy is not routinely instituted unless specific patient circumstances indicate it.

Outcomes from surgical release of de Quervain disease have been uniformly excellent. The “cure rate,” as described by several investigators, represents resolution of symptoms without complications and has been reported to be

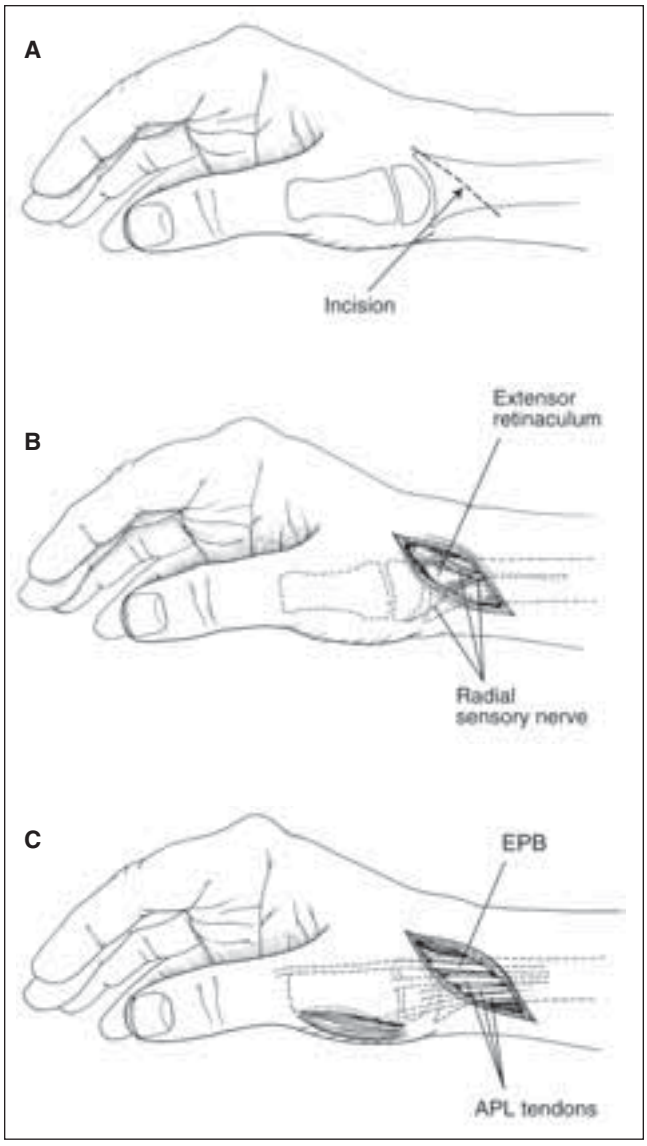


Figure 3. Surgical treatment of de Quervain disease. **(A)** Oblique incision centered over the radial styloid. **(B)** The skin is retracted. Careful blunt dissection will reveal branches of the radial sensory nerve in the subcutaneous tissue. **(C)** The first dorsal compartment is released along its dorsal border, revealing the abductor pollicis longus (APL) and extensor pollicis brevis (EPB) tendons.

≥91%.[2, 43–46] Although most series have been unable to identify risk factors for long-term complications or patient satisfaction after surgical treatment, Ta et al.[44] found a positive correlation between duration of preoperative symptoms and postoperative satisfaction. Patients with preoperative symptoms lasting 9 months or longer were much more satisfied with their surgery than were patients who had been symptomatic for a much shorter period.

Complications

Corticosteroid injection has been associated with fat necrosis, subcutaneous atrophy, and skin depigmentation.[36, 37, 39, 40] The patient should be counseled about the 5% to 10% risk of these complications.[27]

Other complications after surgery include radial sensory nerve injury, incomplete decompression, and volar subluxation of the tendons.[2, 7, 8, 40, 44, 45, 47, 48] Injury to the radial sensory nerve may present with a spectrum of injury, from complete transection to neuroma in continuity to neurapraxia from overzealous retraction. Management of a lacerated radial sensory nerve is controversial; options vary from resection of the lacerated edge more proximally to primary repair using microsurgical techniques. Radial sensory nerve injury is a complication best avoided with careful surgical technique.

Persistent pain from inadequate decompression often represents failure to recognize and release an additional compartment, most commonly that of the EPB; reexploration is usually warranted. Volar subluxation of the APL and EPB tendons is an uncommon complication; it is often associated with a volar rather than dorsal release of the first dorsal compartment, or it may result from complete excision of the retinaculum. Reconstruction of the compartment with a slip of extensor retinaculum is effective in managing the subluxation.[48, 49]

Additional reported complications include scar hypertrophy or tenderness, particularly with longitudinal incisions,[47] reflex sympathetic dystrophy, and continued pain as a result of incorrect diagnosis. Associated missed diagnoses include basilar arthritis of the thumb, instability of the thumb, intersection syndrome, and radial neuritis. Wartenburg's syndrome (ie, superficial radial neuritis) has been shown to compromise the surgical outcome from de Quervain disease. Some patients require proximal neurolysis and repositioning of the nerve deep in the forearm to avoid painful neuropathy.[50]

Summary

de Quervain disease is a commonly encountered wrist pathology involving thickening of the first dorsal compartment of the wrist. Pain occurs during wrist and thumbmotion from resisted gliding of the APL and EPB tendons in the narrowed fibroosseus canal. This condition is more common in women than in men. The diagnosis is clinical and is most closely correlated with a positive Finkelstein test or Eichoff maneuver. Radiographs may be indicated to rule out other wrist pathologies; however, they generally are not recommended in the evaluation of classically presented de Quervain disease. Nonsurgical management is the mainstay of treatment, consisting of rest, thumb spica splinting, and corticosteroid injection. When nonsurgical management fails to provide sustained relief, open surgical release of the first dorsal compartment, with identification of accessory compartments and protection of the radial sensory nerve, may be performed with excellent results.

References

Evidence-based Medicine: There are several level I (references 13, 34-36, and 38), level II (references 7, 8, 32, 44, and 45), level III (references 1–4, 6, 9, 11, 12, 23, 28–31, 40, 43, 46, 47, and 50), level IV (references 10, 21, 22, 41, and 48), and level V (references 25, 27, and 49) studies cited. The remaining references are anatomic, biomechanical, and meta-analysis studies, and review papers.

Citation numbers printed in **bold type** indicate references published within the past 5 years.

1. de Quervain F: On a form of chronic tendovaginitis by Dr. Fritz de Quervain in la Chaux-de-Fonds: 1895. *Am J Orthop* 1997;26:641–644.
2. Finkelstein H: Stenosing tendovaginitis at the radial styloid process. *J Bone Joint Surg Am* 1930;12:509–540.
3. Patterson DC: De Quervain's disease: Stenosing tenovaginitis at the radial styloid. *N Engl J Med* 1936;214:101–102.
4. Keon-Cohen B: De Quervain's disease. *J Bone Joint Surg Br* 1951; 33:96–99.
5. Clarke MT, Lyall HA, Grant JW, Matthewson MH: The histopathology of de Quervain's disease. *J Hand Surg [Br]* 1998;23:732–734.
6. Moore JS: De Quervain's tenosynovitis: Stenosing tenosynovitis of the first dorsal compartment. *J Occup Environ Med* 1997;39:990–1002.
7. Harvey FJ, Harvey PM, Horsley MW: De Quervain's disease: Surgical or nonsurgical treatment. *J Hand Surg [Am]* 1990;15:83–87.
8. Weiss AP, Akelman E, Tabatabai M: Treatment of de Quervain's disease. *J Hand Surg [Am]* 1994;19:595–598.
9. Ranney D, Wells R, Moore A: Upper limb musculoskeletal disorders in highly repetitive industries: Precise anatomical physical findings. *Ergonomics* 1995;38:1408–1423.
10. Schumacher HR Jr, Dorwart BB, Korzeniowski OM: Occurrence of de Quervain's tendinitis during pregnancy. *Arch Intern Med* 1985;145: 2083–2084.
11. Schned ES: DeQuervain tenosynovitis in pregnant and postpartum women. *Obstet Gynecol* 1986;68:411–414.
12. Johnson CA: Occurrence of de Quervain's disease in postpartum women. *J Fam Pract* 1991;32:325–327.
13. Avci S, Yilmaz C, Sayli U: Comparison of nonsurgical treatment measures for de Quervain's disease of pregnancy and lactation. *J Hand Surg [Am]* 2002;27:322–324.
14. Kutsumi K, Amadio PC, Zhao C, Zobitz ME, An KN: Gliding resistance of the extensor pollicis brevis tendon and abductor pollicis longus tendon within the first dorsal compartment in fixed wrist positions. *J Orthop Res* 2005;23:243–248.
15. Loomis LK: Variations of stenosing tenosynovitis at the radial styloid process. J Bone Joint Surg Am 1951;33:340–346.
16. Leslie BM, Ericson WB Jr, Morehead JR: Incidence of a septum within the first dorsal compartment of the wrist. *J Hand Surg [Am]* 1990; 15:88–91.
17. Minamikawa Y, Peimer CA, Cox WL, Sherwin FS: De Quervain's syndrome: Surgical and anatomical studies of the fibroosseous canal. *Orthopedics* 1991;14:545–549.
18. Bahm J, Szabo Z, Foucher G: The anatomy of de Quervain's disease: A study of operative findings. *Int Orthop* 1995;19:209–211.
19. Shiraishi N, Matsumura G: Anatomical variations of the extensor pollicis brevis tendon and abductor pollicis longus tendon: Relation to tenosynovectomy. *Okajimas Folia Anat Jpn* 2005;82:25–29.
20. Aktan ZA, Oztürk L, Calli IH: An anatomical study of the first extensor compartment of the wrist. *Kaibogaku Zasshi* 1998;73:49–54.
21. Chow SP: Triggering due to de Quervain's disease. *Hand* 1979;11: 93–94.
22. Witczak JW, Masear VR, Meyer RD: Triggering of the thumb with de Quervain's stenosing tendovaginitis. *J Hand Surg [Am]* 1990;15: 265–268.
23. Alberton GM, High WA, Shin AY, Bishop AT: Extensor triggering in de Quervain's stenosing tenosynovitis. *J Hand Surg [Am]* 1999;24: 1311–1314.
24. Kutsumi K, Amadio PC, Zhao C, Zobitz ME, Tanaka T, An KN: Finkelstein's test:Abiomechanical analysis. *J Hand Surg [Am]* 2005; 30:130–135.
25. Elliott BG: Finkelstein's test: A descriptive error that can produce a false positive. *J Hand Surg [Br]* 1992;17:481–482.
26. Brunelli G: Finkelstein's versus Brunelli's test in De Quervain tenosynovitis [French]. *Chir Main* 2003;22:43–45.
27. Wolfe S: Tenosynovitis, in Wolfe S, Green DP, Hotchkiss RN, Pederson WC (eds): Green's Operative Hand Surgery, ed 5. Philadelphia, PA: Lippincott, 2005, pp 2150–2154.
28. Chien AJ, Jacobson JA, Martel W, Kabeto MU, Marcantonio DR: Focal radial styloid abnormality as amanifestation of de Quervain tenosynovitis. *AJR Am J Roentgenol* 2001;177:1383–1386.
29. Glajchen N, Schweitzer M: MRI features in de Quervain's tenosynovitis of the wrist. *Skeletal Radiol* 1996;25:63–65.
30. Sopov W, Rozenbaum M, Rosner I, Groshar D: Scintigraphy of de Quervain's tenosynovitis. *Nucl Med Commun* 1999;20:175–177.
31. Nagaoka M, Matsuzaki H, Suzuki T: Ultrasonographic examination of de Quervain's disease. *J Orthop Sci* 2000;5:96–99.
32. Lane LB, Boretz RS, Stuchin SA: Treatment of de Quervain's disease: Role of conservative management. *J Hand Surg [Br]* 2001;26: 258–260.
33. Richie CA III, Briner WW Jr: Corticosteroid injection for treatment of de Quervain's tenosynovitis: A pooled quantitative literature evaluation. *J Am Board Fam Pract* 2003;16:102–106.
34. Zingas C, Failla JM, Van Holsbeeck M: Injection accuracy and clinical relief of de Quervain's tendinitis. *J Hand Surg [Am]* 1998;23:89–96.
35. Witt J, Pess G, Gelberman RH: Treatment of de Quervain tenosynovitis: A prospective study of the results of injection of steroids and immobilization in a splint. *J Bone Joint Surg Am* 1991;73:219–222.
36. Anderson BC, Manthey R, Brouns MC: Treatment of De Quervain's tenosynovitis with corticosteroids: A prospective study of the response to local injection. *Arthritis Rheum* 1991;34:793–798.
37. Neustadt DH: Local corticosteroid injection therapy in soft tissue rheumatic conditions of the hand and wrist. *Arthritis Rheum* 1991;34: 923–926.
38. Jirarattanaphochai K, Saengnipanthkul S, Vipulakorn K, Jianmongkol S, Chatuparisute P, Jung S: Treatment of de Quervain disease with triamcinolone injection with or without nimesulide: A randomized, double-blind, placebo-controlled trial. *J Bone Joint Surg Am* 2004; 86:2700–2706.
39. Sampson SP, Wisch D, Badalamente MA: Complications of conservative and surgical treatment of de Quervain's disease and trigger fingers. *Hand Clin* 1994;10:73–82.
40. Arons MS: de Quervain's release in working women: A report of failures, complications, and associated diagnoses. *J Hand Surg [Am]* 1987;12:540–544.
41. Louis DS: Incomplete release of the first dorsal compartment:A diagnostic test. *J Hand Surg [Am]* 1987;12:87–88.
42. Burton RI, Littler JW: Tendon entrapment syndrome of first extensor compartment (de Quervain's disorder). *Curr Probl Surg* 1975;12: 32–34.
43. Lapidus PW, Fenton R: Stenosing tenovaginitis at the wrist and fingers: Report of 423 cases in 369 patients with 354 operations. *AMA Arch Surg* 1952;64:475–487.
44. Ta KT, Eidelman D, Thomson JG: Patient satisfaction and outcomes of surgery for de Quervain's tenosynovitis. *J Hand Surg [Am]* 1999;24: 1071–1077.
45. Zarin M, Ahmad I: Surgical treatment of de Quervain's disease. *J Coll Physicians Surg Pak* 2003;13:157–158.
46. Gundes H, Tosun B: Longitudinal incision in surgical release of De Quervain disease. *Tech Hand Up Extrem Surg* 2005;9:149–152.
47. Mellor SJ, Ferris BD: Complications of a simple procedure: de Quervain's disease revisited. *Int J Clin Pract* 2000;54:76–77.
48. White GM, Weiland AJ: Symptomatic palmar tendon subluxation after surgical release for de Quervain's disease: A case report. *J Hand Surg [Am]* 1984;9:704–706.
49. McMahon M, Craig SM, Posner MA: Tendon subluxation after de Quervain's release: Treatment by brachioradialis tendon flap. *J Hand Surg [Am]* 1991;16:30–32.
50. Lanzetta M, Foucher G: Association of Wartenberg's syndrome and De Quervain's disease: A series of 26 cases. *Plast Reconstr Surg* 1995; 96:408–412.

Lectureship

Pennsylvania Orthopaedic Trauma Symposium

On September 7–8, 2007, Temple University School of Medicine Department of Orthopaedic Surgery presented the fourth annual Pennsylvania Orthopaedic Trauma Symposium at the Westin Philadelphia. The directors of this symposium were our own Dr. William DeLong, and Dr. Christopher Born, Chief of Orthopaedic Trauma at Brown University. The objective of the conference was to discuss and describe complex upper and lower extremity injuries and demonstrate the use of new techniques in external and internal fixation. In a fully attended auditorium by orthopaedic surgeons, residents, physician assistants, and nurse practitioners, some of the presented topics included: treatment options of distal radius fractures, hemiarthroplasty of the proximal humerus, total elbow replacement, IM nailing of distal and proximal tibia, pilon fractures, femoral fractures, and acetabular fractures. Despite the diversity of the topics, the strategically scheduled panel discussions combined with timely breaks and interactive sessions made it very easy for the audience to transition from topic to topic.

The format of the conference consisted of specific topic presentations by experts in the field, followed by open audience questions and panel discussions. This led to different opinions, emphasizing once again the complexity in the management of some traumatic injuries. There were also two sessions of case presentations in small groups led by the topic presenters. This interactive atmosphere was helpful in discussing some cases in further detail. In addition, two instructional lab sessions, conducted by our industry partners, introduced new techniques in proximal humeral plating, supracondylar nailing and external fixation. During the break times, there were plenty of refreshments available, and our industry sponsors provided information about new innovative commercial products.

At the conclusion of the first day, a reception accompanied by a dinner provided with an opportunity to meet and interact with the presenters in a more casual manner. The second day was also very well attended and the symposium concluded with finishing remarks from the directors thanking the visiting faculty members, the audience and the sponsors. All participants of the symposium received a maximum of 14 credits of continued medical education depending on the level of their participation.

Jung Park, MD

Lectureship

The John Lachman Lecture at the Pennsylvania Orthopaedic Society

Presented by:

MURRAY J. GOODMAN, MD

"AAOS Professional Compliance Program"

The Fourth Annual John Lachman Lecture was presented by Murray J. Goodman, MD, a member of the AAOS Committee on Professionalism. Dr. Goodman related how, in 2004, the Board of Directors of the Academy charged a group of orthopaedic surgeons to develop procedures to review, hear, and adjudicate grievances between Fellows resulting from orthopaedic expert witness testimony. The group broadened this charge and produced standards of professionalism which established mandatory, minimum levels of acceptable conduct for AAOS Fellows and Members. That include: 1) providing musculoskeletal services to patients; 2) professional relationships; 3) orthopaedic expert witness testimony; 4) research and academic responsibilities; 5) advertising by orthopaedic surgeons; and 6) orthopaedist-industry conflicts of interest. The process permits a Fellow or Member to file a formal grievance against another Fellow or Member. Substantial due process is provided including a minimum of two opportunities to be heard. The Committee on Professionalism (COP) conducts initial reviews and hearings and the Judiciary Committee hears appeals of the COP recommendations. The AAOS Board of Directors is designated as the final decision-making body in all professional compliance matters. Those censured, suspended or expelled from the Academy will be identified by name in AAOS publications, the National Practitioner Data Bank, state licensing boards, American Board of Surgery, and state medical societies. The AAOS firmly believes that these procedures meet or exceed the level of professional compliance programs established by other national medical associations.

Dr. Goodman's lecture was well received and clearly in keeping with the Lachman principles of integrity, education and excellence in-patient care.

Joseph S. Torg, MD

Lectureship

The Howard Steel Lecture at the Philadelphia Orthopaedic Society

Presented by:

SCOTT H. KOZIN, MD

"Communication: The Influence of the Orthopaedic Hand Surgeon"

The Howard Steele Lecture, sponsored by the Philadelphia Orthopaedic Society, was held at the Bell Tower on Monday, September 10th, 2007. This lectureship is held annually in honor of Dr. Steele, who received his medical degree and training from Temple University School of Medicine. His long and illustrious career precedes him as he continues to treat patients at the Shriners Hospital for Children, and his contributions to the field of orthopaedic surgery are well noted by us all.

The guest speaker for this event was Dr. Scott Hal Kozin, MD, Associate Professor of Orthopaedic Surgery, Temple University School of Medicine, and Hand Surgeon, Shriners Hospital for Children, Philadelphia.

The lecture was attended by many imminent orthopedic surgeons from the Philadelphia area, including the President of the POS, Andrew Collier, Jr., MD. Most of the major hospitals and orthopaedic surgery departments from the area were well represented by faculty and residents alike.

The evening started with the reception at 6 PM, followed by a lecture by Dr. Kozin which was entitled, "Communication: The Influence of the Orthopaedic Hand Surgeon." His talk focused on many congenital and acquired disorders which limit patients from communicating and expressing themselves due to impairment in upper extremity function. Dr. Kozin stated that patients use their hands for various methods of communication such as writing, sign language, or via computers. He discussed various treatment and management options for these individuals and emphasized how the ability to communicate has such a great impact on patients' functional and emotional outcome.

Dr. Kozin followed his lecture by a brief commentary on Dr. Steele. He mentioned Steele's impact on the orthopaedic community, not only in Philadelphia, but in the US and around the world. He ended his discussion by sharing some of his more light-hearted interactions with Dr. Steele, which led to contributions from the audience about some of their own exchanges with him. The lecture was well attended and well received by all, and we will all look forward to this lectureship next year.

Irfan Ahmed, MD

From left to right: Drs. Weiss, Thoder, Kozin, and Ilyas.

Lectureship

The John Royal Moore/John Lachman Annual Lectureship at the Philadelphia Orthopaedic Society

February 11, 2008

The evening began as the orthopaedic surgeons and residents strolled in from Jefferson, Temple, PCOM, Penn, Hahnemann, and various private practices in the greater Philadelphia area. It was clear from the beginning this was an event that held great respect and honor within the orthopaedic community. The agenda for the evening was an introduction about the lectureship and a very useful and clearly presented lecture by Tom Minas, MD/PhD, entitled, "A Surgical Algorithm for the Management of Patellofemoral Disease."

Our Chairman, Dr. Thoder, began the lectureship with a short history of Dr. John Royal Moore. Dr. Moore was the first Chairman of the Temple University Hospital Department of Orthopaedic Surgery and Sports Medicine. In addition, he became Chairman of Shriners Hospital for Children by the young age of 27.

After the prelude about Dr. Moore, a moving acknowledgement of Dr. Lachman's inspiration for many of the attending orthopods was accompanied by the announcement of his recent passing. Indeed, Dr. Lachman's legacy will live on through all of us as we continue our training and during our career as orthopaedic surgeons.

Next, Dr. Minas, who is director of Cartilage Repair at Harvard's Brigham and Women's Hospital, gave a very useful algorithm for treating the often difficult to treat cartilage defects in a young patient's knees. He gave his preference for a useful diagnostic tool, a spiral CT arthrogram, to help sort out who has true pathology and, more importantly, what the pathology is in these patients. In his opinion, the CT arthrogram was more sensitive and specific than MRI for chondral defects. The outline of his talk is as follows:

Diagnosis	Treatment
Patellar tilt	Arthroscopic lateral retinacular release
Patellar tilt + subluxation + no chondrosis	Medialization TTO*
Patellar tilt + subluxation + grade 1/2 chondrosis	Anteromedialization TTO (Fulkerson)
Patellar tilt + subluxation + grade 3/4 chondrosis	Fulkerson + ACI**
Patellar tilt + subluxation + joint space narrowing	Patellofemoral arthroplasty +/- Fulkerson

*TTO: tibial tubercle osteotomy. **ACI: autologous chondroyte implantation.

In the end, it was a wonderful evening and all that participated gained from an interesting and engaging talk.

Ian Duncan, MD

From left to right: Drs. Thoder, Rehman, Chao, Minas, Duncan, and Foroohar.

Lectureship

The Howard H. Steel Pediatric Orthopaedic Seminar and OITE Review at the Shriners Hospital for Children, Philadelphia

Shriners Hospital for Children, Philadelphia presented the annual Howard H. Steel Pediatric Orthopedic Seminar and OITE Review on November 3, 2007. Renowned panelists included Dr. R. Jay Cummings, Associate Professor of Orthopedics at the Mayo Graduate School of Medicine in Jacksonville, Florida; Dr. Randall T. Loder, Professor of Orthopedic Surgery at the Indiana University School of Medicine; and Dr. Scott J. Mubarak, Clinical Professor of Orthopedics at the University of California Medical Center. The event was moderated by Dr. Peter D. Pizzutillo, Professor of Orthopedic Surgery and Pediatrics at Drexel University College of Medicine.

This seminar provided an update on the latest techniques in diagnosis and management of a number of controversial aspects of pediatric orthopaedics including pediatric spine, hip, and congenital problems, as well as challenges of the lower extremity and fractures. The expert panel reviewed case studies which highlighted these topics and participation from the audience provided an open forum for discussing different strategies and approaches to a variety of pediatric cases. The panel discussions were greatly enhanced by the experiences and opinions from some of the distinguished audience members including Dr. Joseph Thoder, the Chairman of Orthopaedic Surgery at Temple University School of Medicine; Dr. Michael Clancy, Professor and former Chairman of Orthopaedics at Temple University School of Medicine; Dr. Randal Betz, Chief of Staff and Director of Shriners' Spinal Cord Injury Unit, and Professor of Orthopaedics at Temple University School of Medicine; and Dr. G. Dean MacEwan, Director of the Alfred I. DuPont Institute and Professor of Orthopaedics at Shriners Hospital for Children. The event was also marked by the attendance and participation of its namesake, Dr. Howard H. Steel, Emeritus Chief of Staff of Shriners Hospital for Children and Professor of Orthopaedics at Temple University School of Medicine.

The afternoon session included a comprehensive review of pediatric orthopaedic issues for residents preparing to take the Orthopaedic In-Training Exam. A number of high-yield topics were discussed which included Hand and Upper Extremity, reviewed by Dr. Joshua Ratner, Hand Surgeon at Shriners Hospital for Children; Spine, reviewed by Dr. James Guille, Pediatric Spinal Deformity Surgeon at Shriners Hospital for Children; Trauma, reviewed by Dr. Martin Herman, Staff Pediatric Orthopaedic Surgeon at St. Christopher's Hospital for Children and Professor of Orthopedics at Drexel University College of Medicine; and Lower Extremity, reviewed by Dr. James McCarthy, Vice Chairman of Orthopaedics at Shriners Hospital for Children. The conference was well attended by residents and fellows as well as university faculty and community physicians from around the Philadelphia area.

Brian George, MD

Philadelphia Orthopaedic Society Resident Bowl

Resident Bowl

Residents and attendings who represented Philadelphia area orthopedic residency programs gathered for the 9th annual John R. Gregg Memorial Resident Bowl on May 14, 2007. As in years past, six residents representing each Philadelphia training program participated in this "Jeopardy!"-style contest hosted by Master of Ceremonies, Barry Snyder, MD. This annual event, sponsored by the Philadelphia Orthopaedic Society, provides a wonderful opportunity for residents to exhibit knowledge and flex their mental muscle.

Participating residents included: Richard Frisch, Albert Einstein Medical Center; Jay Zampini, Drexel Hospital; Gregory Carolan, Hospital of the University of Pennsylvania; Gregg Martyak, Thomas Jefferson Hospital; Steven Shamash, Philadelphia College of Osteopathic Medicine; and Robert Purchase, Temple University Hospital. With various attendings as scorekeepers and John D. Kelly, IV, acting as Judge, question after question was presented in rapid succession, and answered as quickly as possible by the residents. Excitement heated up in the final moments, as this game was very close. We were very proud to congratulate Robert Purchase as the winner of last year's event, bringing home the trophy for Temple University Orthopaedics once again.

Temple has won five of the last nine competitions, in keeping with Temple's strong teaching tradition under the leadership of Joseph Thoder, MD. We continue to look forward to this fun, challenging academic competition next year, when Temple hopes to continue its winning streak.

Temple Orthopaedics residents have carried on their rich tradition of academic excellence by winning five of the previous nine Philadelphia Orthopedic Society Resident Bowl Championships. A closer inspection of the trophy itself will not only show Temple's impressive record, but also bears the names of five previous chief residents who we are all proud of.

A Review of Our Past Winners

CHRISTOPHER J. MANCUSO — 1999

Dr. Mancuso holds the honor of winning the inaugural Resident Bowl in 1999, starting a championship tradition for Temple Orthopedics. Dr. Mancuso received his AB in Biomedical Ethics from Brown University and his medical degree from Jefferson Medical College in Philadelphia. He completed his Orthopaedic Residency at Temple University Hospital. He went on to a fellowship in Sports Medicine at the Institute for Bone and Joint Disorders in Phoenix, Arizona. He is currently an attending physician in Reading, Pennsylvania, focusing on arthroscopy as well reconstruction of the knee, elbow and shoulder.

RICHARD SAVINO — 2000

Dr. Savino continued the winning tradition of Temple Orthopaedics as the 2000 Resident Bowl champion. Dr. Savino graduated from Boston College, majoring in Biology and Theology while earning a student athletic trainer scholarship. He received his medical degree from The State University of New York Health Science Center at Syracuse and residency at Temple University Hospital. He completed a Fellowship in Sports Medicine and Shoulder Surgery at Johns Hopkins University Hospital. As a Hopkins faculty member, he was a team physician for the Baltimore Orioles and the Johns Hopkins University athletic department. He currently practices in his hometown of Long Island as a member of Long Island Bone and Joint.

SUE Y. LEE — 2004

Sue Y. Lee received her medical degree from Temple University School of Medicine and completed her residency training in Orthopaedic Surgery at Temple University Hospital in 2004. She completed her residency career by winning the 2004 Resident Bowl. She went on to fellowship at the Philadelphia Hand Center at Thomas Jefferson University Hospital. Dr. Lee has presented on a variety of topics including foot and ankle problems, carpel tunnel syndrome, scoliosis and arthritis. She is currently an attending physician at Albert Einstein Medical Center in Philadelphia.

MATTHEW REISH — 2006

Dr. Reish, a Pennsylvania native, obtained a Bachelor of Arts from Dickinson University. Dr. Reish completed his residency training in Orthopaedic Surgery at Temple University Hospital. As chief resident, he won the 2006 Resident Bowl and has left a strong academic and clinical legacy for his junior residents to follow. Dr. Reish completed a fellowship at the Southern California Center for Sports Medicine. He is currently practicing in Lewisburg, PA, in the SUN Orthopaedics group.

ROBERT PURCHASE — 2007

Dr. Purchase, also a Pennsylvania native, attended Washington and Jefferson University for his undergraduate studies and went on to Temple University School of Medicine for his medical degree in 2002. He completed residency training in Orthopaedic Surgery at Temple University Hospital, winning the 2007 Resident Bowl Championship. Dr. Purchase is remembered by his juniors as a great teacher, surgeon and resident advocate. He is currently completing a fellowship at the Orthopaedic Sports Medicine Group in San Francisco.

Abtin Foroohar, MD

Drs. Purchase and Thoder, May 2007.

Departmental News

Faculty

Temple University Department of Orthopaedic Surgery and Sports Medicine

Chairman

Joseph Thoder, MD, *The John W. Lachman Professor*

Professors

William DeLong, MD
Ray Moyer, MD, *The Howard H. Steel Professor*
Joseph Torg, MD
F. Todd Wetzel, MD

Associate Professors

John Kelly, IV, MD, *Vice-Chairman*
Pekka Mooar, MD
Albert Weiss, MD

Assistant Professors

Easwaran Balasubramanian, MD
Asif Ilyas, MD
Stanley Michael, MD
Saqib Rehman, MD
Bruce Vanett, MD

Emeritus Professor

Edward Resnick, MD

Adjunct Faculty — Philadelphia Shriners Hospital

Randal Betz, MD, *Chief of Staff*
Philip Alburger, MD
JahanGir Asghar, MD
Patrick Cahill, MD
Scott Kozin, MD
G. Dean MacEwen, MD
Joshua Ratner, MD
Amer Samdani, MD
William Schrantz, MD
Howard Steel, MD, *Emeritus Chief of Staff*

Adjunct Faculty — Abington Memorial Hospital

Andrew Star, MD, *Chief of Orthopaedics*
Shyam Brahmabhatt, MD
David Craft, MD
Greg Galant, MD
Michael Gratch, MD
Victor Hsu, MD
David Junkin, MD
Moody Kwok, MD
Guy Lee, MD
Thomas Peff, MD
Jeffrey Rubin, MD
T. Robert Takei, MD
John Wolf, MD

Adjuct Faculty — St. Christopher's Hospital for Children

Peter Pizzutillo, MD, *Chief of Orthopaedics*
Martin Herman, MD
Juan Realyvasquez, MD
Shannon Safier, MD

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
Faculty 2008

Joseph Thoder, MD
John W. Lachman Professor
Chairman
Hand & Upper Extremity
General Orthopaedics

Eswarian Balasubramanian, MD
Joint Reconstruction
General Orthopaedics

William DeLong, MD
Orthopaedic Trauma
Sports Medicine
General Orthopaedics

Asif Ilyas, MD
Hand & Upper Extremity
Orthopaedic Trauma

John Kelly, IV, MD
Vice Chairman
Sports Medicine
General Orthopaedics

Stanley Michael, MD
Sports Medicine
Joint Reconstruction
General Orthopaedics

Pekka Mooar, MD
Sports Medicine
Joint Reconstruction
General Orthopaedics

Ray Moyer, MD
Sports Medicine

Saqib Rehman, MD
Orthopaedic Trauma
General Orthopaedics

Edward Resnick, MD
General Orthopaedics
Pain Management

Joseph Torg, MD
Sports Medicine

Bruce Vanett, MD
Joint Reconstruction
General Orthopaedics

F. Todd Wetzel, MD
Spine Surgery

Albert Weiss, MD
Hand & Upper Extremity
General Orthopaedics

News from the Office of Clinical Trials and Research Support

The Office of Clinical Trials and Research Support was founded in 2004 under the direction of Pekka A. Mooar, MD. Supported by the School of Medicine's Office of Clinical Trials, Joanne Donnelly is the full time research coordinator.

The program continues to represent a commitment to enhance resident and faculty research by providing logistical support for all research endeavors by members of the department. These can be pharmaceutical, device clinical trials, or investigator-initiated research projects. We now have an office to turn to for document processing to the Temple Institutional Review Board, budget development, legal agreements, manuscript and exhibit preparation assistance.

Our program continues to work with Arleen Wallen (Office of Clinical Trials), to process all budgets and legal contracts, and Craig Pfister who acts as the industry liaison to bring any clinical and or device trials to the attention of faculty members.

Members of the department continue the tradition of meeting with the members of the Temple Medical Student Orthopaedic Interest Group. Dr. Thoder spoke to the students this past year about a career in orthopaedics and the many sub-subspecialties within the practice. The meeting was well attended and there continues to be much interest from the Temple medical students regarding the field of orthopaedic surgery.

Dr. Mooar and Ms. Donnelly direct the Summer Medical Student Research Program. Students between their first and second years are certified in human subjects ethics and research design. Students have a comprehensive one day in-service with Barbara Kuchan, Associate Director for Information Services and Education Programs and with John Gaughan, PhD, who directs the statistical education portion. The summer program is eight weeks long, and in 2007, the department hosted twelve students. Six papers have been published in the *Temple University Journal of Orthopaedic Surgery & Sports Medicine* as a result of this initiative. In 2008, we will have the pleasure of mentoring fourteen Temple Medical Students who have expressed an interest in orthopaedic surgery.

2007 Summer Medical Student Research Projects:

Dr. Mooar
The Dynamic Hip Screw and Four-Hole Fixation Plate: Still the Gold Standard for Hip Fracture Stabilization?
Nathan Tiedeken, MSII, John Gaughan, PhD

Dr. Mooar
The Incidence and Contributing Factors of Partial Cartilage Delamination Injuries in the Knee
Thomas Riley, MSII, John Gaughan, PhD

Dr. Kelly
Arthroscopic Repair of Subscapularis Tendon: Clinical Results
Pradeep Setty, MSII, John Gaughan, PhD

Dr. Balasubramanian
Use of a Single Dose of Intraoperative Heparin in Both Total Hip and Total Knee Arthroplasties in Reducing the Incidence of Deep Venous Thrombosis (DVT) as Evaluated by Doppler Ultrasound
Rupam Das, MSII, John Gaughan, PhD

Dr. Torg
Meta-Analysis of Tarsal Navicular Stress Fractures
James Moyer, MSII, John Gaughan, PhD

Dr. Thoder
Outcomes of Surgical Decision Making for Unstable Fractures of the Distal Radius: The Temple University Algorithm
Daniel Upton, MSII, John Gaughan, PhD

2008 Summer Medical Student Research Projects:

Dr. Kelly	Completion of an ongoing project studying rotator cuff subscapularis tears
Dr. Mooar	Proximal humerus fractures
Dr. Ilyas	Management of gunshot wound injuries of the hand and wrist
Dr. Kelly	Review of opening wedge high tibial osteotomy results
Dr. Rehman/Dr. Ilyas	Risk factors for compartment syndrome in gunshot fractures of the lower extremities
Dr. Kelly	Review of surgeries for throwing injuries
Dr. Torg	Why do football players break their necks?
Dr. Moyer	Meniscal repairs: outcomes of mini open and inside out repairs
Dr. Torg	Brachial plexus and spinal cord injuries resulting from athletic injury
Dr. Mooar	Evaluation of the quality of digitized films acquired on film first
Dr. Torg	Preventable beach and swimming injuries
Dr. Ilyas	The incidence of radiocarpal fracture dislocations
Dr. Mooar	Open MRI evaluation of patella femoral tracking under load
Dr. Thoder	To be announced . . .

Current Industry-Sponsored Clinical Trials:

"A phase II randomized study investigating the safety, efficacy and pharmacokinetics of Daptomycin versus comparator (Vancomycin or Teicoplanin) in the treatment of subjects undergoing surgical standard of care for osteomyelitis associated with an infected prosthetic hip or knee joint caused by methicillin-resistant staphylococcus aureus or coagulase-negative staphylococci." *(Cubist Pharmaceuticals) Byungse Suh, MD, Principal Investigator Infectious Diseases, Pekka A. Mooar, Sub-Investigator*

"A randomized, double-blind phase 3 study of the efficacy and safety of HZT-510 in subjects requiring NSAID treatment." *(Horizon Therapeutics) Pekka A. Mooar, Principal Investigator*

"Double-blind, multi-center study evaluating the safety of OMS103HP and vehicle in patients undergoing anterior cruciate ligament reconstruction." *(Omeros Corporation) Pekka A. Mooar, MD, Principal Investigator, Ray Moyer, MD, Sub-Investigator, John D. Kelly, IV, MD, Sub-Investigator, Bruce Vanett, MD, Sub-Investigator*

Current Investigator-Initiated Prospective Studies Coordinated by the Office:

"Analysis of osteoactivin in human fracture hematoma." PI: Saqib Rehman, MD, in collaboration with Drs. Steven Popoff and Fayez Safadi, Department of Anatomy and Cell Biology. Temple IRB#10757 (Renewed)

"A comparison of achilles graft placement locations on ACL reconstruction surgery." PI: John D. Kelly, IV, MD, Jonathan Piposar, MSII. Temple IRB#11139

"Osteochondral allograft transplantation for treatment of glenohumeral instability in twenty-five patients." PI: Simon Chao, MD, John Fowler, MD. Temple IRB#11215

Current Faculty and Resident Research Projects Coordinated by the Office:

"Clinical follow-up of gunshot femoral fractures with vascular injury." PI: Saqib Rehman, MD, Omar Bedias, MSII. Temple IRB#11214.

"Micronail use in treatment of distal radius fractures." PI: Asif Ilyas, MD. Temple IRB#11536

"Management of hand infections: A review of infections presenting to the emergency department of a major community medical center." PI: Asif Ilyas, MD, Michael O'Malley, MSIII. Temple IRB#11424

"Management of humerus fractures from gunshot injury." PI: Asif Ilyas, MD, Joseph Dwyer, MSIII. Temple IRB#11422

"Long distal biceps tendon repair: outcomes and complications of a two-incision technique." PI. Alyssa Schaffer, MD, Joseph J. Thoder, MD. Temple IRB#11066

Temple University Hospital
Department of Orthopaedic Surgery and Sports Medicine
House Staff 2007–2008

Wade Andrews, MD
PGY-5

Kristofer Matullo, MD
PGY-5

Joseph Morreale, MD
PGY-5

William Pfaff, MD
PGY-5

Simon Chao, MD
PGY-4

Neil MacIntyre, MD
PGY-4

Carlos Morerya, MD
PGY-4

Alyssa Schaffer, MD
PGY-4

Abtin Foroohar, MD
PGY-3

John Parron, MD
PGY-3

Allen Tham, MD
PGY-3

Irfan Ahmed, MD
PGY-3

Ian Duncan, MD
PGY-2

Brian George, MD
PGY-2

Christopher Kestner, MD
PGY-2

Gbolabo Sokunbi, MD
PGY-2

Nate Bodin, MD
PGY-1

John Fowler, MD
PGY-1

Jung Park, MD
PGY-1

John Richmond, MD
PGY-1

Department of Orthopaedic Surgery and Sports Medicine
Graduating Residents 2008

Wade Andrews, MD

Wade grew up in Greensburg, PA. He graduated from Pennsylvania State University with a Bachelor's in Premedicine. He then completed his medical school at Temple. He and his wife, Genevieve, have one son, Ethan. Wade is pursuing a fellowship in Sports Medicine at Baylor College of Medicine in Houston, Texas.

Kristofer Matullo, MD

Kristofer grew up in southern New Jersey. He attended LaSalle University where he earned a Bachelor's Degree in Biology with a minor in Eastern Religions. Kris completed his medical school training at Temple University. He is married with one child. Kris is completing a fellowship in Hand and Upper Extremity Surgery at the Mayo Clinic in Rochester, Minnesota.

Joseph Morreale, MD

Joe is from the Philadelphia suburbs. He graduated from Penn State with a Bachelor's in Public Relations and Advertising with a post-baccalaureate in premed. He completed his medical training from Jefferson Medical College. He is married with one child. Joe is pursuing a fellowship in Spine Surgery at Yale University, New Haven, Connecticut.

William Pfaff, MD

Bill is a graduate of the University of Delaware where he graduated summa cum laude and earned a Bachelor's Degree in Biochemistry. He is married with four kids. He earned his medical degree at Jefferson Medical College. Bill is pursuing a fellowship in Spine Surgery at Pennsylvania Hospital, University of Pennsylvania Health System.

Temple AO Trauma Fellow 2007–2008

Michael J. Serra, MD

Michael, originally from Ponce, Puerto Rico, is a graduate of Ponce Medical School. His interest in orthopaedic trauma developed as a resident at the State University of New York Downstate Medical Center in Brooklyn, NY. He completed his residency in 2007 and came to Temple as the AO Orthopaedic Trauma Fellow for 2007–2008. Michael's operative and teaching skills in the OR were well appreciated. An avid fan of reggaeton and the iPhone, his humor and good nature will be truly missed. He is a proud new father and will be moving back to Puerto Rico with his family to start private practice. We wish him the best of luck.

Update on the Residency Program

Upon taking over the reigns, the residency program had been without a director for almost a year. I was pleased to find that the program was continuing to function quite effectively due to the diligence of the residents and the commitment of the attending faculty. Also, upon my arrival, I was the recipient of some great news regarding last year's graduating class: Lenny D'Adessi, David Junkin, Robert Purchase, and David Yucha. Every member of the class did exceptionally well on Part 1 of their ABOS Board Exam, with each scoring within the top one-third percentile nationally.

With the closure of Temple Children's Medical Center, our pediatric experience has transferred to a new but familiar site, St. Christopher's Hospital for Children. In many ways, this is a homecoming for us, although St. Christopher's is currently owned by the Tenet Health System and is a primary teaching site of the Drexel University College of Medicine. It is one of only two Level 1 pediatric tertiary care trauma centers in Philadelphia and is staffed by four pediatric fellowship trained orthopaedic surgeons: Dr. Peter Pizzutillo, Dr. Martin Herman, Dr. Juan Realyvazquez, and Dr. Shannon Safier. Despite the disappointment of our Temple Children's Medical Center closing, we are confident that the transfer of our pediatrics rotation to St. Christopher's will actually improve the breadth of our residents' pediatric experience.

To further augment the clinical experience offered to our residents, we are working to add an oncology experience with the addition of a rotation at our clinical partner, the Fox Chase Cancer Center. Fox Chase is a vibrant cancer center with an excellent orthopaedic oncology volume and is staffed by oncology fellowship trained orthopaedic surgeons. On this rotation, the residents will spend time in the operating room as well as in the weekly Sarcoma clinic.

Similarly, several initiatives have been set in motion to enhance the educational experience on our current rotations. Daily morning conference, monthly grand rounds, and indication conferences remain the cornerstone of the educational experience. In addition, rotation specific syllabi are being compiled to provide further subspecialty insight in the form of textbook readings, classic articles, and test-prep questions.

Research efforts continue to be strong amongst the residents. Much of their success is categorized for you in this journal. Beginning next year, on the annual Research Day, a new tradition will be initiated with the presentation of a "Senior Thesis" by each of the graduating chief residents. They will present a research project they initiated and completed during their residency tenure.

Lastly, I'd like to share a few parting words about our graduating residents. Dr. Wade Andrews is moving to Houston for at least the next three years as he and his wife pursue further subspecialty training. Wade has lined up for a Sports Medicine fellowship at Baylor, but also continues to hear the calling towards Hand Surgery. Dr. Kristofer Matullo has answered the call and will be pursuing a Hand Surgery fellowship at the Mayo Clinic in balmy Rochester, Minnesota. Drs. Joseph Morreale and Bill Pfaff, both Jefferson alumni, are following in the tradition of their alma mater and pursuing Spine Surgery fellowships. Joe is headed up to Yale, and Bill is going to Pennsylvania Hospital. I commend them each for their diligence as residents in our program and look forward to having them carry the title of Temple Orthopaedics alumni as they move forward in their professional careers.

Asif M. Ilyas, MD

Snapshots from 2007–2008

Pumping up for a case: (left to right) Gbolabo, Mike, and Kris.

Spine surgeon alert! (left to right) Victor Hsu ’06, F. Todd Wetzel, and Amer Samdani.

A job well done: Brian “Ilizarov” George.

Dr. Peter Pizzutillo and the PGY-3 class: (left to right) Parron, Ahmed, Pizzutillo, Foroohar, and Tham.

Instructions to Authors

Editorial Philosophy

The purpose of the *Temple University Journal of Orthopaedic Surgery and Sports Medicine (TUJOSM)* is to publish clinical and basic science research performed by all departments of Temple University that relate to orthopaedic surgery and sports medicine. As such, TUJOSM will consider for publication any original clinical or basic science research, review article, case report, and technical or clinical tips. All clinical studies, including retrospective reviews, require IRB approval.

Editorial Review Process

All submissions will be sent to select members of our peer review board for formal review.

Manuscript Requirements

Manuscripts are not to exceed 15 double spaced type-written pages and/or 5000 words (minus figures/tables/pictures). The Manuscript should contain the following elements: Title page, Abstract, Body, References, and Tables/Legends. Pages should be numbered consecutively starting from the title page.

(1) Title Page — The first page should contain the article's title, authors & degrees, institutional affiliations, conflict of interest statement, and contact information of the corresponding author (name, address, fax, email address).

(2) Abstract — The second page should be a one-paragraph abstract less than 200 words concisely stating the objective, methods, results, and conclusion of the article.

(3) Body — Should be divided into, if applicable, Introduction, Materials & Methods, Results, Discussion, and Acknowledgements. Tables and figures (in JPEG format) with their headings/captions should be listed consecutively on separate pages at the end of the body, not continuous within the text.

(4) References — Should be listed following the format utilized by JBJS. For example: Smith, JH, Doe, JD. Fixation of unstable intertrochanteric femur fractures. *J Bone Joint Surg Am.* 2002;84:3553–58.

(5) Each page should have continuous line numbers placed, as well as the first author's name, date submitted and page number in the footer.

Submit

- Three hard copies
- Two CDs labeled with the author's last name and manuscript title

Disclaimer: **This journal contains manuscripts that are considered interpersonal communications and extended abstracts and not formalized papers unless otherwise noted.**

We are smith&nephew

Repair, rebuild....restore

We give you advanced products for a continuum of patient care

As a worldwide authority in fracture healing with implants and ultrasound stimulation, arthroscopic joint repair, joint resurfacing and replacement, joint fluid therapy and advanced wound care, we lead the way with innovations and solutions that help you put your patients on the path to lifestyle restoration.

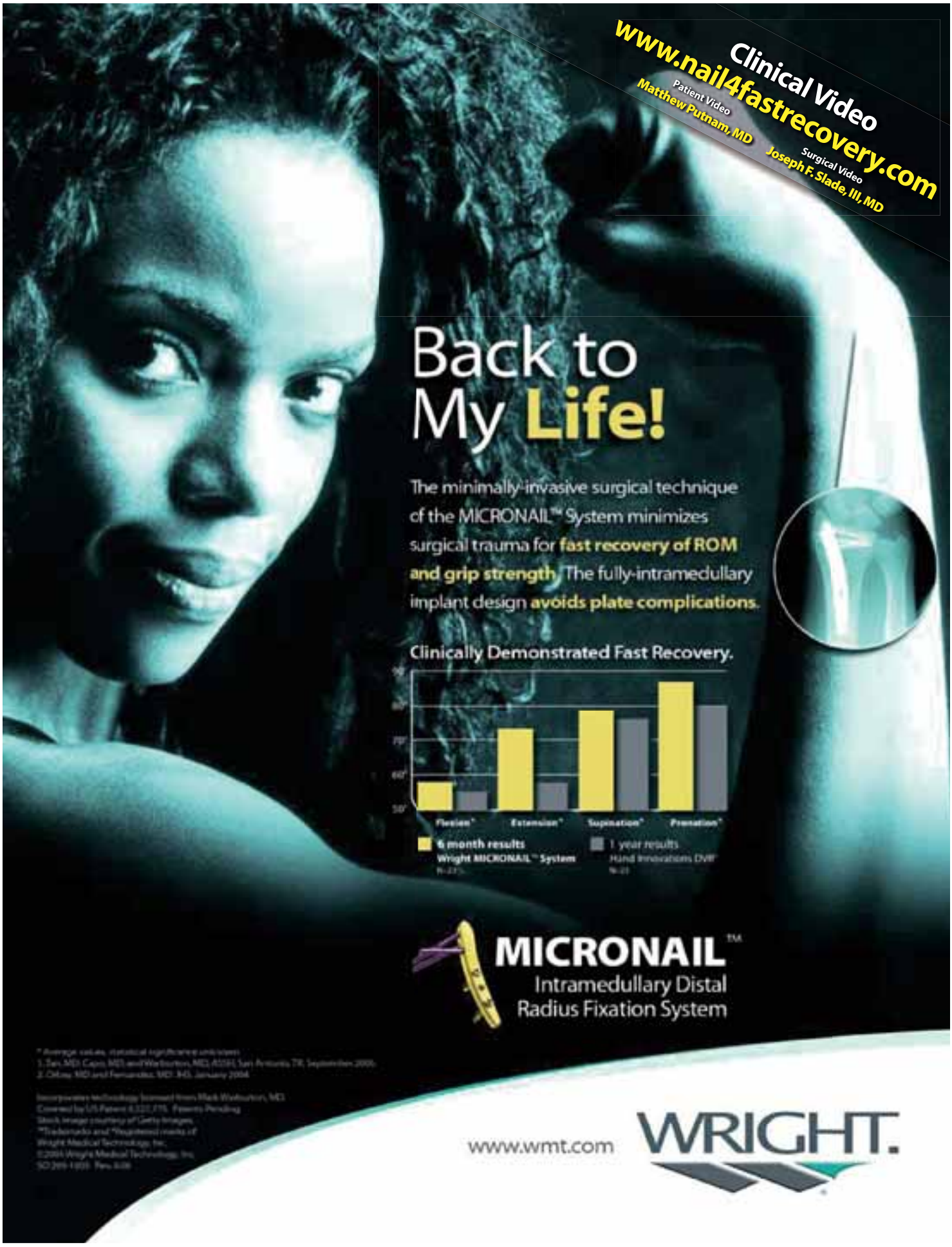
Orthopaedic Reconstruction
Smith & Nephew, Inc., 1450 Brooks Road, Memphis, TN 38116 USA
Telephone: 1-901-396-2121, Information: 1-800-821-5700, Orders/inquires: 1-800-238-7538

Orthopaedic Trauma & Clinical Therapies
Smith & Nephew, Inc., 1450 Brooks Road, Memphis, TN 38116 USA
Telephone: 1-901-396-2121, Information: 1-800-821-5700, Orders/inquires: 1-800-238-7538
Clinical Therapies Service Center: 1-800-836-4080

www.smith-nephew.com

Endoscopy
Smith & Nephew, Inc., 150 Minuteman Road, Andover, MA 01810 USA
Telephone: 1-978-749-1000, Orders/inquires: 1-800-343-5717

Wound Management
Smith & Nephew, Inc., 970 Carillion Parkway, Suite 110, St. Petersburg, FL 33716 USA
Telephone: 1-727-392-1261, Information: 1-800-876-1261, Orders/inquires: 1-800-238-7538


Clinical Video
www.nail4fastrecovery.com
Patient Video
Matthew Putnam, MD
Surgical Video
Joseph F. Slade, III, MD
Back to My Life!
The minimally-invasive surgical technique of the MICRONAIL™ System minimizes surgical trauma for fast recovery of ROM and grip strength. The fully-intramedullary implant design avoids plate complications.
Clinically Demonstrated Fast Recovery.
Flexion*
Extension*
Supination*
Pronation*
6 month results
Wright MICRONAIL™ System
1 year results
MICRONAIL™
Intramedullary Distal Radius Fixation System
www.wmt.com
WRIGHT.

SYNERGY ORTHOPEDICS

866-48-ORTHO (67846)

www.synergyortho.com

SYNERGY ORTHOPEDICS . . .

PROVIDING A PERFECT SYNERGY FOR ALL OF YOUR PATIENT'S POST-OP, RECOVERY AND RETURN TO ACTIVITY NEEDS!

REPRESENTING:

KINEX
Evidence-Based Soft Tissue CPM

DONJOY

AIRCAST®

DONJOY
BONE GROWTH STIMULATION

A family of companies for over 100 years
Greiner & Saur Frank Malone & Son
The leader in Prosthetics & Orthotics
7 Convenient Locations to serve you

605 Spring Garden St
Phila PA 19123
215.627.3400
fax 215.922.6801

108 S. 40th Street
Phila PA 19104
215.222.2309
fax 215.662.0643

8104 Roosevelt Blvd
Phila PA 19152
215.543.1125
fax 215.543.1130

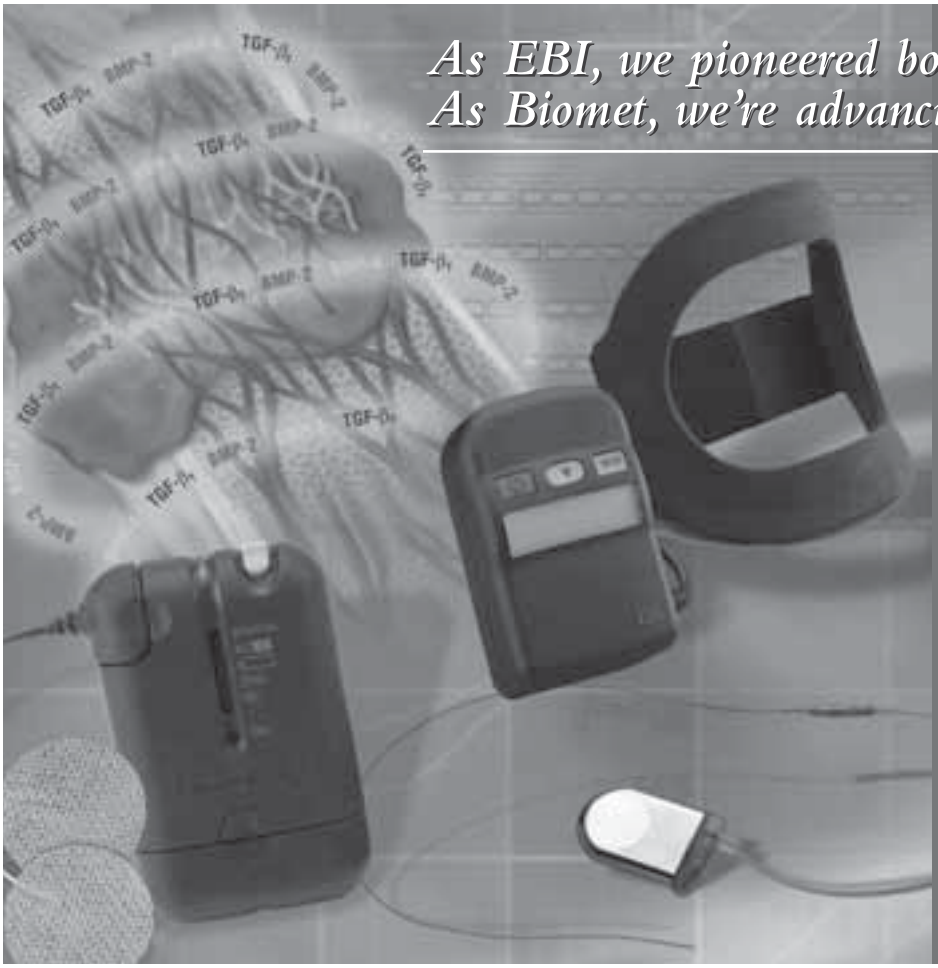
1503 W.Chester Pike
Havertown PA 19083
610.924.0300
fax 610.924.9771

3015 Island Ave
Phila PA 19153
215.365.1532
fax 215.492.9894

Foot & Ankle Inst.
8th & Race St
Phila PA 19107
215.238.6600

230 W. Washington Sq
Phila PA 19106
215.829.6955
fax 215.829.6899

Board Certified Practitioners
State of the Art Prosthetic & Orthotics
Specializing in Myo electric Upper Extremity & C-Leg
lower extremity prosthetics, Sport Knee & Ankle braces,
Lightweight Titanium & Carbon Fiber Artificial Limbs
Energy Storing Feet, Cosmetic Restorations
Diabetic Footwear & Orthopedic Shoes
Visit our website @ www.hanger.com



As EBI, we pioneered bone growth technology.
As Biomet, we're advancing the state of the art.

EBI has changed its name to Biomet …
but not its focus. We are still the leader in bone growth technologies, with a full complement of implantable and non-invasive bone healing devices using direct current, PEMF and capacitive coupling technologies. Our expertise provides the level of excellence every surgeon wants …
and every patient deserves … to help ensure successful outcomes.

Innovation Meets Evolution…EBI is now:

BIOMET®

SPINE
TRAUMA
BRACING
OSTEOBIOLOGICS

1-800-526-2579

www.biometspine.com
www.biomettrauma.com
www.biometbracing.com
www.biometosteobiologics.com

We go beyond

Just Products

Stryker, the Surgeon's Choice for Trauma Education.

We at Stryker know training is a crucial element for delivering long-term outcomes for patients. That is why we have teamed up with leading trauma surgeons from around the world to bring you hands-on training for the latest techniques and newest products.

For more information on a course listed below, ask your sales representative about the Stryker Trauma Surgeon Education Program.

May 2-3, 2008

Stryker Upper Extremity Dissection Course for Residents
Homer Stryker Learning Center
Mahwah, NJ

Course Director
Joseph Slade, MD
Yale-New Haven Medical Center
New Haven, CT

Course Highlights
Didactic and hands-on OR simulation to educate on the latest surgical techniques for the treatment of upper extremity fractures.

May 30-31, 2008

Stryker Trauma Dissection Course for Residents
South Florida Learning Center
Fort Lauderdale, FL

Course Director
Gregory Zych, DO
University of Miami School of Medicine
Miami, FL

Course Highlights
Didactic and hands-on OR simulation to educate on the latest surgical techniques for the treatment of lower extremity fractures.

stryker®

Stryker Orthopaedics 325 Corporate Drive, Mahwah, NJ 07430 **www.stryker.com**

National Medical Imaging

20 FACILITIES IN THE GREATER PHILADELPHIA AREA
AND MARYLAND

FEATURING: High Field MRI, Open MRI, CAT Scan, X-Ray and PET Scan

- *Board certified radiogists specializing in musculoskeletal and neuroradiology*
- *Same day appointments available and 24 hour report turnaround*
- *Online physician access to images and reports*
- *Patients leave with films in hand*
- *American College of Radiology accredited*

AMERICA'S PREMIER MEDICAL IMAGING COMPANY
Preferred By The Region's Top Orthopaedic Surgeons

1.877.SCAN-OPEN

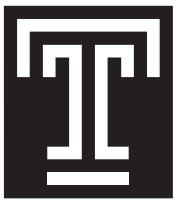
WE APPLAUD

Joseph J. Thoder, MD

AND THE

John Lachman Society

for upholding the
"Tradition of Excellence"



Temple Orthopaedics
& Sports Medicine
Temple University Hospital

Department of Orthopaedic Surgery
Temple University School of Medicine
3401 N. Broad Street
Philadelphia, PA 19140

PRESORTED
BOUND PRINTED MATTER
U.S. POSTAGE PAID
PHILADELPHIA, PA
PERMIT NO. 1044