

Temple University Journal of Orthopaedic Surgery & Sports Medicine



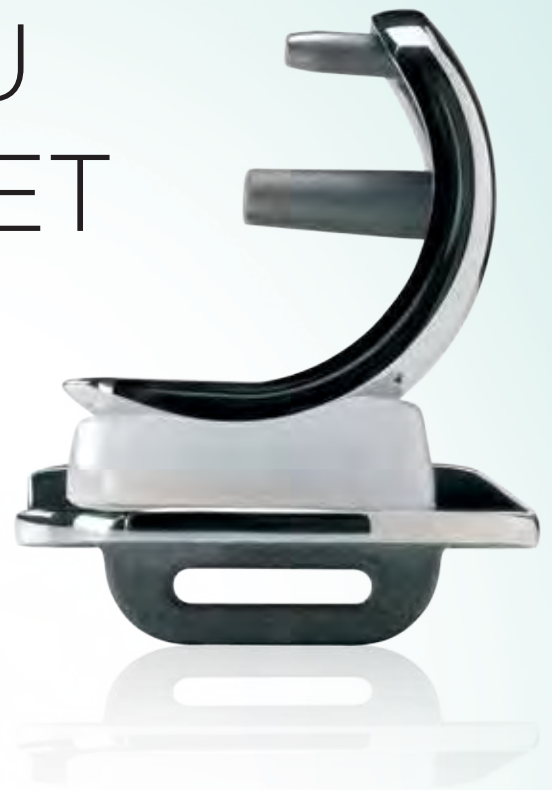
John Michael Daly, MD

Volume 8 Spring 2013

A John Lachman Society Publication



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**Got Concussion?
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The Temple University Concussion and Athletic Neurotrauma Program

Cerebral concussion, traumatic brain injury, transient spinal cord paralysis and brachial plexus injuries are potentially serious insults to the nervous system that are associated with contact athletic injuries. In accord with the principle that the management and return-to-play decisions should only be made by a qualified professional, Temple University has established its **Concussion and Athletic Neurotrauma Program**.

Temple's experienced, multidisciplinary faculty is well-suited to evaluate and manage athletic-induced neurotrauma, utilizing the latest imaging capabilities, neurocognitive **ImPACT™** testing and clinically established **return-to-play** protocols.

Utilizing the facilities of Temple University Hospital, Temple Orthopaedics & Sports Medicine satellite offices, Temple Medical School faculty and in concert with the Shriners Hospitals for Children in Philadelphia, this program is designed to provide the necessary experience to meet the needs of team and family physicians, athletic trainers, athletic administrators, coaches, parents and, most importantly — the athletes.

Research Goals

Current understanding of cerebral concussion and athletic-induced traumatic brain injury is limited to a variety of descriptive classifications and epidemiologic patterns. Lacking is an application of the known underlying pathophysiology to clinical management practice with particular regard to injury prevention. Clearly, much is not known and there are many questions to be answered regarding athletically-induced neurotrauma. The goal of this program is to bring this issue to the same meaningful conclusion that Temple physicians achieved with paralytic spinal cord injuries 35 years ago.



Proper tackling technique protects both head and cervical spine.

Clinical Program

Athletes sustaining impact injuries and experiencing any of the following signs or symptoms should be evaluated and, if indicated, managed by a physician experienced with athletic injuries to the head, spine and brachial plexus:

Central Nervous System

- Loss of consciousness
- Confusion
- Dazed appearance
- Forgetfulness
- Unsteady movements
- Slow cognition
- Personality changes
- Retrograde/antegrade amnesia
- Headache
- Dizziness
- Nausea or vomiting
- Altered sense of well-being

Spinal Cord

- Four extremity paresthesias (numbness)
- Four extremity weakness
- Four extremity transient paralysis

Brachial Plexus

- “Stinger” lasting more than 20 minutes
- “Stinger” with persistent weakness
- Recurrent “stingers”

The neurotrauma team consists of orthopaedic sports medicine specialists, neurologists, neurosurgeons, neurophysiologists, physiatrists and biostatisticians.

ATHLETES REQUIRING EVALUATION AND/OR MANAGEMENT CAN BE SEEN AT TWO OF TEMPLE’S CLINICAL SITES:

Temple University Hospital

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5th Floor Boyer Pavilion
Philadelphia, PA 19140
215-707-2111

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414 Commerce Drive
Fort Washington, PA 19034
215-641-0700

E-mail us at: concussion@tuhs.temple.edu

Website: www.templeconcussion.com



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All articles published in this journal are communications of current research taking place at Temple University and are therefore considered extended abstracts. As abstracts, they are not the property of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine*.

Letter from the Chairman

It is my pleasure to present this year's edition of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine*. Over the years, the *Journal* has evolved to represent the collaborative efforts of the Department's basic science and clinical research activity, contributions from the summer medical student research program, editorials and updates on the Department's extracurricular events.

The Temple University Health System continues to enhance its reputation of scholarly and clinical excellence at both Temple University Hospital and the Temple University School of Medicine. The concept of "Broad Street and Beyond" is coming to fruition, and the Department of Orthopaedic Surgery and Sports Medicine continues to play a prominent role in that vision. In the past year, we have partnered with other departments and TUHS to expand and improve our satellite presence: in Northeast Philadelphia in conjunction with Temple ReadyCare, in Oaks, PA along with Pulmonary Medicine, and in the coming year, a multispecialty facility in Fort Washington, PA.

That being said, the main campus on North Broad Street is a hub of academic, research and clinical excellence. The cornerstone of that campus is the Medical Education and Research Building, otherwise known as the newest medical school. It is that edifice that personifies the man to whom this edition of the *Journal* is dedicated, John Daly, MD, FACS. His tireless energy and dedication to the project have left him with a well deserved tangible representation of his term as Dean and leader of the Medical School.

As always, I wish to thank those organizations and people who make this all possible. The Temple/Shriners Alumni Association and the John Lachman Society members for their continued support of resident education, faculty members Saqib Rehman, MD and Eric Kropf, MD for the resident contributions and Joseph Torg, MD and Pekka Mooar, MD for the medical student research contribution; and Joanne Donnelly for keeping order and direction among those diverse entities. Congratulations to co-editors Matt Kleiner (PGY5) and Rick Tosti (PGY3) as well as Scott Barbash (PGY4) and Colin Mansfield (PGY2) for a job well done. With that said, we proudly present to you Volume 8 of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine*.



Joseph J. Thoder, MD
Professor and Chairman
Department of Orthopaedics and Sports Medicine
Temple University School of Medicine

Letter from the Editor-in-Chief

It has been quite a year for Temple Orthopaedics! Thanks to the hard work of several of our residents and attendings, we have continued to produce high-quality research that has garnered a great deal of national attention. At the 2012 American Academy of Orthopaedic Surgeons in San Francisco, our department had a total of three poster presentations, a scientific exhibit and two podium presentations, including “Best Presentation” awarded to Rick Tosti by the Hand and Wrist Committee for his presentation on “Is Antibiotic Prophylaxis Necessary in Elective Soft Tissue Hand Surgery?”. In addition, faculty member Saqib Rehman, in collaboration with former Program Director Asif Ilyas, published a textbook, *Contemporary Surgical Management of Fractures and Complications*. Furthermore, Temple had several national publications in peer-reviewed journals over the past year — some of which will be featured in this year’s *Temple Journal*.

Volume 8 of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine* is dedicated to John Daly, MD. Dr. Daly is a graduate of Temple University School of Medicine in 1973 and an accomplished surgical oncologist. He served as the Dean of Temple’s medical school for eight and a half years before retiring from the position in 2011.

I have a lot of people to thank. First, I have to thank John Fowler for paving the way as the ultimate editor-in-chief and proponent of the *Temple Journal*. I would like to thank my co-editor-in-chief, Rick Tosti, as well as my fellow editors, Scott Barbash and Colin Mansfield, for their hard work and commitment to making Volume 8 come to fruition. I would also like thank faculty advisors Joseph Torg and Saqib Rehman for their tireless dedication and availability in making the *Journal* a rousing success. Finally, I would like to recognize Joanne Donnelly from the Office of Clinical Trials as well as Program Director Milo Sowards and Chairman Joseph Thoder for their continuous and unconditional support of all of our research efforts.

As an outgoing fifth year resident, I am overcome with a sense of pride in Temple Orthopaedics. In addition to the clinical prowess for which Temple has always been known, we have continued to grow as a leader in academics. I have no doubt that my fellow residents and attendings, with whom I have had the privilege to train, have repeatedly put me in positions where I can not only succeed, but thrive as a clinician and surgeon. Most importantly, over the past five years, I have forged friendships and relationships that will undoubtedly last a lifetime. The people at Temple have and always will be its greatest strength and I am extremely proud to have been a part of it. I believe the best way to reach your destination is to remember all the help you got along the way. For me, Temple will always be home and the foundation of my career success.

Thank you.

Matthew T. Kleiner, MD
Co-Editor-in-Chief
Class of 2013

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 also provides 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 is 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.

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

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*Deceased

(Continued on next page)

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At the annual meeting of the board of directors of the John Lachman Orthopedic Research Fund, the following officers were re-elected for a one-year term:

President: J. Milo Swards, MD
First Vice President: Phil Alburger, MD
Second Vice President: Eric Leby, MD
Treasurer: Albie Weiss, MD
Secretary: Joe Torg, MD

The summer medical school intern program continues to be a most successful program. This past summer, 15 sophomore medical students participated in the program. In addition to a number of the students producing manuscripts suitable for publication in the *Journal*, it became evident that the major value of this program is that in view of the curriculum changes no longer requiring students to rotate through orthopedics, those students interested have an opportunity to interface with our department. Clearly, this has become a major avenue of acquainting students to the residency program.

Once again, the John Lachman Society published and distributed the *Temple University Journal of Orthopaedic Surgery & Sports Medicine*, Volume 7. Eighteen hundred copies of the *Journal* have been distributed as follows: a) active faculty of the Temple University School of Medicine, b) orthopedic surgeons who are alumni of Temple University School of Medicine, c) members of the John Lachman Society, d) department chairman and residency directors of all orthopedic programs throughout the United States, and e) fellowship directors to all orthopedic programs throughout the United States.

Academic support for resident travel to meetings by the John Lachman Orthopedic Research Fund during the period January 1, 2012 through December 31, 2012, involved 15 residents who have attended either formal courses or national meetings.

The Eighth Annual John Lachman Lecture was presented by J. Milo Swards, MD at the annual meeting of the Pennsylvania Orthopaedic Society this past fall which was held in Pittsburgh. A decorated combat surgeon, Dr. Swards presented his experience with advance management techniques of orthopedic injuries resulting from blast trauma. His talk was excellent and well received except for the few non-medical personnel in attendance who experienced syncope episodes at the sight of gross war trauma.

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

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.

The John Lachman Society, through the John Lachman Orthopedic Research Fund and working in close cooperation with the Temple-Shriners' Alumni group, continues its mission to support and enhance both the academic program of the department and the orthopedic residency program.

Joe Torg, MD
Secretary

Report from the Residency Director

It is an honor for me to write the residency program director's introduction to the current edition of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine*. The *Journal* has been a tremendous source of pride for the department and residency, and it continues to bolster the program's reputation for clinical excellence. I would like to thank this year's editors, Matt Kleiner and Rick Tosti, as well as our faculty editors, Joe Torg and Saqib Rehman. I cannot sufficiently describe the amount of work that they all put into ensuring the successful publication of the *Journal* each year. Joe Torg, Pekka Mooar and Joanne Donnelly also deserve recognition for their stewardship of the summer research program, which is the source of an increasing number of manuscripts published in the *Journal*.

Interest in the Residency Program continues to grow. This past year, we received over 600 applications for our four PGY-1 positions. Also, changes are on the horizon again with respect to the guidelines by which we train the residents. Beginning with the next academic year, interns will become fully integrated into the Orthopaedic program instead of being General Surgery interns. While they will still get experience in various General Surgery rotations, they will each spend six months in Orthopaedics. During that time, they will complete a curriculum in surgical skills, using simulation ranging from the familiar suture boards to the use of our space in the anatomy lab in the medical school. All of your contributions to the Lachman Society are very much appreciated as we expect to be requesting grants from the society to support these teaching efforts.

Thanks to all of my colleagues on the faculty at Temple as well as our affiliate institutions, and the supporting members of the John Lachman Society, I continue to have the privilege of directing a strong residency program that improves each year.

J. Milo Sowards, MD

Update from the Department of Orthopaedic Surgery and Sports Medicine Office of Clinical Trials and Research Support

The Office of Clinical Trials and Research Support was established in 2004, under the direction of Pekka A. Mooar, MD and supported by the School of Medicine's Office of Clinical Research Administration, with Ms. Joanne Donnelly as the full-time research and program coordinator.

We have been on this exciting journey for the past nine years, and achieved the goals originally set forth: establishing a stream of clinical trials for all interested attending surgeons creating direction support and encouragement to the residents in their pursuit of investigator initiated research, fostering collaborative projects with Pathology, Microbiology, Radiology, Anesthesia and continuing our work in the Basic Science departments of Anatomy and Cell Biology.

We have also established and maintained the popular Temple Medical Student Summer Orthopaedic Research Program (TSSORP) under the leadership of Dr. Torg and supported by Dr. Mooar and myself. This program provides any Temple medical student interested in Orthopaedics with an eight-week summer program on how to implement a research study with a hands-on approach. Students have an orientation which includes our research librarian and statistician. Students come away knowing how to think of a research topic, perform the literature search, submit the necessary documents to the Temple IRB for approval, data mine from our new electronic medical record system and, most of all, begin the writing process. We meet with the students on Tuesday and Wednesday mornings to go over their projects and offer guidance and assistance. Students are also encouraged to go to the OR and see as many cases as they wish during this time, as well as attend office hours. After this program, students have a keen insight into Orthopaedics from a truly unique prospective. Students also get to be first author on their research projects published in the TUJOSSM journal.

I am happy to report that this summer we will host 12 Temple Medical Students into the program. Below is a list of projects that we will undertake:

2012 Summer Medical Student Research Projects:

See Journal under "Medical Student Research Projects"

2013 Summer Medical Student Research Projects:

Dr. Torg (*4 projects*)

- Reliability of Neurocognitive Testing: A Pilot Study (*continued from last year*)
- Performance Enhancing Drugs and Morality: A Commentary
- Conflict of Interest: A Real or Imagined Problem in the Practice of Orthopaedics
- Pre-Disposing Factors Responsible for Post-Concussion Sequelae

Dr. Mooar (*1 project*)

- Is TNT (Toradol, Neurontin, Tylenol) an Effective Post-Op TKA, THA Pain Management Program?

Dr. Weiss (*1 project*)

- Financing of Orthopaedic Graduate Medical Education: The Role of Non-Profits in the Development of Extramural Funding (*continued from last year*)

Dr. Rehman (*3 projects*)

- Development of a Clinical Treatment Guideline for the Orthopaedic Management of Open Long Bone Fractures at TUH
- Development of a Clinical Treatment Guideline for the Orthopaedic Management of Femoral Shaft Fractures at TUH
- Development of a Clinical Treatment Guideline for the Orthopaedic Management of Proximal Tibial and Tibial Shaft Fractures at TUH

Dr. Kropf (*1 project*)

- Tunnel Enlargement Socket: Aperture Fixation vs Tight Rope Fixation in ACL Reconstruction

Current Industry-Sponsored Clinical Trials Drug or Device:

Smith and Nephew

(TRUST) Trial to Evaluate Ultrasound in the Treatment of Tibia Fractures

Saqib Rehman, MD, Principal Investigator; Alyssa Schaffer, MD, Sub-Investigator; J. Milo Sowards, MD, Sub-Investigator; Phase IV Device. Enrollment completed, 21 subjects. Study closed to enrollment.

Baxter Healthcare

A Prospective Randomized Controlled Single-blinded Multicenter Study to Evaluate the Efficacy and Safety of Floseal® for Hemostasis in Primary Unilateral Total Knee Arthroplasty (TKA)

Pekka Moorar, MD, Principal Investigator, Phase IV Device. Enrollment completed, 3 subjects.

Stryker

(INSITE) Intramedullary Nail Versus Sliding Hip Screw Intertrochanteric Evaluation: A Multi-Center Randomized Controlled Trial of Intramedullary Nail Versus Sliding Hip Screw in the Management of Intertrochanteric Fractures of the Hip

Saqib Rehman, MD, Principal Investigator; Bruce Vanett, MD, Sub-Investigator; Christopher Haydel, MD, Sub-Investigator; Phase IV Device. Enrolling 7 subjects to date.

EMSI

The Electrostim Medical Services, Inc. (EMSI) Bone Growth Stimulator (BGS) Clinical Study for the Treatment of Long Bone Fractures Acquired Secondary to Trauma Where Serial Radiographs Taken at Least 90 Days Apart Have Shown No Visible Progressive Signs of Healing

Pekka Moorar, MD, Principal Investigator, Phase IV Device (starting March 2013).

Department of Defense

Assessment of Severe Extremity Wound Bioburden at the Time of Definitive Wound Closure or Coverage: Correlation with Subsequent Post-Closure Deep Wound Infection (Bioburden Study)

Saqib Rehman, MD, Principal Investigator. Prospective cohort observational study (March 2013).

Current Investigator and Resident Initiated Studies Coordinated by the Office:

The Prevalence of Methicillin Resistant Staph Auresus (MRSA) Colonization Among Resident Physicians at an Urban Teaching Hospital. *Renewed until 13-Jan-2014.*

Alyssa Schaffer, MD, Principal Investigator (*IRB Approval #13721*)

Comparison of Autograft and Allograft ACL Reconstruction: Long Term Histologic Analysis. *Renewed until 13-Jan-2014.*

Eric J. Kropf, MD, Principal Investigator (*IRB Approval #13719*)

S. Ali, S. Huebner, F. Groshek, A. Schaffer. The Floating Fat Sign of Trauma. *Canadian Association of Radiologists Journal*. Accepted for publication.

S. Popinchalk, A. Schaffer. Physical Examination of Upper Extremity Compressive Neuropathies. *Orthopedic Clinics of North America* 2012;43(4):417–430.

Joanne Donnelly



John M. Daly, MD
Dean of Temple University School of Medicine 2002–2011

Dedication

John Michael Daly, MD

JOSEPH TORG, MD

As suggested by Joe Thoder, Department Chair, and unanimously and enthusiastically agreed upon by the editorial board, this volume of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine* is dedicated to John M. Daly, Dean of the Medical School from 2002 to 2011. And what a dean he was: surgeon extraordinaire, internationally renowned academic animal, leader of men, visionary and role model for the ages. Such platitudes clearly describe the man but first let us examine his short comings.

I have known John Daly for the past 38 years. Our first encounter occurred when he was a medical student at Temple on an orthopedic rotation and I was a young faculty member. As a student, he appeared capable, enthusiastic, and destined for a career as an orthopedic surgeon. But as we all know, he rejected or was rejected by orthopedics and pursued a general surgery residency. What happened? Was he not physically capable of managing large bone and joint problems? Was he too intellectually challenged to handle the concepts of orthopedic principles and practice? Did he lack the eye-hand coordination and cognitive skills to deal with the arthroscope and other advanced orthopedic devices?

John Daly, a general surgeon! Such a disappointment! But he did recover as an itinerant surgeon at the University of Texas School of Medicine, Cornell University Medical College, the Weill Medical College of Cornell University, and the University of Pennsylvania, where our paths crossed once again.

And let me share another Daly vignette that occurred when we were both on the staff at Penn back in the 80s. While vacationing at the Jersey shore, I was asked by a friend to see a patient who had been admitted to a local hospital and was scheduled for a “diagnostic laparotomy” because of what was undiagnosed abdominal pain. Having spent the first year of my orthopedic residency at Temple on general surgery and being somewhat vaguely familiar with

inter-abdominal problems, opening the belly without a diagnosis just didn’t seem cool. So I called my good friend John Daly, explained my concern and arrangements were made to transfer the patient to Penn. And my good friend John Daly then, on the basis of his extraordinary clinical acumen and experience, diagnosed acute mumps pancreatitis, initiated appropriate conservative, non-surgical management that resulted in a complete recovery without sequela. What made the experience more meaningful was that surgical interven-

tion would have most certainly resulted in disaster. And my good friend John Daly — what a guy — clinician, diagnostician, academic — the whole enchilada.

But let us examine John Daly in a more serious vein. I can attest to the fact that he is a man of faith, has been a committed husband and father, a most supportive friend of Temple Orthopaedics and the School of Medicine and a great humanitarian. With an unassuming demeanor, he maintains a low profile, avoids rhetorical bombast and self promotion, and is modest almost to a fault.

And did he recover as a general surgeon! During his travels, he produced 250 pub-

lications in peer review journals, amassed a total of \$2,831,000 as principal investigator in 20 research grants, and was awarded honorary doctorate degrees from both the University of Glasgow and the University of Dublin — a classic example of Irish cohesiveness.

But let’s talk about his really important contributions. John Daly’s tenure as Dean of the Medical School was initiated by the threat of the loss of the academic accreditation of the medical school. And with diligence and foresight, he initiated a transformital program that involved the academic curriculum, faculty acquisition and, of course, the design and construction of the new Medical Education and Research Building, the signature accomplishment of a magnificent career. And today, the MERB is euphemistically referred to as “Daly’s finest erection.”



The house that Daly built

Electronic Medical Records: An Epic Disaster?

JOSEPH TORG, MD

What can we say about electronic medical records? First is to recognize that they are potentially preferable to the traditional medical records which are non-potable, segmented, often incomplete and subject to the varies of unintelligible physician handwriting.

So now we have electronic medical records which we have been told will vastly improve patient care, implement cost-effective measures that will dramatically reduce costs, and facilitate practice models so as to maximize physician efficiency and effectiveness. Available evidence clearly indicates that just the opposite is occurring. Let me explain.

According to a recent report by the Rand Corporation published in the January 2013 edition of *Health Affairs*, electronic health records have not produced a decrease in health care costs but have rather seen an increase of \$800,000,000,000 (that's \$800 billion!) since their first report in 2005. This is in contradistinction to their initial prediction that the widespread use of EMRs could save the health care system \$81 billion annually. So what happened? First, Rand admits that their earlier estimate was "overly optimistic" as was the Congressional Budget Office overstatement of project savings. Second, Congress and the Obama administration spent billions of dollars in federal stimulus money to encourage doctors and hospitals to pay for the installation of electronic record systems. And lastly, critical analyses of current systems clearly indicate that they are much more oriented to increasing provider billings than in improving medical care or cost effectiveness. As reported by Reed Abelson and Julie Creswell recently in the *New York Times*, "there is increasing concern that electronic records have actually added to costs by making it easier to charge more for some services." They also point out that RAND's 2005 report was paid for by a group of companies "that have profited by developing and selling electronic records systems to physician practices and hospitals. To be noted, one of these companies, Cerner Corporation, revenues has nearly tripled from \$1 billion in 2005 when his report was released to a projected \$3 billion in 2013.

In a report on how the growth of electronic medical records eases the path to inflated medical billing, Fred Schulte points out that in the rush to get the program off the ground, federal officials failed to impose adequate controls over billing software despite warnings from "several prominent medical fraud authorities." As a result Medicare, regulators now acknowledge they are struggling with a surge of

aggressive and expensive billings by doctors and hospitals linked to the rapid proliferation of billing software and electronic medical records. And it has been acknowledged that billing abuse (fraud) has taken a back seat to steps to entice the medical community to embrace the new technology. This, of course, is in keeping with the thinking that two wrongs make a right.

The recent report of Daniel R. Levinson, Inspector General of the Department of Health and Human Services entitled "Early Assessment Finds that CMS Faces Obstacles in Overseeing the Medicare EMR Incentive Program" is clearly indicative of the conundrum that the rush to implement EMR has resulted. Predicated on the "new talk" concept of "meaningful use" in a 150-page manual on electronic medical records, "meaningful use" remains an enigma. However, it presumably has not been determined "whether professionals' and hospitals' self-reported meaningful use information met meaningful use measure criteria." But CMS does not verify the accuracy of professionals' or hospitals' self-reported meaningful use information prior to payment or as well as post-payment audits. As well, the report concludes that electronic health record technology is not sufficient to verify self-reported information and may not always be accurate.

Dr. Anne Marie Valinoti has clearly expressed my views in her recent article published in the *Wall Street Journal* where she point out that "it seems that this is all about taking care of the chart as opposed to taking care of the patient . . . in that demonstrating meaningful use of EMR may be getting in the way of meaningful encounters with our patients." "It's hard to be both stenographer and empathetic listener at the same time."

It is my view that electronic medical record systems have been introduced without adequate "clinical trials" by a governmental bureaucracy intent on controlling a large segment of the economy with a "damn the torpedoes — full speed ahead" mentality. I would further suggest that the major burden of implementation has been thrust upon the physician now saddled with the collection of worthless data by an inordinately complicated and time-consuming medical records system. It is generally agreed by users of the system that EMR decreases physician efficiency by 25% and this impression has been substantiated by system implementation of decreasing patient scheduling loads by 25%. Of course, the ready explanation of system implementers is that this is a function of the learning curve and familiarity with

the system will resolve the increased time expenditure phenomenon. I submit that the inordinate time-consuming factors are systematic and unrelated to user familiarity.

User familiarity will not obviate the labyrinth of diagnostic “bullets” and billing-orientated quires to justify level of service.

User familiarity will not obviate the multiple log-in/password issues compounded by the absurd, short automatic bureaucratic log out times presumably imposed to protect patient confidentiality. What happened to the user ID card swipe system available for other systems including later Epic editions?

User familiarity will not obviate the time necessary for physicians to perform the functions of a transcriptionist and edit their dictations or typewritten documentation.

User familiarity will not obviate the delay in the incorporation of radiology images within the electronic medical record.

User familiarity will not obviate screens that require repetitive selection of facility, location, or service.

User familiarity will not obviate network and printer server failures that limit access and functionality to the electronic medical record system.

So there you have it — a politically motivated, inordinately expensive, user unfriendly system that has yet to demonstrate an ability to improve the quality of patient care.

EMR Is the Way to Go

SAQIB REHMAN, MD

EMR is the way to go. Rather than fight it, we should work to optimize it.

Imagine that you go to your bank to make a withdrawal, they pull out your paper record file, realize something is missing, then make their best estimate at what your balance is. Or you make an airline reservation with a travel agent who doesn't use computers and has to put everything in a paper file and issue a paper ticket. Or you take your car to the dealer to be serviced, but they can't find that paper file on your car to know when your last oil change and tire servicing was. Of course, these situations would be considered unacceptable to most Americans in 2013. So how can it possibly be acceptable to keep medical records in paper charts, especially knowing what we know as physicians? When just about everything in our world is being computerized for obvious reasons of efficiency, space-saving, accuracy, and accessibility, how can we possibly cling to paper medical records?

As a practicing physician, I will readily admit that some aspects of seeing patients in the office is better without EMR. Dictating into a Dictaphone on the fly as I go from patient to patient is certainly faster than having to type or use Dragon software. But that's about where the advantages end.

How does a health system-wide EMR help me? Let me count just some of the ways:

1. Progress notes: If I need to look up my old notes in a paper chart, I'm at the mercy of whoever has arranged the papers in the chart (and God forbid it had to be recently pulled out and photocopied for legal or other purposes). Obviously not an issue in EMR.

2. Lab results and imaging reports might be in there if I look, but if it's not there, that could just mean that it fell out of the chart.

3. Prescriptions: When did I last prescribe moxib for this patient? Who knows? I would have to go through all those carbon copy scripts that are in that little envelope in the chart, hoping that they are all there.

4. Stolen Rx pads? It's happened to me. Not a problem when you are eprescribing. I thought Dr. Torg wrote a paper on the benefits of eprescribing . . .

5. No more chart multiplicity: With paper charts, there would be multiple charts in different locations with different things in them. And I would not even consider trying to find notes on this patient from other physicians, which are also in their own paper charts sitting on a shelf in yet another office.

6. Drug checker: My EMR can tell me if there are unsafe drug-drug interactions. (Previously, I had to pull out my smartphone, open Epocrates, and run a check myself.)

7. Reports easy to find: Need that EMG report or other report that other departments in your hospital do a crappy job in providing to you? Your staff looks bad, and you look bad as your patient sits waiting inexplicably as you try to get the report. With EMR, it's now right there — no waiting around.

8. More thorough documentation for billing purposes. With macros and shortcuts, I can make sure that those compliance people are not on my case about underdocumentation of history that was collected and examination that was done.

9. Better documentation of patient phone calls/requests. With paper charts, every method that we tried didn't seem to work. With EMR, there is a clear, consistent, and accurate method that is properly documented.

10. It's a better research tool. Our particular EMR is not quite there yet, but the accuracy, consistency, and accessibility of electronic data far surpasses having to sift through boxes of charts with no way to scan through data other than to leaf over every page. We have been literally unable to do certain research projects because of the resources needed to do massive chart reviews on crappy paper charts with useless (often illegible) information in them. That being said, our particular EMR, and most EMRs, are not optimized for research purposes. This has been somewhat of a disappointment, but we are working to improve this by integrating our EMR data with third party solutions for research data registries and searchable data warehousing.

11. Accessibility: For the obsessive doctor, EMR allows them to check records on patients from multiple offices, from their home, and even from their smartphone. For the doctor who is not quite obsessive, but simply wants the information there when they ask for it, how can you go back to "waiting for the paper chart" or going by memory about a patient's condition. Taking this a step further, the increased accessibility appeases to the obsessive patients, who want to have access to at least a part of their medical record. Many EMRs (including ours) allow patients to do this. This, in turn, also helps researchers reach out to patients to conduct questionnaire surveys.

Good medicine and careful documentation go hand in hand. Our profession would not have made significant

advances in patient care without attention to accurate medical documentation. If you are a doctor who doesn't ever look in the chart, then EMR is clearly an obstacle to efficient clinic hours. But I would argue that that is just not good medicine. Just as the American public, on the whole, will be demanding that their physicians have accurate documentation of their medical history, we as physicians should recog-

nize that EMR, for many of the reasons I have outlined above, is simply better medicine. Clearly, EMR is in its infancy compared with electronic data management in many industries. But it is the future, and is not going away. Rather than oppose it, we should be looking for ways to improve it, particularly with regards to research optimization.

Distinguished Alumnus

John A. Bergfeld, MD

This issue of the *Temple University Journal of Orthopaedic Surgery & Sports Medicine* marks the third Editorial Board's selection of a Distinguished Alumnus who has graduated from the Temple University School of Medicine and/or completed his or her Orthopedic residency at the Temple University Hospital. The purpose of this selection is to acknowledge the accomplishments of individuals who have excelled in their academic, scientific, and/or humanitarian endeavors. The acknowledgement will be made when appropriate and not necessarily on an annual basis.

It is a distinct pleasure for the editorial board to recognize John Bergfeld, a graduate of the Temple University School of Medicine, for numerous service and academic accomplishments over his 40-year career. He is a graduate of Bucknell University where he excelled as a hard-hitting fullback on the football team. He then entered Temple and achieved two major accomplishments: met his wife Wilma and received a Doctor of Medicine degree.

After completing his residency, he served in the Navy as Chief of Orthopaedics of the United States Naval Academy, and Naval Hospital, Annapolis, MD and aboard the USS Dubuque (1970–1973) with rank of Commander MC USNR.

John has served as a Board member of the American Academy of Orthopaedic Surgeons, 1997–2003; President of the American College of Sports Medicine, 1984–1985; President of the American Orthopaedic Society for Sports Medicine, 1992–1993, President of the International Society of Arthroscopy, Knee Surgery and Orthopaedic Sports Medicine, 2005–2007; and Chairman, International Anterior Cruciate Ligament Study Group.

He has served for 26 years as Team Physician for the Cleveland Browns of the NFL as well as for the Cleveland Cavaliers of the NBA from 1986–2001. He also has been physician to the Cleveland Ballet, 1976–1990; Baldwin Wallace College, 1996–present; and the Cleveland Metropolitan Schools, 1976–present. He presently serves as consultant to the Cleveland Browns and Cavaliers and has presented multiple endowed lectureships, both in the USA and internationally.

As the Head of the Section of Sports Medicine at the Cleveland Clinic from 1976 to 2002, he has trained over 50 post graduate fellows (known as the Warthog Society), several of which are physicians for professional teams, Division I colleges and chairmen of their Departments of Orthopaedics. He has published over 90 articles for international/national publications, books and chapters.

John's academic, research, and teaching endeavors have covered the spectrum of orthopedic sports medicine. However, he is somewhat of an exception in his appreciation of the fact that the anterior cruciate ligament is not the only structure in the knee. Clearly, his interest and work dealing with both the function and problems of the posterior cruciate ligament have been exceptional. We, therefore, find it appropriate to republish his paper "A Biomechanical Comparison of Posterior Cruciate Ligament Reconstruction Techniques," previously published in the *American Journal of Sports Medicine*.

Clearly, John Bergfeld's many contributions to orthopedic surgery and orthopedic sports medicine have reflected extremely well on himself, his associated institutions, and the Temple University School of Medicine. The editorial board is delighted and honored to recognize John as a Distinguished Alumnus.



Joe Torg, MD

A Biomechanical Comparison of Posterior Cruciate Ligament Reconstruction Techniques

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Abstract

Most posterior cruciate ligament reconstruction techniques use both tibial and femoral bone tunnels for graft placement. Because of the acute angle the graft must make to gain entrance into the tibial tunnel, abnormal stresses are placed on the graft that could lead to graft failure. An alternative technique for posterior cruciate ligament reconstruction involves placement of the bone plug from the graft anatomically on the back of the tibia (inlay), preventing formation of an acute angle at the tibial attachment site. We used six pairs of human cadaver knees to compare the biomechanical properties of these two techniques. One knee from each pair underwent tunnel reconstruction while the other knee underwent inlay reconstruction. There was significantly less anterior-posterior laxity in the inlay group when compared with the tunnel group from 30° to 90° of knee flexion and after repetitive loading at 90° of knee flexion. Evaluation of the grafts revealed evidence of mechanical degradation in the tunnel group but not in the inlay group. The inlay technique resulted in less posterior translation with less graft degradation than did the tunnel technique for posterior cruciate ligament reconstruction.

The PCL is the primary restraint to posterior tibial translation in the intact knee. It has been reported that 5% to 20% of all ligament injuries to the knee involve the PCL.^{4, 9, 13, 14, 23, 29} Posterior cruciate ligament injuries have been divided into those that are isolated and those that are combined with other injuries. Posterior cruciate ligament injuries that occur with other major knee ligament injuries appear to fare better with surgical reconstruction rather than nonoperative management for symptoms of instability. The appropriate treatment for isolated PCL injuries is less obvious because instability is often asymptomatic. Although the natural history of these injuries is unclear, there is evidence that certain PCL injuries will lead to instability, pain, and osteoarthritis of the knee.⁶

Several studies have reported good results with nonoperative treatment for isolated PCL injuries,^{11, 12, 16, 26, 32} while other studies have shown poorer long-term results that deteriorate with time.^{8, 21} Increased articular contact pressures have been demonstrated in the medial and patellofemoral compartments after sectioning of the PCL in cadaver knees,³¹ which probably accounts for the increased incidence of degenerative changes observed in these compartments in patients with a PCL-deficient knee. Furthermore, damage to the articular cartilage of these compartments may be underestimated when viewed by conventional radiographs.⁸ Although several clinical studies have documented degenerative changes in the medial compartment and patellofemoral joint after isolated PCL injuries, the severity of these changes does not appear to be related to the amount of abnormal posterior laxity.⁶

Thus, the indications for PCL reconstruction are not clear-cut, and whether PCL reconstruction will alter the natural history of the PCL-deficient knee is currently unknown. Clinical results after PCL reconstruction have not been as predictable as those after ACL reconstruction.¹ Current techniques for PCL reconstruction in general have yielded inconsistent results and do not appear to eliminate abnormal posterior laxity in the knee.²² It is currently unclear whether PCL reconstruction techniques can restore normal knee laxity *in vivo* and thus alter the natural history of the PCL-deficient knee.

Most PCL reconstruction techniques use both tibial and femoral bone tunnels for graft placement (Fig. 1). Grafts placed through the tibial bone tunnel are required to make at least a 90° turn at the posterior aspect of the tibia. Placing this degree of bend in the tendon graft at the tibial tunnel creates increased internal tendon pressures.³⁰ In addition, the acute angle that the graft must make on the posterior tibia may predispose the graft to “saw” on the tibia and further degrade its mechanical integrity. Furthermore, the normal anatomy of the PCL is not reproduced by the tunnel technique in which the graft must enter the joint through a tibial drill hole. This drill hole entry site is difficult to locate properly, especially if the procedure is performed arthroscopically. These factors may contribute to the variable clinical results after PCL reconstruction.



Figure 1. Lateral (A) and AP (B) views of the tunnel technique of PCL reconstruction.

Most of these factors could be avoided if the orientation of the tibial attachment site of the graft could be altered. The anatomic tibial inlay technique of PCL reconstruction uses the same femoral bone tunnel but employs direct screw attachment of the bone plug from the graft to the proximal posterior tibia (Fig. 2). This technique more closely replicates the anatomic insertion site of the PCL on the proximal

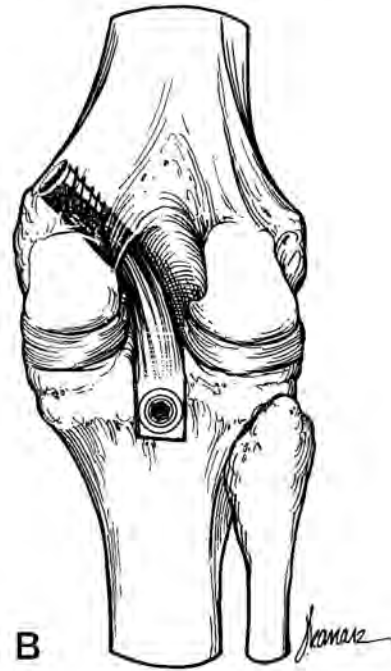
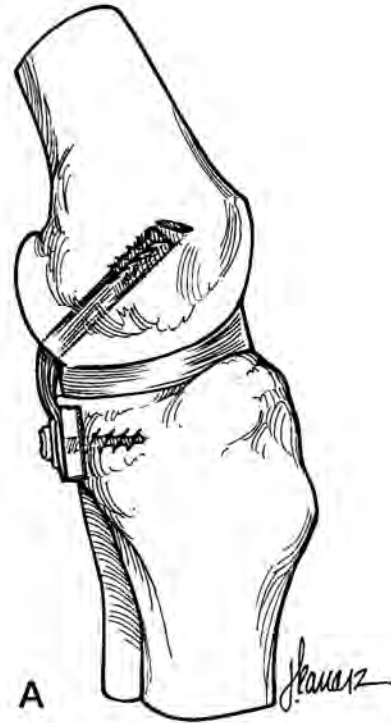


Figure 2. Lateral (A) and AP (B) views of the inlay technique of PCL reconstruction.

posterior tibia and avoids the excessive bending of the graft to gain entrance into the tibial bone tunnel that is necessary in the tunnel PCL reconstruction technique.

Jakob and Rügsegger²⁰ as well as Berg³ have previously described this technique of PCL reconstruction. Although they have advocated this technique for its theoretical advantages regarding graft fiber orientation, there have been no

substantial clinical or basic research studies to validate this concept. The purpose of this study was to compare the anterior-posterior (AP) stability provided by the inlay technique and the tunnel technique of PCL reconstruction. Specifically, we compared AP laxity at four positions of knee flexion and three positions of tibial rotation for the tunnel and inlay techniques of PCL reconstruction.

Materials and Methods

Six pairs of fresh-frozen cadaver knees were used in this study. Donors were all men with a mean age of 65 (± 9) years. Only knees without evidence of knee abnormalities, including prior knee surgery, abnormal knee ligament laxity, or significant degenerative joint disease, were included. Specimens were amputated transfemorally and transtibially.

Specimen Preparation and Instrumentation

The knees were thawed, and the tibia and femur were scraped clean of soft tissue to within 10 cm of the joint line. Skin, subcutaneous fat, and muscle around the knee joint were excised, leaving only the joint capsule, ligaments, popliteus muscle, and extensor mechanism. The portion of the fibula distal to the fibular neck was resected, and the proximal tibiofibular joint was stabilized with a 4.5-mm cortical screw. The proximal end of the femur and distal end of the tibia were potted in aluminum tubes with polymethyl methacrylate. Transfixion pins within the tubing were used to eliminate rotation at the polymethyl methacrylate-tube interface. A custom-made testing apparatus with six degrees of freedom was constructed, similar to that described by Fleming et al.¹⁵ A Bionix 858 MTS with Testar software (MTS Systems Corporation, Eden Prairie, Minnesota) was used to apply shear loads to the knee while displacement was measured. The potted femoral end of the specimen was clamped into a yoke attached to the load ram of the MTS, which applied an AP shear force to the knee. The epicondylar axis of the knee joint was placed at the pivot axis of the femoral yoke. The knee joint flexion angle was adjusted with the yoke and locked at the desired flexion angle before testing. A bearing system allowed free motion of varus-valgus angulation. The potted tibial end was mounted in a clamp housed within a bearing mechanism that allowed axial rotation and could be locked if desired. The tibial bearing mechanism was mounted on the plate of an X-Y table, allowing free translation of the tibia in the coronal plane (Fig. 3).

Anterior-posterior displacement was measured as the amount of translation of the tibia relative to the femur in the midsagittal plane. An AP ramp load of 150 N was applied to the femur and measured by the MTS load cell. The linear variable displacement transducer of the MTS measured the amount of displacement of the femur. Tibial rotation was locked during AP testing. Neutral rotation was defined as midway between tibial rotations produced by 5 N•m of internal and external tibial torque, as previously described by

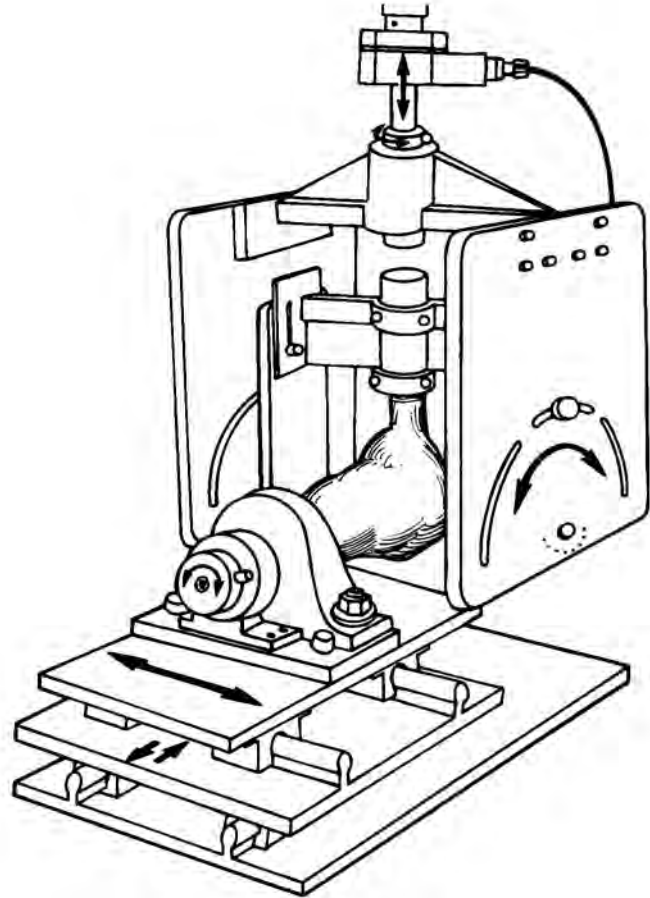


Figure 3. The custom-made testing apparatus allowing six degrees of freedom.

Markolf et al.²⁴ Torque was measured with a calibrated torque wrench that was applied to the tibial pot with the tibial clamp unlocked, allowing free rotation. Positions of internal and external rotation were defined as those resulting from application of 5 N•m of internal and external tibial torque. The yoke of the testing apparatus held the knee in various amounts of knee flexion while an AP force was applied with the MTS machine.

Testing Procedures

The intact knees were mounted on the custom-made apparatus and subjected to AP testing at 0°, 30°, 60°, and 90° of knee flexion with the tibia locked in neutral, internal, and external rotation. A 150-N AP force was applied at a rate of 0.2 Hz to the femoral yoke at the level of the joint line. Tibial rotation was allowed between tests when the knee flexion angle was being changed; neutral rotation was redefined at each new knee flexion angle. Tibial rotation was locked at various knee flexion angles while varus-valgus angulation was unconstrained and the tibia was allowed to translate in the coronal plane during AP loading. Under each testing condition, the knee was loaded six times. The first three loading cycles were used to precondition the knee, while the

latter three loading cycles were used for data collection. In all cases the load-deformation curve became reproducible after two loading cycles.

Anterior-posterior knee laxity was defined as the AP knee displacement of the tibia that occurred relative to the femur between the limits of 150-N anterior and 150-N posterior loads. This convention was chosen to load the ACL and used as a reference. Because the ACL was not transected, it is reasonable that the reference for displacement measurement was an anteriorly applied load to the tibia that engaged the ACL. These tests were performed using the load-defined feedback loop option on the MTS system. The neutral position for AP translation was defined as the inflection point identified during anterior loading, representing loading of the ACL. This zero-load position of the MTS was maintained while changing the knee flexion angle and tibial rotation between testing cycles.

PCL Sectioning

After laxity data had been obtained from the intact knees, a posterior arthrotomy was made, and the PCL and meniscofemoral ligaments were transected. The meniscofemoral ligaments were transected because they are closely associated with the PCL and have been shown to contribute to posterior knee stability.¹⁹ The arthrotomy was repaired, and AP loading was repeated under the previously listed testing conditions. Because the specimen was not removed from the testing jig between the loading conditions, the zero-load neutral position could be maintained throughout the testing sequence.

PCL Reconstruction

One of the knees from each pair was randomly assigned to the tunnel group and underwent a tibial tunnel PCL reconstruction technique. The contralateral knee was assigned to the inlay group, which had the PCL reconstructed using the anatomic tibial inlay technique, involving direct screw attachment of the graft bone plug to the proximal tibia. Autogenous central one-third bonepatellar tendon-bone grafts with 30-mm bone plugs were harvested and used as the graft material in both groups. In both groups, a 10-mm femoral tunnel was made that entered the knee in the distal anterior footprint of the native PCL in the region of the isometric point, as previously described.^{5, 7, 17} The bone tunnel was made using a drill and a PCL femoral drill guide (Acufex, Mansfield, Massachusetts). In both groups, the posterior capsule was opened to expose the proximal posterior tibia.

In the tunnel group, a drill and the PCL tibial drill guide were used to make a tibial tunnel that exited the proximal posterior tibia approximately 1 cm distal to the joint line, in the center of the tibial insertion of the PCL. The tibial side of the graft was secured with a 9 x 20 mm interference screw (Acufex). In all cases, the bone plug was placed with the patellar tendon fibers positioned anteriorly, while the screw was placed in the posterior aspect of the tunnel, between the

bone plug and the posterior tunnel wall. The bone plug was placed 5 mm inferior to the opening of the tibial tunnel in all cases.

In the knees in the inlay group, a bone trough was created with osteotomes at the insertion site of the PCL on the posterior proximal tibia. The tibial side of the graft was secured flush to the posterior surface of the proximal tibia with a 4.5-mm bicortical screw (Synthes, Paoli, Pennsylvania) and a washer and a nut. This method of fixation differs slightly from that used clinically in that a 6.5-mm cancellous screw and washer are used for patients. This slight modification was necessary to achieve stability in the older osteoporotic specimens used in this study.

The grafts were tensioned in a manner similar to that described by Pearsall et al.²⁷ In both groups, the tibial side of the graft was secured first, and the femoral side of the graft was tensioned to 89 N with the knee flexed 90°. An anterior force of 156 N was applied to the proximal tibia, simulating an anterior drawer maneuver, and a 9 x 20 mm femoral interference screw (Acufex) was placed to secure the femoral side of the graft. Because of the osteoporotic nature of the specimens, fixation of the grafts to the tibia and femur was augmented with polymethyl methacrylate at the bony interfaces between the graft bone plug and the bone tunnel or trough. Laxity testing was repeated under the same conditions as previously described.

Effect of Repetitive Loading

After completion of mechanical testing of the PCL-reconstructed knees (72 cycles), the knees from both groups were tested again with a 150-N AP force with the knee flexed at 90° and in neutral tibial rotation to determine the effects of repetitive loading.

Graft Evaluation

At the conclusion of mechanical testing, the grafts were removed from the knees of both groups and inspected for defects. The grafts were evaluated for thinning in the region of the proximal posterior tibia by gross inspection and quantified with relative optical density measurement using BioQuant software (R & M Biometrics, Nashville, Tennessee). Standard red-green-blue (RGB) measurements were made with the resultant density determined by the square root of $R^2 + G^2 + B^2$.

Statistical Analysis

The data consisted of translational measurements (in millimeters) from the same knee under three different loading conditions (intact, PCL cut, and PCL reconstruction) measured at several different angles. This introduced a correlation structure between the observations obtained from the same knee. Therefore, repeated-measures analysis of variance was used for statistical analysis. Pair-wise comparisons between different conditions were performed using the Bonferroni adjustment for multiple comparisons. All modeling

was performed using SAS software (SAS Institute Inc., Cary, North Carolina) running on a Sun Sparc workstation (Sun Microsystems, Inc., Palo Alto, California). A post hoc power analysis was performed on laxity measurements obtained at 90° of knee flexion. A Student's paired *t*-test was used to determine statistical significance in relative optical density measurements between the tunnel and the inlay grafts.

Results

Neutral Tibial Rotation

With the tibia in neutral rotation, the mean AP laxity in the inlay-reconstructed knees was significantly less than in the PCL-intact state at all knee flexion angles except 0° (Fig. 4A). In the tunnel group, the mean laxity after reconstruction was greater than in the intact knee at all flexion angles, but the differences were not significant (Fig. 4B). Mean laxity measurements after reconstruction in the inlay group were significantly less than those in the tunnel group at 30°, 60°, and 90° of knee flexion (Fig. 5).

Internal Tibial Rotation

With the tibia in internal rotation, AP laxity in the inlay-reconstructed knees was not significantly different from that in the intact state at any flexion angle tested (Fig. 6A). In the tunnel group, the mean laxity in the reconstructed state was greater than that in the intact state at all flexion angles, but this increase was significant only at 90° (Fig. 6B).

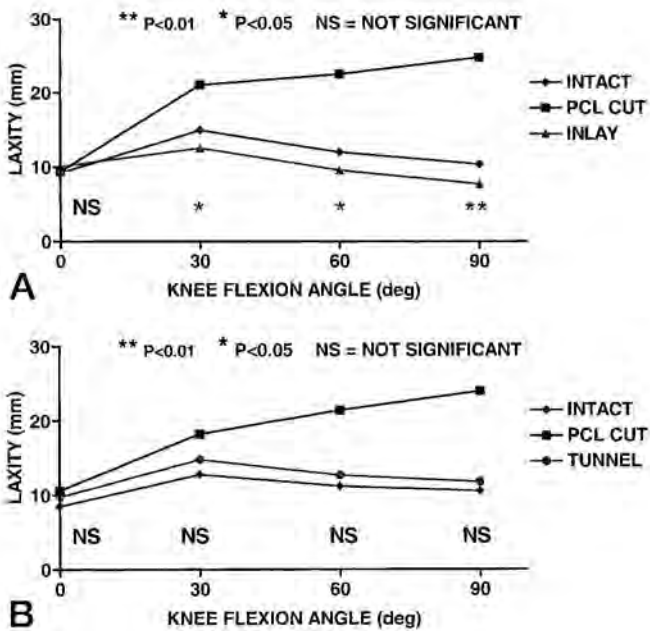


Figure 4. (A) Knee laxity measurements at four flexion angles with the tibia in neutral rotation in the group with the inlay PCL reconstruction. The reconstruction measurements were compared with those in the same knees with the PCL intact and cut. (B) Knee laxity measurements in the tunnel-reconstruction group compared with the PCL intact and cut states for the same knees.

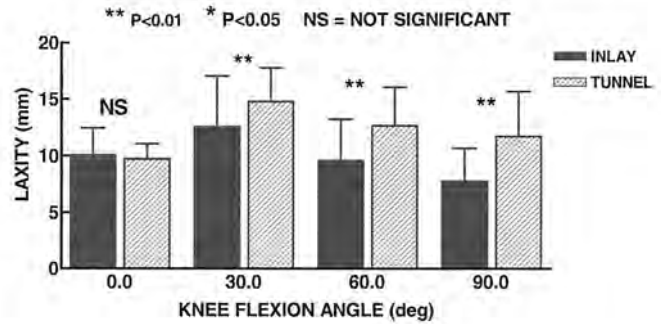


Figure 5. Knee laxity at 90° of knee flexion with neutral tibial rotation: a comparison of inlay and tunnel PCL reconstruction techniques.

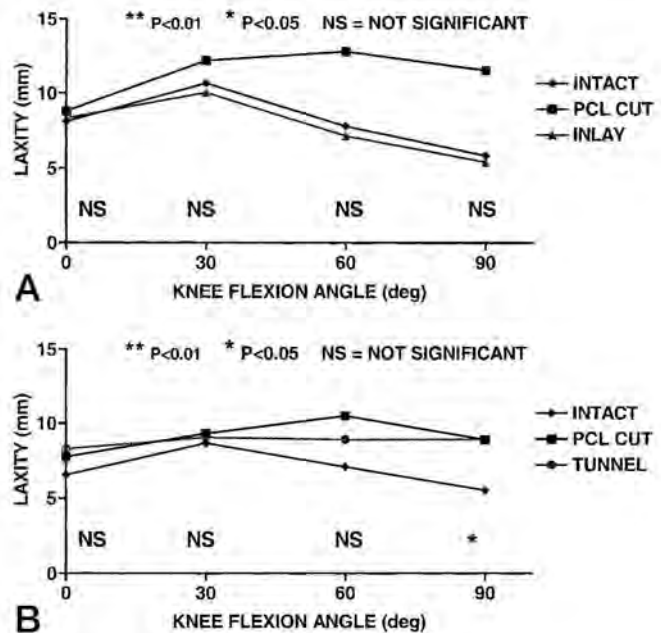


Figure 6. (A) Knee laxity measurements at four flexion angles with internal tibial rotation in the inlay PCL reconstruction group. The reconstruction measurements were compared with those in the same knees with the PCL intact and cut. (B) Knee laxity measurements in the tunnel-reconstruction group compared with the PCL intact and cut states for the same knees.

External Tibial Rotation

With the tibia in external rotation, mean laxity after inlay PCL reconstruction was less than that in the intact state at all flexion angles tested, but the differences were not significant (Fig. 7A). Mean laxity after tunnel PCL reconstruction was greater than in the intact state, but, again, the differences were not statistically significant at any flexion angle tested (Fig. 7B).

Statistical Analysis

A pair-wise comparison of laxity measurements at 90° of knee flexion is shown in Table 1. A post hoc power analysis at the 5% significance level revealed that a 2-mm difference in laxity could be detected at 68% power and that a 3-mm difference in laxity could be detected at 83% power.

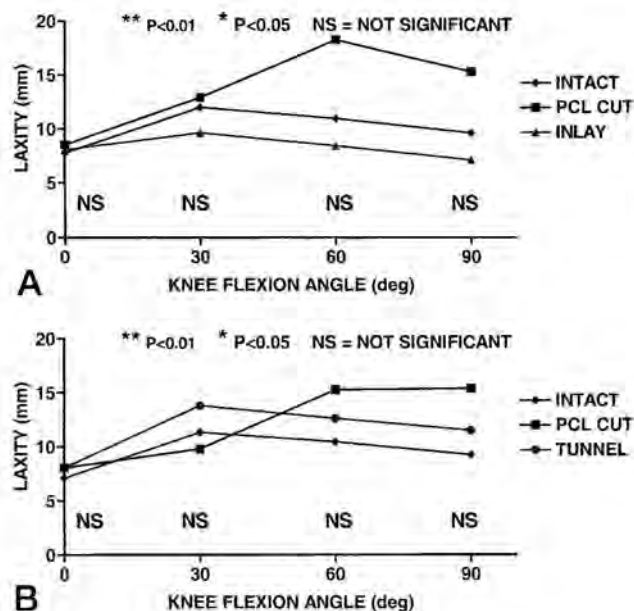


Figure 7. (A) Knee laxity measurements at four flexion angles with external tibial rotation in the inlay PCL reconstruction group. The reconstruction measurements were compared with those in the same knees with the PCL intact and cut. (B) Knee laxity measurements in the tunnel-reconstruction group compared with the PCL intact and cut states for the same knees.

Table 1. Pair-wise Comparison of Laxity Measurements at 90° of Knee Flexion for Inlay Versus Tunnel PCL Reconstruction

Condition	Difference (mm)	Standard Error	P Value
Neutral rotation	3.8	0.79	<0.001
Internal rotation	3.4	1.34	0.06
External rotation	4.8	1.76	0.04

Effects of Repetitive Loading

After 72 loading cycles, both groups had increased laxity compared with the amount of laxity after initial fixation. However, the final laxity measurements in the inlay group were not significantly different from those in the intact state, while those in the tunnel group were significantly more than in the intact state (Fig. 8).

Graft Evaluation

The grafts from the tunnel group had appreciable thinning and fraying at the site of maximal graft curvature around the proximal posterior tibia, whereas the grafts from the inlay group had no appreciable defects (Fig. 9). The thinning of all grafts was quantified by relative optical density measurements, and a significant difference ($P < 0.05$) was found between the groups (inlay group, 49 relative units; tunnel group, 117 relative units).

Discussion

The PCL has been the subject of numerous recent investigations. Many basic science studies have advanced our

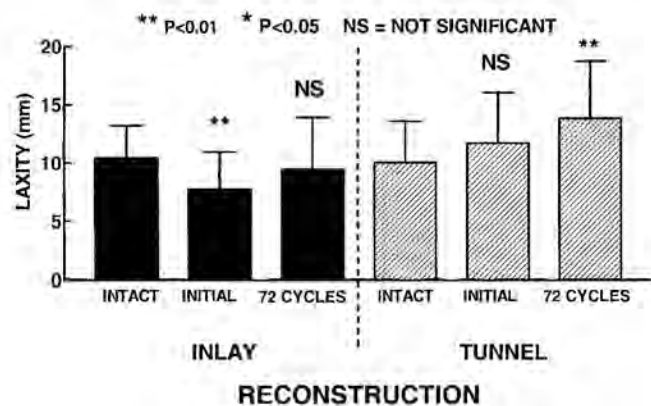


Figure 8. The effects of repetitive loading (72 cycles) at 90° of knee flexion with neutral tibial rotation. Laxity in the intact knee is compared with laxity immediately after reconstruction (initial) and after 72 loading cycles.



Figure 9. Transilluminated grafts from a matched pair of knees after the completion of mechanical testing. The graft on the left is from a knee that underwent the inlay reconstruction while the graft on the right is from the contralateral knee that underwent tunnel reconstruction.

understanding of the kinematics of the PCL-deficient knee and the PCL-reconstructed knee. Previous studies have documented the importance of femoral tunnel placement and

have shown that nonisometric positioning of the graft best corrects abnormal posterior laxity.^{2, 5, 10, 17} We agree with the findings of Bomberg et al.,⁵ Burns et al.,⁷ and Galloway et al.¹⁷ that support making the femoral tunnel in the distal footprint of the native PCL. These studies have contributed to a growing knowledge base and have aided surgeons in better understanding the PCL. However, all of the biomechanical studies to date have used a cadaver knee model with a tibial tunnel technique of PCL reconstruction. A normal laxity pattern has been achieved after a tunnel technique of PCL reconstruction in cadaver knees with isolated PCL deficiency.^{24, 25} However, clinical results after this type of reconstruction have been less conclusive.²² More recent biomechanical studies have investigated the results of double-bundle PCL reconstruction. Race and Amis²⁸ reported that only a doublebundle reconstruction restored normal knee laxity across the full range of knee motion. Harner et al.¹⁸ found that a double-bundle reconstruction better approximated both normal knee laxity and normal PCL force.

In our study, the grafts were tensioned on the femoral side after securing the tibial side of the graft to the proximal tibia. This convention was chosen so that the grafts in both groups could be tensioned similarly. In addition, this technique has been shown to result in higher tension on the intraarticular portion of the graft when compared with tensioning on the tibial side of the graft.²⁴ Both reconstruction techniques restored function of the anterolateral bundle of the PCL and significantly reduced abnormal posterior laxity in the PCL-deficient knee. With neutral tibial rotation, the inlay technique of PCL reconstruction resulted in less posterior laxity than the tunnel reconstruction after initial fixation. With internal tibial rotation, the laxity pattern of the inlay group better approximated the intact knee laxity than did the tunnel group. With external tibial rotation, both reconstruction techniques replicated the intact knee laxity. After 72 loading cycles, the laxity of both reconstructions increased, suggesting that both the inlay and tunnel grafts stretched. However, after repetitive loading the inlay reconstruction still approximated intact knee laxity, while in the tunnel group laxity was significantly increased. Although grafts applied with both reconstructive techniques appear to stretch out with repetitive loading, the inlay reconstruction appears to result in less laxity for a given graft tension. This suggests that a lower graft force is required in the inlay group to restore a given laxity.

There was visible evidence of mechanical degradation of the grafts in the tunnel group and no evidence of mechanical degradation in the inlay group. This degradation may be one of the causes of clinical failure after tunnel reconstruction. Another possible cause of tunnel technique failure could be inconsistency in the placement of the tunnel outlet in the posterior tibia. Accurate tunnel placement may be difficult, especially when done arthroscopically. Our study represents a “best-case scenario” for placement of the tibial tunnel, with the drill guide placed in the center of the PCL insertion

through an open incision. Consistent placement of the drill guide with arthroscopic techniques may not be so accurate.

Although we have demonstrated that the inlay reconstruction better restrains posterior translation in the PCL-deficient knee, there are some limitations to our study. One weakness of this study was that the same graft pre-tension load was used for all specimens. The selected load of 89 N was adequate to restore normal AP laxity in the tunnel group after initial fixation. However, this same load appears to have overconstrained the knees in the inlay reconstruction group after initial fixation. The 156-N anterior drawer load applied during tensioning may be higher than what could be consistently obtained manually in the operating room. Perhaps less graft tension or less anterior drawer force should be used to correct laxity to normal at the time of initial fixation when performing the inlay PCL reconstruction. Maybe overconstraint should be the goal at the time of surgery to account for stretch of the graft that could occur with repetitive loading. These issues are currently unresolved.

This study used paired cadaver knees with one knee undergoing one type of reconstruction and the other knee undergoing the other type of reconstruction. Although the differences in laxity in the intact and PCL-deficient states were not significant between sides, the comparisons are less statistically powerful because the same knee did not undergo both PCL reconstruction techniques. In addition, static shear loads were applied to the knee during testing. Although this type of loading has been traditionally used for knee laxity testing, this may not represent physiologic loading conditions.

Thinning and fraying of the grafts were identified in the tunnel reconstruction group but not in the inlay group. Although we find it interesting that grafts from the inlay group did not appear to be thinned, the mean age of the specimens was 68 years of age. Perhaps grafts from a younger cadaveric population would demonstrate less mechanical degradation.

Another problem in this study was that we did not observe a statistically significant increase in laxity at 0° of knee flexion in either group after transection of the PCL. This is contrary to what has been reported in another study²⁴ and suggests a methodological error. The testing jig that we constructed aligned the knee according to the angle made by the tibia and femur and did not take into account individual variability among the test specimens. Many cadaver knees from older donors have slight flexion contractures. Forcibly extending the knee to 0° probably was beyond the normal physiologic limit in some specimens. This leads to tightening of the capsule and other secondary restraints, resulting in less laxity.

Further studies are needed to clarify the natural history of the PCL-deficient knee and to determine whether this natural history can be altered with PCL reconstruction. If abnormal laxity cannot be adequately corrected and maintained, PCL reconstruction will probably not alter the natural history of

the PCL-deficient knee. Current techniques of PCL reconstruction appear to be inadequate.²² The anatomic tibial inlay technique of PCL reconstruction may better correct abnormal posterior laxity and could potentially result in lower graft forces. Further study is needed to clarify these issues.

Acknowledgments

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Use of the Articulating Tensioning Device ("Push Pull Device")

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So when do you use that thing you learned about in the AO course? It's that little device in your Synthes basic instrument set that provisionally goes on the end of the plate and is used to either compress or distract your fracture. Sounds good, but the problem is that it requires you to extend your incision quite a bit longer than planned. And with dynamic compression plates, when do you really need it? Here are the two uses and some situations where you might want to pull that "ATD" out.

Compression

Keep in mind that with the advent of locking plates, dynamic compression with oval holes has been somewhat compromised with those combi-hole plates, and left out altogether with many other plate designs. Certain fracture patterns like subtrochanteric femur fractures, and to a lesser degree, humeral and tibial shaft fractures, really require good compression, if you are plating them, to heal properly and avoid nonunion. And you often can't get enough compression with eccentric drilling and dynamic compression built into the plate design. So don't be afraid to secure your plate on the neutral side, apply that ATD to the end of the plate, hold your fracture in place with a clamp, and compress the fracture with that ATD!

Distraction

We've all been in a fracture case when you just can't get the fracture distracted enough manually to get it reduced, and it's not really amenable to using the large femoral distractor. Proximal posteromedial tibia plateau fractures are a good example. You think you are going to get it reduced, it needs a plate, but you just can't get it to go those last few millimeters or so. Just put either the plate you plan to use for definitive fixation, or maybe a 1/3 tubular plate, put some screws in on one side of the fracture, then put the ATD on the other end of the plate and distract it until it reduces.

Final Tips for Using the ATD

1. Make sure that your ATD works with the screws (3.5 and/or 4.5) that you are using.
2. Be careful with screw placement in the ATD itself as errant technique here can leave a stress riser just beyond the end of the plate.
3. Make sure your fracture is well aligned, and held in place with a clamp before compressing.
4. Make sure that the plate is lightly clamped to the bone on the ATD side before compressing or distracting (you only have one point of fixation on that side, and the fracture can sometimes angulate or plate can go off bone).

How I Apply a Cast — Tips and Techniques

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For any limb, you need to have a good assistant to hold the limb. Even for a cast on a limb that's not grossly unstable, the part to be casted still needs to be stabilized in some way in order to not be working on "a moving target." Ask an assistant to steady and maintain "functional position." In the case of a short leg cast, a metal stand to support the ankle will do. In the example of a short cast, the ankle should be held that 90° or as close as possible.

I almost always use a stockinette to protect the patient from the cast rubbing at its edges. I cut a small section out on the anterior aspect of the ankle to prevent irritating wrinkles from forming here. For a short arm cast, cut a thumb hole with a small tab of stockinette based distally to be able to fold back over the loop of cast through the thenar web space to protect the thumb from rubbing on the cast (especially with fiberglass).

I use standard cotton Webril. The rule of thumb here is "little Webril, big plaster" in choosing the size to apply. For a short leg cast, use either four inch and three inch. I usually roll the Webril on from top to bottom trying to place a uniform layer from top to bottom overlapping by about 50%. Usually, two or three thicknesses is enough. Be careful not to apply too much padding as this is unnecessary and results in a cast NOT securing the limb. I will usually apply an extra double thickness of Webril at the prominences such as the malleoli, the achilles, and the heel. Also, an extra thickness or two provides a nice cushion at the ends and edges of the cast. Roll the Webril on without wrinkles accomplishing this either by stretching the Webril to prevent wrinkles or by tearing it and apply it at a different angle at the next lower level. I try not to lift the Webril off the patient as lifting the padding tends to allow you to pull the Webril too tight at one edge, thereby creating bands that can be constricting.

Once the Webril is in place, I usually use fiberglass casting tape. Despite the fact that it is more expensive for each roll, fiberglass is certainly lighter and stronger. This allows you to use fewer rolls at first and you will find you encounter fewer times that the cast will fail needing a new application. Fiberglass is also less messy. (You DO have to be careful you don't get it on you hands, clothing, or office equipment and furniture, however. The only way to remove it is by an acetone scrub.) For a short leg cast in an average-sized patient, you usually need to use two four-inch rolls of fiberglass and one three-inch roll. I still use fairly cold water as this allows me to work a little more slowly and carefully. This is a big advantage because fiberglass certainly dries fast enough that

you do not have to wait long for it to set. Also, using cold water, you can apply the cast at a much more uniform and smooth thickness. In essence, it gives you more control when you use cold water.

Again, I start at the top to let gravity help me — overlapping the fiberglass material by 50% as I come down and I try to put a uniform thickness throughout the cast. Do not lift the fiberglass roll off the patient since by lifting the roll off the intended site with the casting material, you can make one edge tight causing little spirals of pressure points. I keep the material against the patient's limb to minimize the chance of causing a pressure point and also by doing so makes for a nice uniform thickness of the cast. I go from top to bottom covering by 50% and, if I reached the bottom, I start back up again. The second roll is started at this "initial finish point" and I continue back up toward the knee. Again, applying the cast in this fashion allows a nice uniform thickness which translates into the sleekest, lightest, but strongest finished product. Now, before I reach the top of the cast as I am rolling, I turn down the stockinette over the previously applied layer and I can cover the stockinette and seal it with the second roll of fiberglass as I coming up. At this point, I rub the fiberglass to smooth and integrate the layers and, in doing this, I also create a mold as needed for holding the fracture in position.

Before the fiberglass sets (hardens), I use a pair of dedicated fiberglass cutting scissors and I cut out a portion over the dorsum of the toes to allow the toes to move freely (if the fracture allows). This creates a little plantar plate distally; I then fold the stockinette back over the fiberglass. I then add a three-inch roll of fiberglass starting distally and working up the foot and ankle. At this point, I also will "Cadillac" the cast with a roll of color if the patient requests this. I have tried to stock a variety of two-inch colors and use one (or occasionally two) to finish off the cast. Patients often feel a little better about being in a cast if they can smile at a color. Truth be told, I may add a little thickness to the heel and around the ankle as I finish by a rolling the three-inch up the leg if necessary. If it's a nonweightbearing cast, I don't think any further additional material is necessary. If it is a weight-bearing cast, sometimes there is still a little equinus deformity despite trying to reduce it to 90 degrees; in this instance, usually you can use a two-inch or three-inch roll of the casting material to bunch up and add some height to the heel attaching, of course, with the last few feet of that roll. This balances the ankle for ambulation and avoids pushing the

patient into “back knee” as they walk. Their knee should always slightly flex as they progress forward with weight-bearing.

I always warn the patient about the signs of a tight cast: excessive, unremitting PAIN and the feeling of a VERY tight cast. Also, inform the patient — and relatives — about what to do if there is any rubbing of the cast causing sores, ulcers, blisters, or any significant irritation. You must tell them of the consequences of a cast problem and that if any of these occur — especially a tight cast — that they are emergencies that need to be treated as such by immediate, right now, attention — either loosening or removing the cast.

To loosen a cast, you need to cut ALL layers. Whether you bivalve or univalve the cast, the Webril also needs to be split so that any circular dressing is released completely (even sticky, blood soaked gauze can form constrictions). Bivalving a cast and removing the anterior portion of the cast, cutting all the Webril so it is not circular and holding the resultant splint in place with loosely wrapped Ace wraps is the safest method when possible. I never wrap Kling or Kerlex gauze under a cast.

If you still want to use plaster (which is clearly less expensive but messy, weaker, and heavier), place a towel or cloth on the floor. For a short leg cast, I use three six-inch rolls (or two six-inch rolls and a four-inch roll depending on the patient’s size). Again, use cold water as it gives you better control especially when you are first beginning to apply casts. It will take longer to dry. Rubbing “like you love it” will result in a much better, stronger cast as well as will look better and have less chance of causing any irritation from irregularities in the cast (see above discussion re: Webril and fiberglass application).

Apply the Webril as directed above. Then to apply the cast, set the plaster in the water (cold or cool water) and wait for the bubbles to stop forming; squeezing the two ends of the rolls to prevent a “banana.” Now apply the plaster directly on the patient (don’t lift roll) and cross 50% of the layer above. Do not tuck; just roll it and the plaster would gently fold into itself and, again, create a much smoother, more uniformly layered cast. Making tucks takes time and also slows your application time. So you can put on as good a cast as possible, give yourself as much time by using cold water and don’t waste time on tucks. Apply enough rolls of

the plaster to secure the limb. Don’t worry about rubbing the cast until all the rolls are applied; this will save time and assure that the plaster will be molded into one single (stronger) layer. Then begin rubbing to compress the layers together and smooth the plaster. Always rub it in the opposite direction you placed the plaster on so that the edges won’t wrinkle (if the last roll is from top/down, rub up; if distal to proximal, rub downward). As the plaster begins to set, the plaster gets to the “cardboard stage.” Now the plaster has become clearly a little more tacky and less slippery. It is at this point, if needed, you can apply your molds using the thenar eminences to apply the mold. Don’t keep your hands in one spot; gently move them a little to prevent an excessive pressure point. After the plaster hardens enough to stop applying a mold, trim the edges of the cast and apply a sealing roll as needed.

Be sure to again inform the patient and relatives about cast problems (one of the true orthopedic emergencies) and give them some tips on cast care. It will take 24 to 48 hours for the plaster to dry (and reach maximum hardness) so keep the patient from walking on the cast for two days.

To remove a cast, remember that the cast saw vibrates so the soft Webril padding — and your skill — all serve to keep you from cutting the patient. Wet Webril or blood-soaked Webril makes it easier to cut or burn the patient. Also listen to the patient — if he or she protests too much, reevaluate whether you may be actually injuring them. Usually you are not, but be sure. Hold the saw with one hand and use the thumb as a prop against the cast to steady and guide your cutting. Remember, the saw blade is circular so you can use this to your advantage. After the initial gentle, careful “plunge,” move the saw steadily distally; not plunging multiple times instead of moving distally makes it less likely you will come against the patient’s skin. This technique allows the incline of the saw blade to always serve as a “plunge guide.” Make your cuts away from bony prominences — and away from neurovascular structures — whenever possible. Pop the cast open with the spreaders and then cut the stockinette and Webril. Remove the cast. Patients should wash, not scrub skin at first and use cream or lotion on skin for a while. Splint the limb if/as necessary for awhile after removal of the cast.

Connective Tissue Growth Factor (CTGF) Regulates BMP Signaling During Osteoblast Differentiation

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Abstract

Connective tissue growth factor (CTGF) and bone morphogenetic protein (BMP)-2 are both produced and secreted by osteoblasts. Both proteins have been shown to have independent effects in regulating osteoblast proliferation, maturation and mineralization. However, how these two proteins interact during osteoblast differentiation remains unknown. In this study, we compared the differentiation of KO and WT osteoblasts to investigate the effects of CTGF and BMP-2 on osteoblast development and function *in vitro*. In cultures not stimulated with BMP-2, the absence of endogenous CTGF did not affect osteoblast maturation and mineralization. There was no significant difference in alkaline phosphatase (ALP) activity and staining, alizarin red staining or mRNA expression of runt related transcription factor 2 (*Runx2*) and osteocalcin (*Oc*). Interestingly, in WT and KO osteoblast cultures stimulated with BMP-2, KO osteoblasts exhibited enhanced osteoblast differentiation. There was a significant increase in the number and size of mineralized nodules, as well as *Runx2* and *Oc* mRNA expression in KO osteoblast cultures. The increase in osteoblast differentiation was accompanied by increased protein levels of phosphorylated Smad 1/5/8 and mRNA expression levels of bone morphogenetic protein receptor Ib. The present findings demonstrate, through functional studies, a novel function of endogenous CTGF in regulating osteoblast development and function by inhibiting BMP signaling.

Introduction

Osteoblast differentiation is a complex process, which involves the commitment of mesenchymal cells to osteoblasts followed by synthesis and deposition of bone matrix proteins. The development of pre-osteoblasts to matrix-secreting osteoblasts encompasses three phases: 1) proliferation, 2) maturation and 3) mineralization.¹ These phases require the appropriate expression of several osteoblast markers, including runt-related transcription factor 2 (*Runx2*),

osterix, alkaline phosphatase (*Alp*), and osteocalcin (*Oc*) to ensure proper osteoblast development and function. This process is highly regulated by local factors such as bone morphogenetic proteins (BMPs). BMP-2 has been widely studied and is known to induce bone formation *in vivo* and promote osteoblast differentiation *in vitro*.²⁻⁴ The mechanism by which BMP-2 promotes osteogenesis is well understood. BMP-2 exerts its effects through the canonical Smad pathway involving Smads 1, 5, and 8, which are phosphorylated by serine/threonine kinase receptors composed of type I and II components. Once activated, Smads 1, 5, and 8 form a complex with Smad 4, which translocates to the nucleus and induces the transcription of target genes, such as *Runx2*.^{5,6}

In addition to BMP-2, connective tissue growth factor (CTGF) has been shown to regulate osteogenesis. CTGF knockout (KO) mice exhibit skeletal dysmorphisms due to defects in chondrogenesis and extracellular matrix production.⁷ Recently, our lab did an in-depth characterization of CTGF KO mice and found these mice to exhibit numerous site-specific defects in the axial, appendicular, and craniofacial skeleton.⁸ CTGF is expressed and secreted by osteoblasts during bone formation and fracture healing. *In vitro* studies have shown that CTGF promotes the proliferation and differentiation of osteoblasts.^{9,10} These studies support a role for CTGF as a regulator in osteoblast development and function, but how CTGF regulates such processes remain unknown.

CTGF is a matricellular protein that interacts with several growth factors, including BMPs. Studies revealed that CTGF interacts with BMP-2 and BMP-4 through its von-Willebrand type C and C-terminal domains.^{11,12} More specifically, when CTGF interacts with BMP-4, CTGF sequesters BMP-4 thereby preventing the ligand from binding to its cognate receptor, BMPR-1a, thus inhibiting BMP signaling.¹¹ Despite these findings, it remains unclear how CTGF and BMP-2 interact to regulate osteoblast differentiation. In this study, we utilized primary osteoblasts derived from calvaria of E18.5 CTGF wild-type (WT) and KO embryos to investigate the interaction of CTGF and BMP-2 during osteoblast differentiation.

Material and Methods

Source of Animals

CTGF heterozygous mice (CTGF^{+LacZ}) were used as breeders to obtain CTGF KO (CTGF^{LacZ/LacZ}) mice as previously described.¹³ Genotype was determined as previously described.¹³ All animals were maintained and used according to the principles in the NIH Guide for the Care and Use of Laboratory Animals (U.S. Department of Health and Human Services, Publ. No. 86-23, 1985) and guidelines established by the IACUC of Temple University.

Primary Osteoblast Cell Culture

Primary cells were isolated from parietal calvaria of embryonic day 18.5 CTGF wild-type (WT) and knockout (KO) embryos from which the cranial sutures were removed to reduce non-osteoblast cell contamination. Calvaria pieces were placed in digestion media consisting of 0.1% Collagenase (Sigma)/2.5% trypsin and subjected to a series of digestions of 5, 15, 30, 20, 15, and 15 minutes at 37°C. The purpose of the first digestion is to remove non-osteoblastic cells and this digestion was discarded. The osteoblast cell population was obtained from the remaining digestions. Cells were plated in 100 mm dishes (Corning) at 5×10^5 cells/plate in Alpha Minimal Essential Medium (α -MEM; Mediatech) supplemented with 10% fetal bovine serum (FBS; HyClone). The cells were incubated at 37°C with 5% CO₂ with a change of media every three days until they reached 80% confluence. For experiments, cells were cultured in osteogenic media containing 50 μ g/ml ascorbic acid (Sigma) and 10 mM β -glycerophosphate (Sigma) in addition to α -MEM/10% FBS to stimulate osteoblast differentiation.

BMP-2 Stimulation

Recombinant BMP-2 (R&D Systems) was reconstituted to a concentration of 10 μ g/ml in sterile 4 mM HCl containing 0.1% BSA and stored at -20°C. Cells were treated with a standard concentration of 100 ng/ml of BMP-2 every three days during osteoblast differentiation. For evaluating levels of phosphorylated Smad1/5/8, WT and KO cells were serum starved for 24 hours then stimulated with BMP-2 for 5–60 minutes. For evaluating BMP receptor levels, WT and KO cells were stimulated with BMP-2 for zero and eight hours.

Cell Proliferation and Spreading

Cell number was determined using the CyQUANT® NF Cell Proliferation Assay Kit (Molecular Probes) according to the manufacturer's protocol. Briefly, CTGF WT and KO osteoblasts were plated at 4×10^3 cells/well in a 96 well plate (Falcon) in α -MEM/10% FBS. On Days 1, 3, and 7, media was aspirated and replaced with DNA binding dye solution. Cells were incubated at 37°C for one hour and samples were measured using a Wallac 1420 fluorometer. Cell number was calculated based on a standard curve generated for primary osteoblasts. Phase contrast images of cells were taken on

Days 1, 3, and 7 with the Nikon Eclipse TE300 inverted microscope. For cell spreading experiments, eight-chamber glass slides (Lab-Tek II) were coated with 1% Bovine Serum Albumin (BSA) (Sigma) or 2 μ g/ml of Fibronectin (FN) and incubated at room temperature under sterile conditions overnight. WT and KO osteoblasts were plated at 2×10^3 cells/chamber and incubated for eight hours at 37°C. Cells were fixed and stained for actin using the Actin Cytoskeleton and Focal Adhesion Staining Kit (Millipore). Cells were imaged on a Nikon Eclipse E1000 fluorescence microscope, and images were digitized for cell area measurements using Image J software.

Alkaline Phosphatase Staining and Activity

CTGF WT and KO cells were plated in a 48-well plate (Corning) at 1.1×10^4 cells/well in osteogenic media, which was changed every three days. The osteoblast cultures were stopped at Day 14 to evaluate the production of alkaline phosphatase. Alkaline phosphatase staining was performed using the Leukocyte Alkaline Phosphatase Kit (Sigma). Cells were washed with 1X HBSS and fixed in a citrate buffer containing acetone and formaldehyde. Following fixation, cells were washed with ddH₂O and incubated with a staining solution consisting of equal parts of sodium nitrite solution, FRV-alkaline solution and naphthol AS-BI alkaline solution for 25 minutes at room temperature. Cells were washed with ddH₂O and allowed to air dry. Wells were observed and images taken using the Nikon Eclipse TE300 inverted microscope. Quantification of alkaline phosphatase production was determined using Quantichrom™ Alkaline Phosphatase Assay Kit (BioAssays Systems). Cells were lysed in ddH₂O water containing 0.2% Triton X-100 for 20 minutes at room temperature. Cell lysates were collected and the assay was carried out according to the manufacturer's protocol. Alkaline phosphatase activity was normalized to total protein content. Total protein content was determined using BCA protein assay kit (Pierce) on identical cultures.

Alizarin Red Staining

CTGF WT and KO osteoblast cultures were stopped at Day 21 to evaluate mineralization. For alizarin red staining, cells were washed in 1X HBSS and fixed in 10% paraformaldehyde for 15 minutes at room temperature. Cells were washed with 1X PBS and stained with 40 mM Alizarin Red S (Sigma) for 15 minutes at room temperature. Cells were washed with ddH₂O and allowed to air dry. Wells were observed and images taken using the Nikon Eclipse TE300 inverted microscope.

RNA Isolation and Quantitative PCR

Total RNA was isolated from CTGF WT and KO osteoblasts at Days 7, 14, and 21. To evaluate changes in BMP receptor levels, CTGF WT and KO osteoblasts were serum starved for 24 hours, stimulated with BMP-2 (100 ng/ml),

and RNA was collected at zero and eight hours. RNA was isolated from cell cultures using Trizol reagent (Invitrogen) according to the manufacturer's directions. RNA was purified using the RNeasy Mini Kit (Qiagen) and treated with DNase using the RNase-Free DNase Kit (Qiagen). RNA quality and quantity was determined using spectrophotometry and the integrity of all samples was confirmed using 1% formaldehyde-agarose gel. For cDNA synthesis, 1 µg of cDNA was transcribed from total RNA using SuperScript® First-Strand Synthesis System (Invitrogen). Gene expression for runt-related transcription factor 2 (*Runx2*), osteocalcin (*Oc*), bone morphogenetic protein receptor Ia (*BMPR-Ia*), and bone morphogenetic protein receptor Ib (*BMPR-Ib*) was determined by qPCR, as described previously.⁸

Protein Isolation and Western Blotting

WT and KO cell monolayers were washed in cold 1X PBS and lysed in 1X RIPA (Millipore) for one hour at 4°C. Cell lysates were centrifuged and the resultant supernatants were used for determination of protein concentration using BCA Protein Assay Kit (Pierce). Western Blot was performed as previously described.⁹ The membrane was blocked with 5% BSA/1X PBS-Tween20 for one hour and incubated with the following primary antibodies: anti-rabbit phospho-Smad (p-Smad) 1/5/8 (1:1000; Cell Signaling) and anti-rabbit actin (1:1000; Sigma) overnight at 4°C. The membrane was washed with 1X PBS-Tween20 and incubated with horseradish-peroxidase conjugated donkey anti-rabbit (1:10,000; Jackson ImmunoResearch) for one hour at room temperature. The membrane was washed again, incubated with SuperSignal West Pico Chemiluminescent Substrate (Thermo Scientific), and exposed to film. Quantification of the bands was done using Image J software.

Statistical Analysis

Unpaired Student's t test was used to determine whether the absence of CTGF had any effect on quantitative parameters related to osteoblast proliferation, maturation, and mineralization compared to WT. Data are expressed as ± SEM. A P-value <0.05 was considered statistically significant.

Results

CTGF KO Osteoblasts Display Reduced Cell Spreading But Increased Cell Proliferation During Early Differentiation

To determine whether the absence of CTGF affects osteoblast proliferation, we examined the proliferative capacity of WT and KO osteoblasts at Days 1, 3, and 7. At Day 1 after plating, there was no significant difference in cell number between WT and KO osteoblasts (Fig. 1A, B: top panel). However, by Day 3, KO osteoblasts showed increased proliferation compared to WT osteoblasts (Fig. 1A). Interestingly, a representative phase contrast image showed a population of KO osteoblasts, which appeared smaller, suggesting reduced cell spreading, whereas the WT osteoblasts appeared

larger, suggesting increased cell spreading (Fig. 1B: middle panel). This change in KO cell behavior was more apparent in Day 7 cultures. By Day 7, the WT osteoblasts reached confluence and therefore stopped proliferating, whereas the KO osteoblasts still continued to proliferate due to their smaller cell shape. The phase contrast image at this time point displayed a clear difference in cell shape between WT and KO osteoblasts (Fig. 1A, B: bottom panel). To confirm that the KO osteoblasts spread less than the WT osteoblasts, we plated the cells on BSA and FN and measured the cell area after immunofluorescence staining for actin. When plated on either substrate, KO osteoblasts exhibited reduced cell spreading compared to WT osteoblasts (Fig. 1C and 1D). Collectively, these data demonstrate that the reduced spreading of KO osteoblasts allows these cells to continue to proliferate for a greater period of time to reach a confluent state.

CTGF KO Osteoblasts Display Normal Maturation and Mineralization In Vitro

To investigate the role of CTGF during osteoblast differentiation, we cultured primary WT and KO osteoblasts for a period of 21 days. We evaluated osteoblast maturation at Day 14 by ALP staining and activity, and there was no difference in osteoblast maturation between WT and KO cultures (Fig. 2A: left panel and B). Next, we examined osteoblast mineralization at Day 21 by Alizarin red staining. In both WT and KO cultures, osteoblasts started to aggregate, which is demonstrated by an increase in Alizarin red staining at sites of the cell aggregations (arrows). There was no delay in osteoblast mineralization in the KO cultures, which were similar in appearance to the WT cultures (Fig. 2A: right panel). *Runx2* is an essential transcription factor for osteoblast differentiation and is known to up-regulate other critical genes important for later stages of osteoblast differentiation, such as *Oc*. Therefore, we measured *Runx2* mRNA expression in WT and KO cultures at Day 7. Although the KO cultures showed an increase in *Runx2*, it was not significant (Fig. 2C). In addition, there was no difference in *Oc* mRNA expression between WT and KO cultures (Fig. 2D). These data demonstrate that osteoblasts can differentiate normally in culture in the absence of endogenous CTGF production (KO osteoblasts).

CTGF KO Osteoblasts Exhibit Enhanced Differentiation in Response to BMP-2

BMP-2 is a well-known osteoinductive agent both *in vivo* and *in vitro*.²⁻⁴ CTGF interacts with BMPs,^{11, 12} but it is unknown how CTGF and BMP-2 interact during osteoblast differentiation. To examine this interaction, we treated osteoblast cultures with rBMP-2 for 21 days. Interestingly, ALP staining at Day 14 revealed the presence of nodules in the KO cultures, which were not seen in the WT cultures (Fig. 3A: left panel). There was no difference in ALP activity between WT and KO cultures. Alizarin red staining at Day

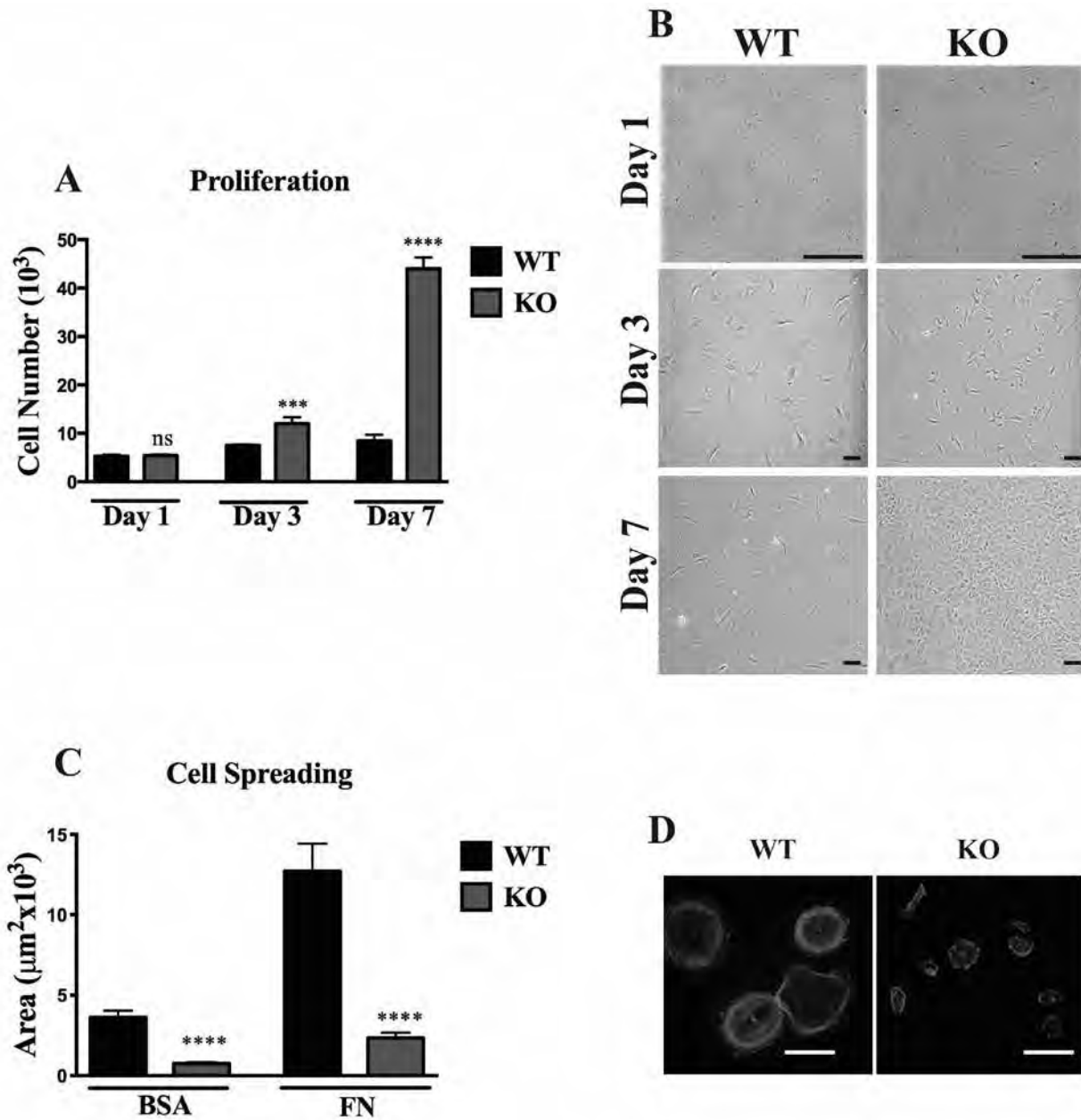


Figure 1. CTGF KO osteoblasts display increased proliferation. (A) The proliferation of CTGF WT and KO osteoblasts was assessed on Days 1, 3 and 7. Cell numbers were based on fluorescence at 520 nm. (B) Phase contrast images of cells at Day 1, Day 3, and Day 7. (C) WT and KO osteoblasts were plated on BSA and FN and cell area (spreading) was measured eight hours later. (D) Immunofluorescence staining for actin in WT and KO cells plated on FN. ***P < 0.001; ****P < 0.0001. Scale bar: 50 μm (Day 1); 10 μm (Days 3 and 7); 100 μm (actin staining). Abbreviations include bovine serum albumin (BSA) and fibronectin (FN).

21 showed the presence of small, mineralized nodules in WT cultures, whereas the KO cultures displayed a greater number of nodules, which fused with one another to form larger mineralized nodules (Fig. 3A: right panel). In addition, *Runx2* and *Oc* mRNA expression levels were significantly up-regulated in CTGF KO cultures (Fig. 3D). These data demonstrate that osteoblast differentiation is accelerated and enhanced in response to exogenous BMP-2 in KO compared to WT cultures.

Increased BMP signaling in CTGF KO osteoblasts

Smads 1, 5, and 8 are important mediators in the BMP signaling pathway.⁵ To investigate whether the enhanced osteoblast differentiation seen in the CTGF KO cultures is attributed to an increase in p-Smad 1/5/8 levels, we treated WT and KO osteoblasts with BMP-2 for 5 to 60 minutes. p-Smad 1/5/8 protein levels increased with BMP-2 stimulation in both WT and KO osteoblasts, yet p-SMAD 1/5/8 levels were greater in KO compared to WT osteoblasts at all

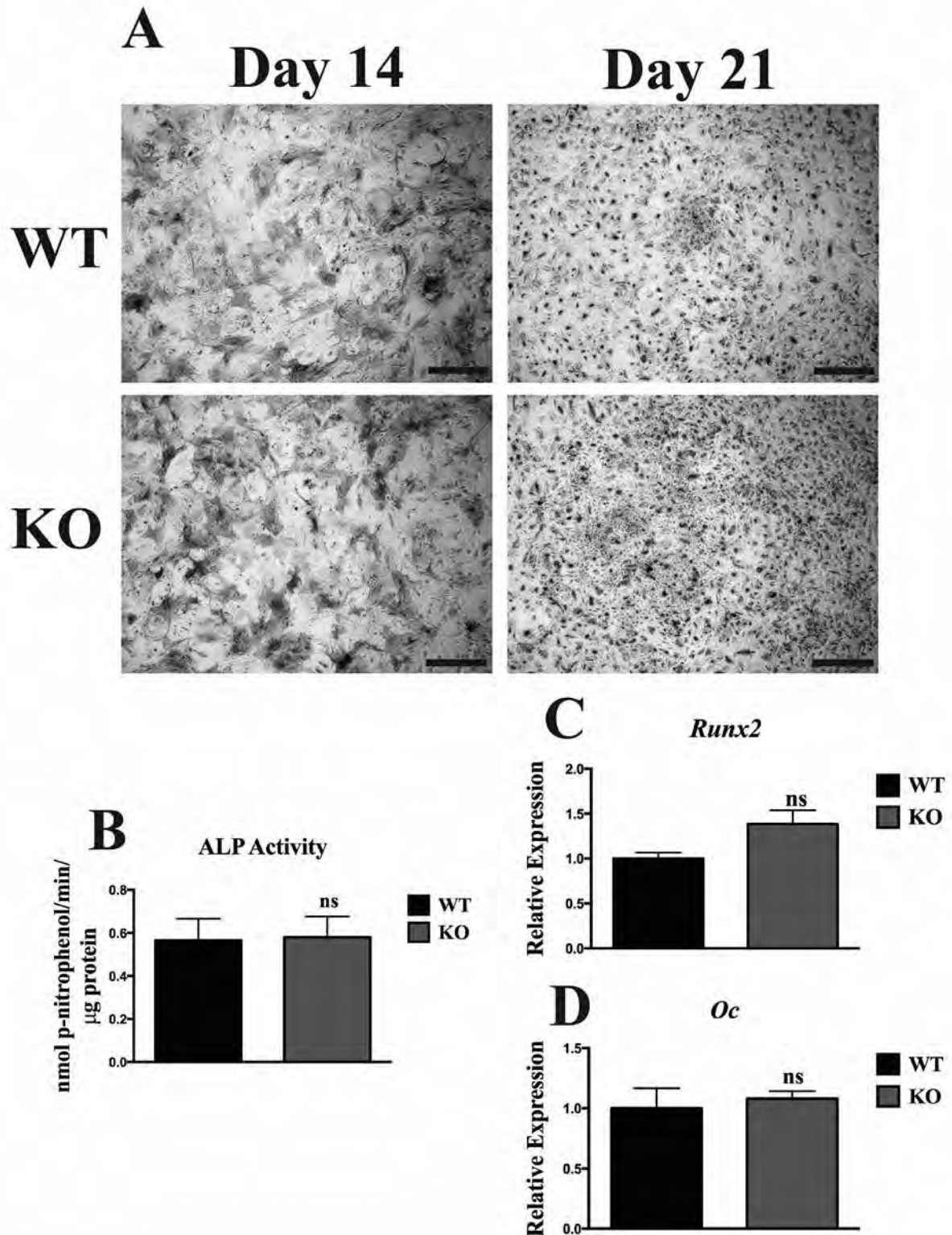


Figure 2. CTGF KO osteoblasts exhibit normal differentiation *in vitro*. (A) ALP staining at Day 14 of osteoblast culture (left panel) and Alizarin Red S staining at Day 21 (right panel). (B) ALP activity quantified at Day 14 of culture. (C and D) mRNA gene expression of *Runx2* at Day 7 of culture (C) and *Oc* at Day 21 (D). Scale bar: 50 µm. Abbreviations include alkaline phosphatase (ALP), runt-related transcription factor 2 (*Runx2*) and osteocalcin (*Oc*).

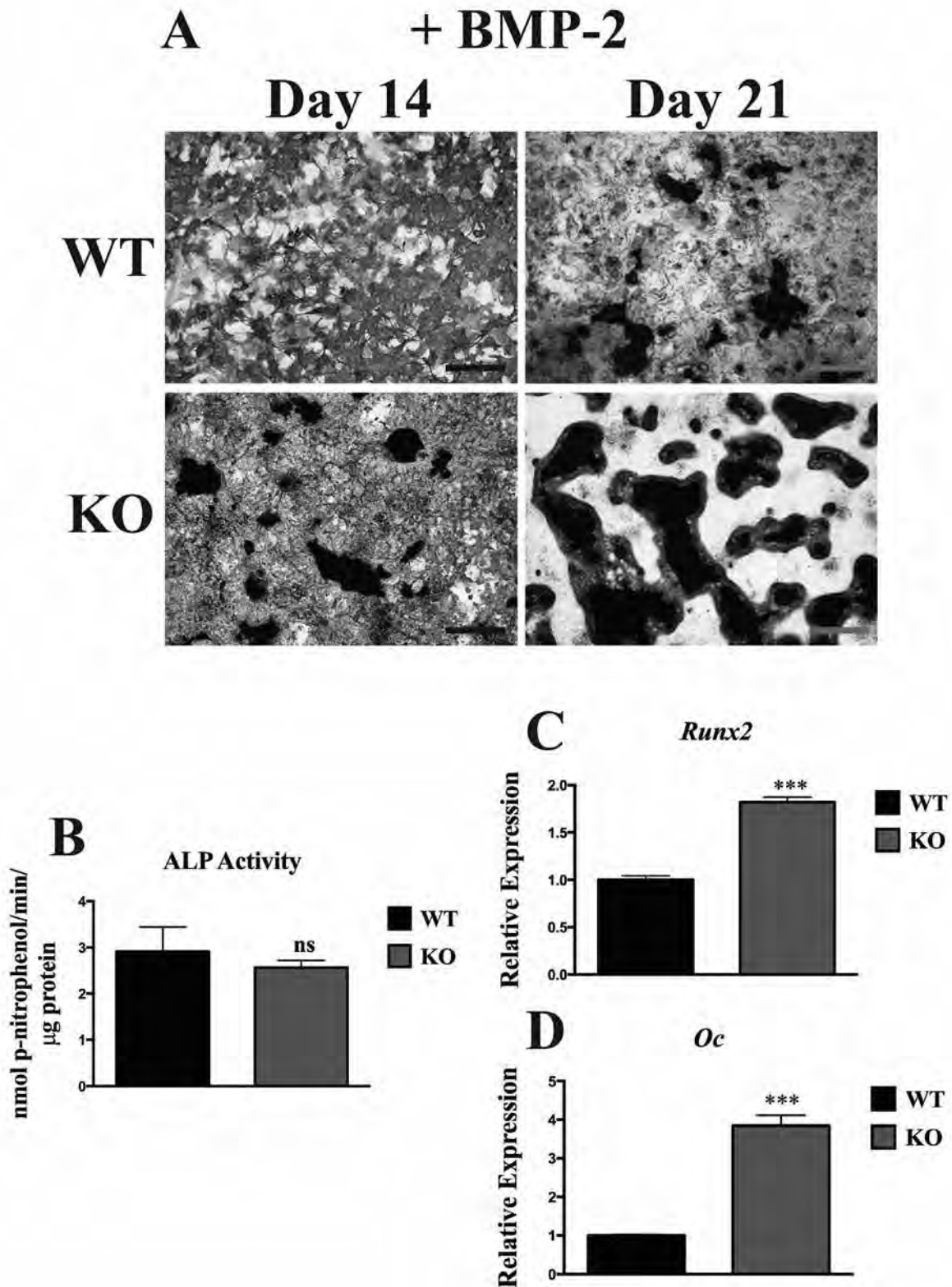


Figure 3. CTGF KO osteoblasts exhibit enhanced maturation and mineralization in the presence of BMP-2. (A) ALP staining at Day 14 of osteoblast culture (left panel) and Alizarin Red S staining at Day 21 (right panel). (B) ALP Activity was measured at Day 14 of culture. (C and D) mRNA gene expression of *Runx2* at Day 7 (C) and *Oc* at Day 21 (D). ***P < 0.001. Scale bar: 50 µm. Abbreviations include alkaline phosphatase (ALP), runt-related transcription factor 2 (*Runx2*), and osteocalcin (*Oc*).

time points (Fig. 4A). Since the BMP-2 ligand/receptor complex activates Smads 1, 5, and 8, we investigated the expression of signaling receptors, *BMPR-1a* and *BMPR-1b*. We stimulated WT and KO cultures with BMP-2 for zero and eight hours, and evaluated changes in mRNA expression of BMP receptors. In un-stimulated conditions there were no significant differences in *BMPR-1a* and *BMPR-1b* expression between WT and KO osteoblasts. However, upon stimulation with BMP-2, *BMPR-1a* levels decreased 0.5- and 0.75-fold in WT and KO osteoblasts, respectively (Fig. 4B). The observation that *BMPR-1a* was down-regulated upon BMP-2 stimulation suggests that this receptor does not play a critical role in BMP-2-induced osteoblast differentiation. When WT and KO osteoblasts were treated with BMP-2 and assessed for *BMPR-1b* expression levels, *BMPR-1b* levels increased by 10- and 35-fold in WT and KO osteoblasts, respectively. Interestingly, at eight hours, KO osteoblasts displayed an increased expression of *BMPR-1b* compared to WT osteoblasts (Fig. 4C). These data demonstrate that KO osteoblasts exhibit increased signaling in response to BMP-2, and suggest that *BMPR-1b* is the prominent receptor required for BMP-induced signaling in osteoblast cultures.

Discussion

CTGF interacts with numerous growth factors and matrix proteins to regulate various cellular processes such as migration, adhesion, proliferation, and differentiation.¹⁴ These processes are important for proper osteoblast development and function. Previous studies have shown that CTGF interacts with BMP-2 and BMP-4. One group demonstrated that CTGF interacts with BMP-4 and prevents BMP-4 from binding to its receptor, *BMPR-1a*, thereby inhibiting the action of BMP-4 during embryonic patterning.¹¹ Another group demonstrated that CTGF interacts with BMP-2 and together, these proteins can modulate chondrocyte proliferation and differentiation.¹² Both proteins are produced and secreted by osteoblasts, and have independent effects in regulating osteoblast proliferation, maturation and mineralization. However, the interaction between CTGF and BMP-2 has yet to be explored during osteoblast differentiation. In this study, we compared the differentiation of KO and WT osteoblasts to investigate the effects of CTGF and BMP-2 on osteoblast development and function *in vitro*.

During the first phase of osteoblast differentiation, the cells actively proliferate in culture and express cell cycle and cell growth regulated genes. When cells come into contact with each other, they undergo cell contact inhibition, which initiates arrest of cell growth.¹⁵ Our data shows that WT osteoblasts spread more, indicated by a significantly larger average cell area, than KO osteoblasts (Fig. 1C, D). Therefore, WT osteoblasts reach confluence and cell contact inhibition, earlier than KO osteoblasts. As a result, the KO osteoblasts continue to proliferate for a longer period of time until they achieve a confluent state (Fig. 1A, B). We believe this is

one possible explanation for the significantly higher cell numbers in KO compared to WT osteoblast cultures at Days 3 and 7. To fully understand the proliferative behavior of WT and KO osteoblasts, future studies will involve FACS analysis to compare cell cycle markers, such as cyclins and cyclin-dependent kinases.

The second and third phases of osteoblast differentiation are matrix production/maturation and mineralization, respectively. Following cell cycle arrest, the osteoblasts undergo a series of morphological changes and temporally express *Alp*, *type I collagen*, and *osteocalcin*, all of which are necessary for the synthesis of a mineralized bone matrix.¹⁵ We evaluated these two phases in osteoblast cultures derived from CTGF WT and KO embryos. Under normal osteogenic culture conditions that were not stimulated with exogenous BMP-2, there was no difference in ALP staining and activity, alizarin red staining, or the mRNA expression of osteoblast markers when comparing WT and KO osteoblast cultures (Fig. 2). These results are contradictory to what has been previously published regarding the differentiation of osteoblasts derived from CTGF KO mice. This previous study showed a significant reduction in the differentiation of CTGF KO compared to WT osteoblasts.¹⁰ One possible explanation for the difference in our results from those previously published may be related to cell plating densities used in the two studies. The authors of the previous study used a significantly lower cell plating density that was used in this study. Interestingly, when we plated WT and KO osteoblasts at half the normal cell density which is still higher than that used in the Kawaki et al. study, the KO osteoblasts showed less ALP activity at Day 14 than WT, but by Day 21 the levels of ALP activity in WT and KO cultures were comparable (data not shown). Another possible reason for the discrepancy may be related to the time points that were chosen to evaluate osteoblast differentiation in the previous study. Our results suggest that CTGF is not essential for osteoblast differentiation under unstimulated conditions.

However, when we treated WT and KO osteoblast cultures with BMP-2, the KO osteoblasts exhibited a markedly accelerated differentiation. It is well-documented that *Runx2* is required for osteoblast differentiation.^{16, 17} This essential transcription factor is expressed throughout osteoblast differentiation and it up-regulates several downstream genes necessary for later stages of osteoblast differentiation, such as *type I collagen* and *Oc*.^{18, 19} Interestingly, studies have shown that BMPs up-regulate *Runx2* mRNA expression and inhibition of BMP signaling disrupts the ability of *Runx2* to stimulate osteoblast differentiation *in vitro*.⁶ Our data shows that upon stimulation with BMP-2, *Runx2* mRNA expression levels were significantly up-regulated in KO osteoblast cultures, which resulted in enhanced osteoblast maturation and mineralization compared to WT osteoblast cultures. It is important to note that when we measured ALP activity in these cultures, even though the results were not significant, the KO osteoblasts showed a decrease in activity (Fig. 3B).

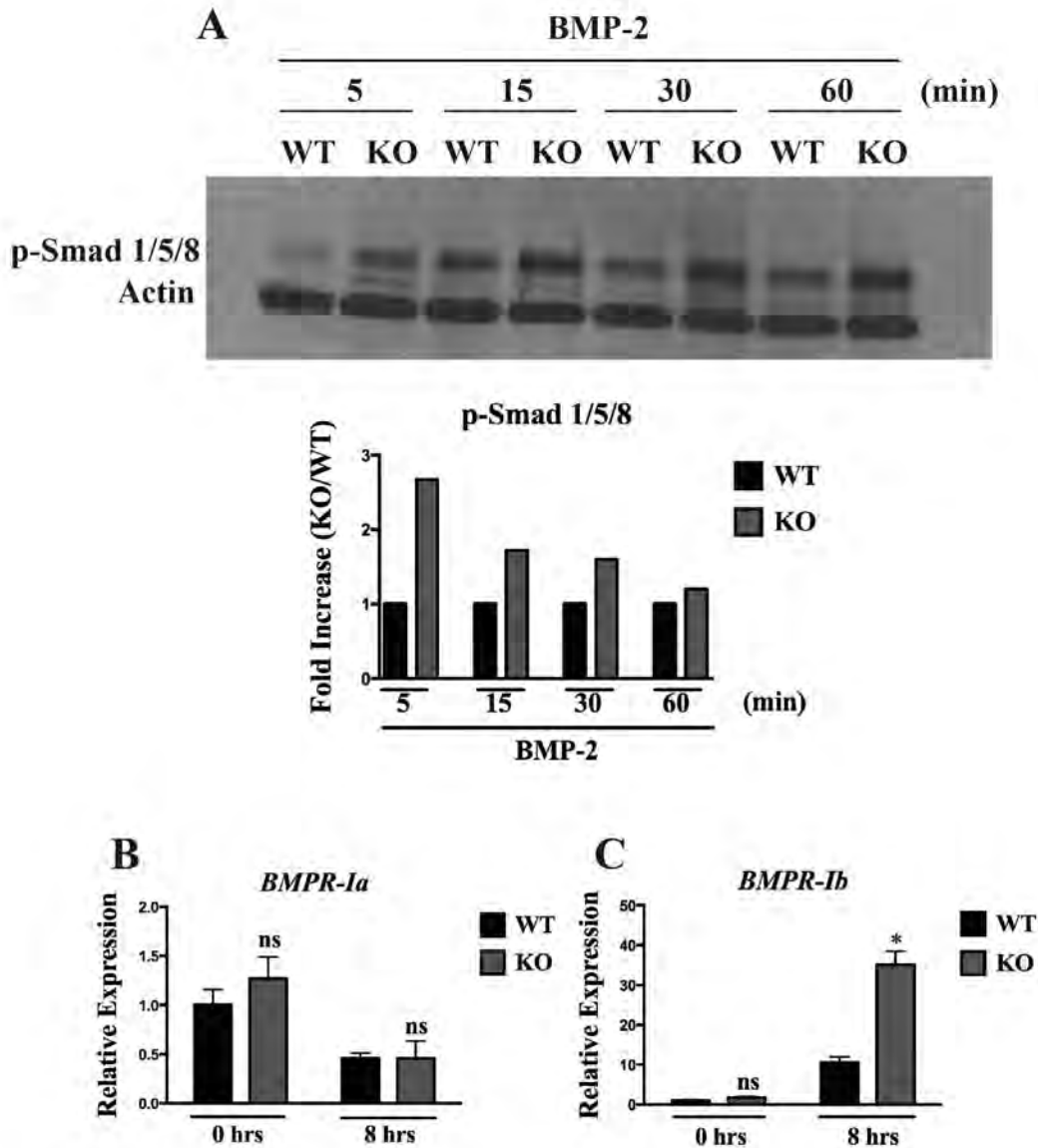


Figure 4. BMP signaling is increased in CTGF KO osteoblasts. Representative Western blot analysis using 15 µg total protein from WT and KO osteoblast cultures treated with BMP-2 for the indicated time points. (A) p-Smad 1/5/8 levels and quantification. p-Smad 1/5/8 expression levels were normalized to actin and data are expressed as fold increase compared to WT cultures at each timepoint. (B) mRNA expression levels of BMPR-1a in the absence and presence of BMP-2. (C) mRNA expression levels of BMPR-1b in the absence and presence of BMP-2. *P < 0.05. Abbreviations include bone morphogenetic protein receptor-1a (BMPR-1a) and bone morphogenetic protein receptor-1b (BMPR-1b).

A possible explanation for this decrease is at this time point the osteoblasts are forming mineralized nodules, and it is known that cellular levels of *Alp* mRNA decreases as the cultures progress into the mineralization phase.¹⁵

Since BMP-2 signals through the canonical Smad pathway, we evaluated levels of p-Smad 1/5/8 in WT and KO osteoblast cultures. We show that KO osteoblasts have increased levels of p-Smad 1/5/8, suggesting increased BMP signaling (Fig. 4A). Previous studies have shown that BMPR-1b plays a significant role in osteoblast differentiation. Primary osteoblasts derived from transgenic mice over-expressing a truncated dominant negative BMPR-1b under the type I collagen promoter exhibited impaired osteoblast

differentiation due to inhibition of BMP signaling.^{20, 21} We show that BMPR-1b is significantly up-regulated after treatment with BMP-2 in KO osteoblast cultures compared to WT osteoblast cultures. In contrast, addition of BMP-2 into WT and KO osteoblast cultures decreased the expression of BMPR-1a. This finding is consistent with a previous study, in which BMP-2 treatment of 2T3 cells, an osteoblast cell line, resulted in decreased expression of BMPR-1a during osteoblast differentiation.²⁰ Taken together, these findings suggest that the absence of endogenous CTGF results in an increase in BMP signaling through BMPR-1b, which activates Smads 1, 5, and 8, resulting in up-regulation of *Runx2* levels thereby accelerating osteoblast differentiation.

In conclusion, our findings are the first to demonstrate, through functional studies, a novel function of endogenous CTGF in regulating osteoblast development and function by inhibiting BMP signaling. The findings are consistent with earlier studies suggesting that CTGF can act to inhibit BMP-2 and BMP-4 by preventing the ligands from binding to its cognate receptor. Based on the observations made in this study, endogenous CTGF appears to inhibit the effects of BMP-2 on osteoblast differentiation. In the CTGF KO osteoblasts where this inhibition is absent, BMP-2 has an enhanced differentiation effect via increased Smad signaling presumably through the BMPRII-1b. This results in increased transcription of *Runx2* and other downstream factors required for osteoblast differentiation. This is a novel mechanism that warrants further investigation. How does endogenous production of CTGF regulate BMP-2 bioavailability and/or receptor levels? Based on our results, one would predict that use of the monoclonal anti-CTGF antibody, FG-3019, alone or in conjunction with BMP-2 treatment, may enhance bone formation in certain clinical scenarios (see Lambi and Popoff in this edition).

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Medical Student Research Project

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Spectrum of Vitamin D Deficiency in an Orthopaedic Outpatient Setting

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Abstract

Background: Vitamin D, otherwise known as the “sunshine vitamin,” is vital to the mineralization of healthy bone. The primary objective of this retrospective study is to examine the prevalence of vitamin D deficiency among symptomatic orthopaedic outpatients. The secondary objective is to identify risk factors that predispose individuals to becoming vitamin D deficient. Understanding these risk factors may offer valuable insight to the prevention and reversal of the vitamin D deficient state that plays a critical role in the development of osteomalacia, fracture, neuromuscular pain and extra-skeletal disease.

Methods: A retrospective review was conducted on 70 symptomatic outpatients seen at the orthopaedic clinic at Temple University Hospital between January and May of 2010. All patients with a vitamin D 25-hydroxy (25-OHD) test ordered were included. Correlations between serum 25-OHD concentration and patient age, gender, BMI, ethnicity and presenting orthopaedic symptom were evaluated for significance. A univariate and multivariate analysis of an ordinal logistic regression was performed.

Results: Vitamin D sufficiency (25-OHD ≥ 34 ng/mL) was present in only 11% of the orthopaedic outpatients. Thirty-one percent were deficient (25-OHD 11–20 ng/mL) and 29% were severely deficient (25-OHD ≤ 11 ng/mL). Vitamin D deficiency was significantly associated with younger age ($P = 0.0177$, OR = 0.964, CI 0.936–0.994), African-American ethnicity ($P = 0.0171$, OR = 6.245, CI 1.385–28.151), and chondromalacia of the patella ($P = 0.0283$, OR = 4.352, CI 1.169–16.208). Vitamin D status did not significantly differ between men and women ($P = 0.5475$) and did not significantly correlate with BMI ($P = 0.205$). In a multivariate model, only age and ethnicity were significant independent predictors of vitamin D deficiency.

Conclusions: Our findings suggest that vitamin D deficiency is very prevalent among orthopaedic outpatients. We propose that individual risk can be predicted using an algorithm based on age and ethnicity alone.

Introduction

Vitamin D is well known for its role in developing healthy bones. A century ago, it was discovered that this “sunshine vitamin” maintains the homeostasis between calcium and phosphorus, which is vital to bone mineralization. Classically, its deficiency state presents as rickets in children and osteomalacia in adults. It can also present with neuromuscular pain syndromes, muscle weakness and fractures secondary to decreased bone mineral density.^{1,2}

Over the last decade, however, vitamin D has been receiving new praise. Recent studies have revealed its cardioprotective effects in heart failure, anti-proliferative effects in cancer and immunomodulatory effects in multiple sclerosis, psoriasis, rheumatoid arthritis, inflammatory bowel disease and type I diabetes.³ In light of this new understanding, the potential extra-skeletal manifestations of an undiagnosed vitamin D deficiency are now of great concern.

The primary objective of our study is to determine the prevalence of vitamin D deficiency among symptomatic orthopaedic outpatients in North Philadelphia, PA. Our secondary objective is to identify risk factors that can predict a vitamin D deficiency. Higher levels of melanin seen in darker pigmented individuals act as a natural sunscreen, limiting cutaneous production of vitamin D. Thus, certain minority populations are predisposed to deficiency.⁴ We hypothesize that the spectrum of vitamin D deficiency in this predominantly African-American community with musculoskeletal complaints will show suboptimal concentrations of vitamin D.

Materials and Methods

A retrospective review was performed on 70 outpatients seen at the orthopaedic clinic at Temple University Hospital between January and May of 2010. All patients presenting with musculoskeletal symptoms who had a 25-hydroxy (25-OHD) test documented in their medical record were included in this study. If multiple studies were performed, only the first 25-OHD concentration was included. Patients receiving vitamin D supplementation at the time the 25-OHD concentration was measured were excluded.

Our primary outcome was to identify how many patients were vitamin D sufficient, insufficient, deficient and severely

deficient. Vitamin D status was determined by serum concentrations of total 25-OHD, which represents the sum of its two naturally occurring forms, ergocalciferol (25-OHD₂) and cholecalciferol (25-OHD₃). Total 25-OHD is a superior indicator of vitamin D status compared to its biologically active metabolite 1,25-(OH)₂D₃ calcitriol because its longer half-life more accurately reflects vitamin D stores obtained from sunlight and diet over longer periods.⁵ 25-OHD concentrations were measured using a Liquid Chromatography/Tandem Mass Spectrometry assay. There is currently no universal consensus as to what level of 25-OHD constitutes a deficiency.² The values we selected are based on our own orthopaedic practice (Table 1).

Table 1. Classification of Vitamin D Status by 25-OHD Concentration^a

Vitamin D Status	25-OHD Concentration
Sufficient	≥34 ng/mL
Insufficient	21–33 ng/mL
Deficient	11–20 ng/mL
Severely Deficient	≤10 ng/mL

^a25-OHD = 25-hydroxyvitamin D

Our secondary outcome was to determine the association between vitamin D deficiency and patient characteristics that included age, gender, body mass index (BMI), ethnicity and presenting orthopaedic symptom. BMI was calculated using heights and weights documented within a year of the 25-OHD test. Ethnicity was self-reported on the patient intake form. Orthopaedic symptom was identified by the International Classification of Disease (ICD-9) diagnosis corresponding to the office visit the 25-OH test was ordered. There were 12 categories of diagnosis including osteoarthritis, chondromalacia of the patella, loose body in knee, joint pain, rheumatism, dorsopathy, osteopathy and chondropathy, fracture, sprain, dislocation, contusion and surgical complication. In most cases, multiple diagnoses were recorded.

All demographic and clinical variables were analyzed statistically for a correlation with low levels of vitamin D at onset. Both univariate and multivariate analyses of an ordinal logistic regression were used to calculate odds ratios (OR) with 95% confidence intervals (CI). All P values less than 0.05 were considered significant.

Results

Vitamin D sufficiency (25-OHD ≥34 ng/mL) was present in only 11% of the orthopaedic population. Thirty-one percent were deficient (25-OHD level 11–20 ng/ml) and 29% were severely deficient (25-OHD ≤11 ng/mL).

Vitamin D deficiency was significantly associated with younger age (P = 0.0177), African-American ethnicity (P = 0.0171) and chondromalacia of the patella (P = 0.0283) on univariate analysis (Table 2). Older patients were 4% less likely to be deficient than younger patients (OR = 0.964, CI

Table 2. Univariate Analysis of Risk Factors for Vitamin D Deficiency^a

Risk Factor	P value ^b	Odds Ratio	95% Confidence Limits	
Age	0.0177	0.964	0.936	0.994
Gender	0.5475	1.365	0.495	3.763
African-American	0.0171	6.245	1.385	28.151
Caucasian	0.1443	0.248	0.038	1.612
Body Mass Index	0.2050	1.044	0.977	1.115
Osteoarthritis	0.9009	0.944	0.382	2.331
Chondromalacia Patellae	0.0283	4.352	1.169	16.208
Loose Body	0.4841	0.473	0.058	3.854
Joint Pain	0.1003	2.214	0.858	5.724
Rheumatism	0.7124	0.823	0.293	2.313
Osteopathy	1.0000	1.000	0.264	3.782
Chondropathy	0.1800	2.564	0.647	10.158
Fracture	0.9863	0.990	0.309	3.168
Sprain	0.1612	0.333	0.071	1.551
Dislocation	0.1149	2.470	0.803	7.598
Contusion	0.0871	0.088	0.005	1.425
Surgical Complication	0.1443	0.248	0.038	1.612

^aOutcome measured was vitamin D deficiency

^bP value of <0.05 is significant

0.936–0.994). African-American patients were six times more likely to be deficient (OR = 6.245, CI 1.385–28.151), and patients diagnosed with chondromalacia of the patella were four times more likely to be deficient (OR = 4.352, CI 1.169–16.208). Vitamin D status did not significantly differ between men and women (P = 0.5475) and did not significantly correlate with BMI (P = 0.205). In a multivariate model, only age (P = 0.018, OR = 0.964, CI 0.936–0.994) and African-American ethnicity (P = 0.0153, OR = 6.541, CI 1.433–29.857) were significant independent predictors of vitamin D deficiency.

Using the multivariate model, we formulated an algorithm that predicts individual vitamin D status (Table 3). Probability of deficiency can be calculated by substituting the patient’s age and ethnicity (“1” if African-American, “0” if not African-American) into the equation. For example, a 50-year-old African-American will have a 6.27% chance of being vitamin D sufficient, a 24.7% chance of being insufficient, a 37% chance of being deficient and 32% chance of being severely deficient. Therefore, the probability that this middle-aged African-American patient has sub-optimal levels of vitamin D exceeds 90%.

Discussion

The purpose of our study was to describe the spectrum of vitamin D deficiency among orthopaedic outpatients at Temple University Hospital in North Philadelphia, PA. This patient population represents a specific high risk group, namely African Americans living in an urban community. We found African-American status to be a statistically significant predictor of vitamin D deficiency on both univariate and multivariate analysis.

Previous studies looking at this high-risk population have drawn similar conclusions. In a study conducted at Fox

Table 3. Individual Prediction Algorithm for Vitamin D Status

Probability of being Sufficient (PROB S) ^a	$\frac{e^{-2.647} + .0364 [AGE] - 1.878 [AA]}{1 + e^{-2.647} + .0364 [AGE] - 1.878 [AA]}$
Probability of being Insufficient (PROB I)	$\frac{e^{-.7447} + .0364 [AGE] - 1.878 [AA]}{1 + e^{-.7447} + .0364 [AGE] - 1.878 [AA]} - (\text{PROB S})$
Probability of being Deficient (PROB D)	$\frac{e^{0.8116} + .0364 [AGE] - 1.878 [AA]}{1 + e^{0.8116} + .0364 [AGE] - 1.878 [AA]} - (\text{PROB I}) - (\text{PROB S})$
Probability of being Severely Deficient (PROB SD)	$1 - (\text{PROB D}) - (\text{PROB I}) - (\text{PROB S})$

^aFor each patient, substitute their age into [AGE] and 1 into [AA] if they are African American or 0 into [AA] if not African-American.

Chase Cancer Center on adult African-American men living in North Philadelphia, 61% were found to have 25-OHD levels below 15 ng/mL, with a mean of 13.7 ng/mL.⁶ Data from the National Health and Nutrition Examination Survey (NHANES III) demonstrated a significantly higher prevalence of vitamin D deficiency in minority populations when compared to white populations.⁷ In a study published by the Mayo Clinic at an inner-city health center in Minneapolis, deficiency (25-OHD <20 ng/mL) was seen in 100% of African-American patients and 93% of patients presenting with persistent musculoskeletal pain.⁸ Similar data has been published for minority pediatric populations living in low-income, urban areas.^{9,10}

Older age significantly decreased individual risk for being vitamin D deficient on univariate and multivariate analysis. The Mayo Clinic has described similar findings.⁸ Other studies, in contrast, report a high prevalence of vitamin D deficiency in the elderly due to reduced sunlight exposure, decreased efficiency of cutaneous production, poor nutritional intake and decreased renal metabolism.¹¹

Chondromalacia of patella was a statistically significant predictor for vitamin D deficiency on univariate analysis. To our knowledge, this relationship has not been published in other studies. Chondromalacia of patella is characterized by anterior knee pain secondary to soft-tissue swelling of the patellar cartilage of unclear etiology.¹² Surgery remains the current standard of treatment, yet some patients do not experience complete resolution of symptoms. Our findings suggest a potential therapeutic role for vitamin D supplementation in these patients.

Gender and BMI were not found to be significantly related to a vitamin D deficient state. Women, especially postmenopausal women, are at high risk for becoming deficient.^{7,13} The relationship between vitamin D deficiency and determinants of obesity such as BMI, waist circumference and metabolic syndrome remain controversial.^{14,15}

There are some limitations of our study. First, the ICD-9 diagnosis might not reflect prior or chronic orthopaedic issues of the patient. Second, we only included patients seen from January through May of 2010. Data collection year-round could improve our study as 25-OHD concentrations exhibit seasonal variation.¹⁶ Third, we did not exclude other

patient populations considered at risk for vitamin D deficiency including those with chronic kidney disease, liver disease, hyperthyroidism, HIV and burn injury.¹

Our study is unique in that we have developed an algorithm that predicts where an individual would fall on the spectrum of vitamin D deficiency using age and ethnicity as variables. The potential value of this study to be used as a screening tool in outpatient clinics serving inner-city populations is profound. Vitamin supplementation is safe and relatively inexpensive — a cost-effective way to prevent and reverse a deficiency state that has been implicated in the pathogenesis of disease affecting almost every organ system in the body. We hope our simple algorithm can be adopted and utilized by the medical community in order to enhance awareness to this rising condition and potentially identify symptomatic individuals at risk.

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Medical Student Research Project

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Complications of FiberWire Fixation of Achilles Tendon Ruptures: A Case Series

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Abstract

Background: Temple University Hospital successfully repairs many Achilles tendon ruptures surgically. However, we feel obligated to report two unusual cases where patients experienced suture and skin breakdown after otherwise successful surgeries. In both cases, FiberWire sutures were used. The purpose of this study is to document these two cases and to conduct a systematic literature review.

Methods: Two patient charts were reviewed with their consent and IRB approval. A systematic literature review was conducted using MEDLINE and Cochrane Database.

Results: After surgical repair, both patients developed late wound dehiscence and purulent drainage from the wound site. In one case (Case 2), the tendon repair completely broke down. There was an excessive amount of hypergranulation tissue in both cases, possibly indicating a foreign body reaction.

Conclusions: FiberWire is commonly used in many orthopedic procedures, but to our knowledge, complications have only been seen in Achilles tendon repair. Our current hypothesis is that the superficial locations of FiberWire sutures in Achilles tendon repair may contribute to wound breakdown based on our findings and published literature.¹⁸ We hope that our article prompts additional reporting of FiberWire-associated complications in Achilles tendon repair as well as the pathophysiology of FiberWire breakdown.

the literature whether non-operative or operative treatment is most effective for the treatment of this injury. The goal of treatment is to restore normal strength, full ankle range of motion, normal function, and minimize complications of weakness, re-rupture, infection, and disability.⁴⁻⁸ The most current meta-analysis of 14 randomized controlled trials favored operative intervention as the re-rupture rate was significantly lower with surgical treatment.⁹ Surgical intervention does allow accelerated rehabilitation, earlier weight bearing, and earlier return to work as compared to traditional casting protocols.¹⁰⁻¹³

While there is no universal agreement as to what suture is best for fixing Achilles tendon ruptures, most American surgeons prefer braided, non-absorbable sutures.¹⁴ These include braided polyethylene (Ethibond®) and braided polyblend polyethylene sutures (FiberWire®, Orthocord®, Ultrabraid®). Laboratory experiments have demonstrated that FiberWire suture has superior tensile strength over Ethibond.¹⁵⁻¹⁷ FiberWire (Arthrex, USA) was one of the first high tensile strength sutures developed and has been used extensively by orthopedic surgeons for a variety of orthopedic procedures including rotator cuff repairs, quadriceps and patellar tendon repairs, and Achilles tendon repairs. Its core is made of ultra-high molecular weight polyethylene, surrounded by a braided polyester jacket, and it is then externally coated with silicon.¹⁸ Although surgical treatment has many advantages as noted above, there are also potential complications as with all operations. The major risks associated with Achilles tendon repair center on deep infection and skin healing problems, accentuated by the superficial position of the tendon beneath the skin and lack of soft tissue coverage.⁴⁻⁸ Most tendon ruptures occur in the hypovascular zone 2 to 6 centimeters above the tendon insertion site on the calcaneus.² This site has very little subcutaneous coverage and may explain some of the reasons for the complications that are seen after operative repair. Previous laboratory studies have documented higher bacterial adherence in braided non-absorbable sutures than in nonbraided sutures.¹⁹ Some studies have shown higher rates of bacterial ingrowth with FiberWire compared to Ethibond;¹⁹ others have shown chronic inflammation *in vivo* with FiberWire.¹⁸ The purpose

Introduction

Acute Achilles tendon rupture is a common injury in adults. The estimated incidence is 5.5–9 ruptures per 100,000 people in North American adults,¹ is most common in males in the third and fourth decade, and has a high prevalence during sporting activities.¹ Diagnosis is usually readily apparent by physical exam including decreased plantar flexion strength, a palpable gap at the site of the rupture, and a positive Thompson test.¹⁻³ Occasionally, an MRI may be needed to aid in the diagnosis. There still exists some controversy in

of this study is to present two cases of delayed infection after Achilles tendon repair with FiberWire. This report may raise awareness in the orthopedic community of potential issues with this suture material.

Materials and Methods

After obtaining IRB approval, patient charts for the two cases were collected retrospectively with their consent. The entire history, operative notes, postoperative visits, and pathology reports after reoperation were all analyzed. A literature review using MEDLINE and the Cochrane Library was also conducted.

Case Series

One patient (Case 1), a 24-year-old male, ruptured his right Achilles tendon and had a surgical repair in California. He had no immediate problems, but nine months postoperatively, he presented to the clinic complaining of pain and wound problems. Physical exam then showed no palpable gap in the tendon and a negative Thompson's sign, but he did exhibit wound breakdown with excessive granulation tissue. He was subsequently taken to surgery where suture remnants were removed, cultures were taken, and a cast was applied. Wound cultures grew Methicillin resistant staphylococcus aureus and appropriate IV, then oral, antibiotics were prescribed. Local wound care and cast changes led to slow, but eventual wound healing. Range of motion and strength returned over 2–3 months and the patient eventually returned to full function.

The second patient (Case 2) was a 47-year-old male who ruptured his right Achilles tendon stepping off a street curb. He had the classic physical findings of a palpable gap, positive Thompson sign, and weakness of plantar flexion strength. He had no associated medical diseases such as previous steroid injections, use of fluoroquinolone antibiotics, or preexisting foot or ankle structural abnormalities.^{2,3} He did have poorly controlled hypertension, which was stabilized preoperatively. He elected to undergo operative repair and this procedure was done at Temple University Hospital using #2 FiberWire sutures with a Krackow type suture repair. He was casted postop in equinus and then started on our standard postop rehabilitation program at the two-week mark, when the cast was removed and replaced with a CAM boot with a variable angle ankle joint. He had no postop wound problems and was walking in shoes with a silicone rubber heel insert without difficulty. Three months postop, he returned to the clinic with pain, swelling, and drainage from his posterior heel wound. Unfortunately, his blood pressure then was significantly elevated and could not be adequately controlled and thus, only a limited incision and drainage could be done under local anesthesia with sedation. Wound cultures grew MRSA and appropriate antibiotics were administered. The wound did not heal and he

underwent successful split thickness skin grafting to the wound. He did regain full ankle motion and strength over several months and did eventually return to work.

Discussion

Postoperative infection is a known complication of all operative procedures, but the delayed onset of these infections and the severity of the complications in our patients made these cases notable. Neither of our patients had contributory medical conditions, both were compliant with the postop rehabilitation regimen, and both developed significant problems more than three months after their operative procedures.

There is a paucity of literature documenting the complications of FiberWire suture in otherwise successful surgeries. A systematic literature search using MEDLINE and the Cochrane Library yielded only one case series.¹⁸ Five Army soldiers, who underwent transtibial or transfemoral amputations after severe trauma, developed wound problems in their stumps after fascial closure with FiberWire sutures. These complications included sinus tract formation, clear wound drainage, and amorphous tissue formation around the sutures. Pathologic examination of the suture material and granulation tissue revealed multinucleated giant cells that had engulfed the silicone outer coating of the sutures. One culture grew MRSA. The sutures were removed and replaced with Ethibond sutures and the wounds healed.¹⁹ The common symptoms in the previously mentioned case series and ours included delayed wound healing and chronic inflammatory reaction. Both of our wounds became infected with MRSA. Removal of the suture remnants, IV antibiotics, and aggressive local wound care did lead to eventual healing in all patients.

FiberWire is used in a variety of orthopedic procedures due to its increased strength and lower rate of breakage.^{15–17} We have not frequently seen these severe healing problems in shoulder, elbow, or quadriceps tendon repairs. We, therefore, feel that the superficial position of the Achilles tendon repair may contribute to an enhanced inflammatory response. Also, the giant cell inflammatory response seen in response to the silicone outer covering of FiberWire has been seen before with silicone spacers used in radial head and great toe implants in sensitive patients. We do not know why certain patients are more likely to develop these hypersensitivity reactions and this issue needs further investigation. These issues, however, do point out the need to reevaluate the use of FiberWire sutures in Achilles tendon repairs and to consider possible use of less reactive sutures in this area.

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Nerve and Tendon Injury with Percutaneous Fibular Pinning: A Cadaveric Study

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Abstract

Objective: The purposes of this study were to measure the average distance from a percutaneous pin in each quadrant of the distal fibula to the sural nerve and nearest peroneal tendon, and define the safe zone for pin placement as would be used during surgery.

Method: Ten fresh-frozen cadavers underwent percutaneous pin fixation into four quadrants of the distal fibula. The sural nerve and peroneal tendon were identified as they coursed around the lateral ankle. Distances from the K-wire in each quadrant to the anatomic structure of interest were measured.

Results: Average distances (mm) from the K-wire to the sural nerve in the anterolateral, anteromedial, posterolateral, and posteromedial quadrants were 19.1 ± 8.9 (range, 5.1–35.5), 12.8 ± 8.2 (range, 0.3–27.8), 12.6 ± 6.8 (range, 3.0–27.8), and 5.9 ± 5.5 (range, 0.1–19.9), respectively. Average distances from the K-wire to the nearest peroneal tendon in the anterolateral, anteromedial, posterolateral, and posteromedial quadrants were 15.7 ± 4.4 (range, 9.5–23.1), 11.9 ± 5.2 (range, 3.2–21.7), 6.3 ± 3.9 (range, 0.1–14.4), and 1.0 ± 1.6 (range, 0–5.6), respectively.

Conclusions: Percutaneous pinning of distal fibula fractures is a successful treatment option with minimal complications. Our anatomical study found the safe zone of percutaneous pin placement to be in the anterolateral quadrant. The sural nerve can be as close as 5.1 mm and the peroneal tendons as near as 15.7 mm. In contrast, the posteromedial quadrant was associated with the greatest risk of injury to both the sural nerve and peroneal tendons.

Introduction

Distal tibia and fibular fractures are frequently treated with open reduction and internal fixation of the tibia and fibula, with fibular fixation typically consisting of plate and screw fixation.¹ With tibial pilon fractures and some extra-articular distal tibia fracture patterns, the fibular fracture often does not involve the ankle joint, and the surgeon has to decide whether or not fibular fixation is needed.² Unfortu-

nately, soft tissue concerns with these injuries may preclude fibular plating, or lead to wound complications when plating is done through usual extensile incisions. Closed reduction and percutaneous pinning is a surgical treatment option for displaced distal fibular fractures and segmental distal fibular fractures.^{3–5} Percutaneous pinning is a successful treatment method for elderly patients and those with multiple medical comorbidities who are prone to wound complications and osteoporotic bone such as diabetics and chronic steroid users.^{5–8} The percutaneous technique avoids significant stripping of the soft tissue envelope and provides lateral column stabilization. In the absence of fibular fixation in concomitant distal tibia fractures, there is destabilization of the lateral column depending on fracture configuration and associated ankle injuries. Further, the fibula fracture has the potential to affect tibial length, alignment, and rotation.^{2, 3} This ultimately can affect functional outcome, tibial malunion rate in combined tibia-fibula fracture, and post-traumatic ankle arthrosis.^{9, 10}

The goals of fibular pinning or an intramedullary rod are to improve bending stability of the tibia and fibula fractures, and to some degree, maintain fibular length. Because this is often done as a percutaneous method, the peroneal tendons and sural nerve are at risk for injury. Furthermore, we have noted that the incidence of painful implants is not insignificant in our practice, potentially in part due to irritation of nearby anatomic structures. The proximity of percutaneously-placed fibular pins to the nearby structures, namely the peroneal tendons and sural nerve, has not been described. The purpose of this anatomic study is to measure the distance from the percutaneous pin in the distal fibula to these anatomic structures and define the safe zone for pin placement correlated with fluoroscopic images as would be used during surgery.

Materials and Methods

Ten fresh-frozen cadaver lower extremities with an average age of 78 years (range, 57–95 years) were dissected after percutaneous pinning of the distal fibulas. All procedures were performed on left fibulas from six female and four male cadavers in the prone position and ankles in the resting equinus position. Plantar flexion angles were measured with a

goniometer for each cadaver and averaged 33.8 degrees (range, 17–51 degrees). No cadavers had evidence of lower extremity bony disease or trauma. Under mini C-arm fluoroscopic guidance, four Kirschner wires (K-wires) (1.1 and 2.0 mm) were inserted with a Small Battery Drive drill (Synthes, West Chester, PA).

One orthopaedic trauma-trained fellow performed all percutaneous pin placements. K-wires were inserted through the skin 1 to 2 cm distal to the tip of the lateral malleolus and directed towards and parallel to the intramedullary canal as in standard approach for fibular intramedullary fixation. One K-wire was placed into each of four different quadrants of the distal fibula and verified by anteroposterior and lateral fluoroscopic imaging. The four quadrants as viewed from the axial plane were defined as anteromedial, anterolateral, posteromedial, and posterolateral (Figures 1 and 2). A chief-level orthopaedic surgery resident dissected the lateral ankle after all four pins were inserted. The dissection and percutaneous pinning was supervised by one orthopaedic trauma fellowship-trained attending.

Each cadaveric dissection was performed without disrupting local anatomy and included identification of the sural nerve and its branches (SN), and the peroneal tendons (PT). Using a single incision, the PT were dissected from approximately 5 cm proximal to the lateral malleolus to an area several centimeters distal to the K-wires along the lateral border of the foot. The shortest distance from the center of each K-wire to the closest section of the sural nerve, whether a branch or the nerve proper, was measured with a Brown & Sharpe caliper (Dial-Cal Metric Model no. 599-579-14; North Kingstown, RI). Distances to the nearest tenth of a millimeter were recorded. The same procedure was repeated for PT, measuring the shortest distance between each K-wire and the nearest tendon. K-wires that penetrated the sural nerve or peroneal tendons were given a distance of 0 mm and wires that abutted against these structures were recorded as 0.1 mm. All measurements were performed and recorded by three different individuals. Measurements were then averaged and the range, standard deviation, and variance were calculated.

Results

The sural nerve and peroneal tendons were identified in all cadavers. The distances of the K-wire to these anatomical structures are summarized in Tables 1 and 2. Two of the 10 K-wires in the posteromedial quadrant (PM-Q) were found to be abutting the sural nerve. In four of the 10 specimens, the PM-Q K-wire was found to be piercing the peroneal tendons and in three separate specimens abutting the tendons as they curved anteriorly around the distal fibula. The PM-Q K-wire was an average distance of 5.9 mm (range, 0.1 [abutting the nerve]–19.0 mm; SD 5.52) from the sural nerve and an average of 0.96 mm (range, 0 [piercing the tendon]–5.6 mm; SD 1.61) from the peroneal tendons.

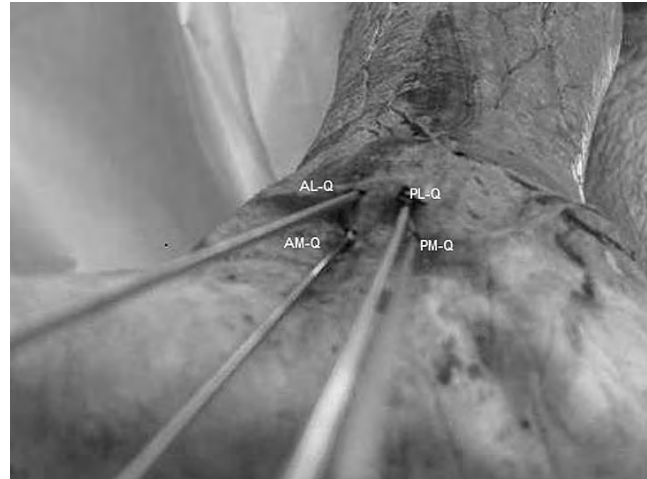


Figure 1. Axial view of K-wire placement in distal fibula of left cadaver leg. AL-Q = anterolateral quadrant; AM-Q = anteromedial quadrant; PL-Q = posterolateral quadrant; PM-Q = posteromedial quadrant.

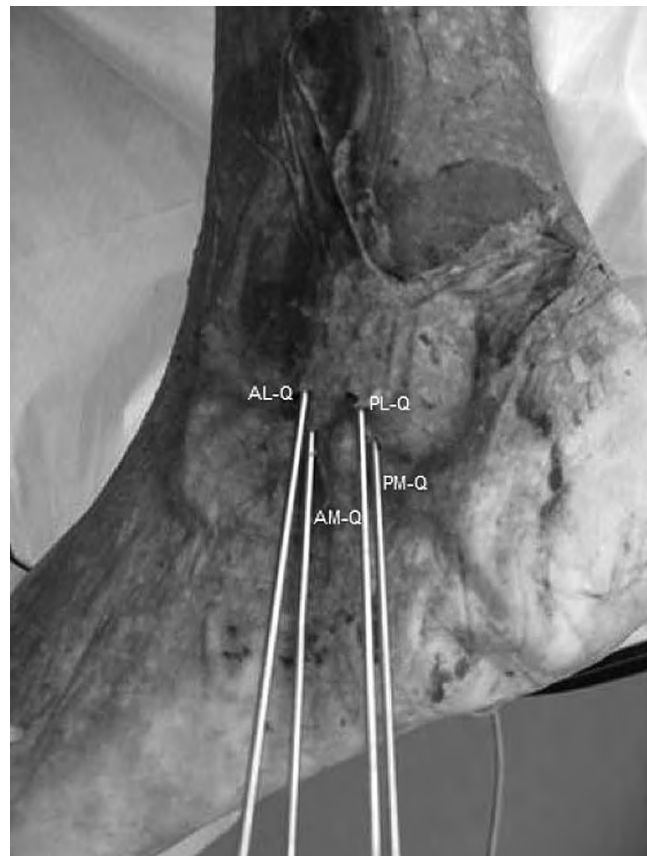


Figure 2. Lateral view of K-wire placement in resting plantar flexion.

In one of 10 cadavers, the K-wire abutted the peroneal tendons during insertion into the posterolateral quadrant (PL-Q); the average distance between PL-Q K-wire and the tendons was 6.3 mm (range, 0.1–14.4 mm; SD 3.9). In one cadaver, the PL-Q K-wire was only 3 mm from a branch of the sural nerve and the average distance from wire to sural nerve was 12.56 mm (range, 3–27.8; SD 6.82).



Figure 3. Lateral fluoroscopic image of K-wires after insertion into distal fibula.

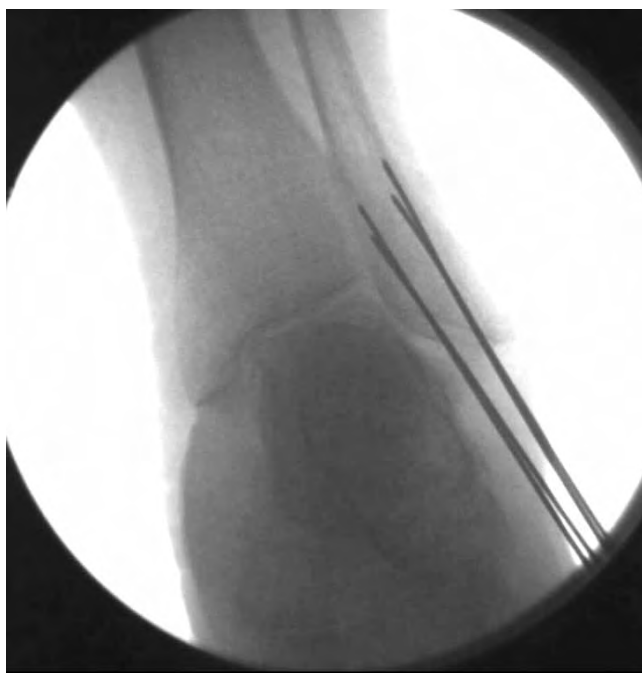


Figure 4. Anteroposterior fluoroscopic image of left ankle showing K-wires in four quadrants.

No K-wires in the anteromedial quadrant (AM-Q) contacted the nerve or tendons, although in one cadaver the wire was only 0.3 mm from a branch of the sural nerve. The average distance between AM-Q K-wire and nerve was 12.82 mm (range, 0.3–27.8; SD 8.22). K-wires were an average distance of 11.92 mm (range, 3.2–21.7 mm; SD 5.2) from the peroneal tendons.

Table 1. Distances and Injury to Sural Nerve After K-wire Placement into Four Quadrants of Distal Fibula

Quadrant	Avg.	Min–Max	SD	Variance	# Pierced or Abutted	% Injured
Anterolateral	19.1	5.1–35.5	8.9	80.1	0	0
Anteromedial	12.8	0.3–27.8	8.2	67.6	0	0
Posterolateral	12.6	3.0–27.8	6.8	46.5	0	0
Posteromedial	5.9	0.1–19.0	5.5	30.5	2	20

Distances are in millimeters.

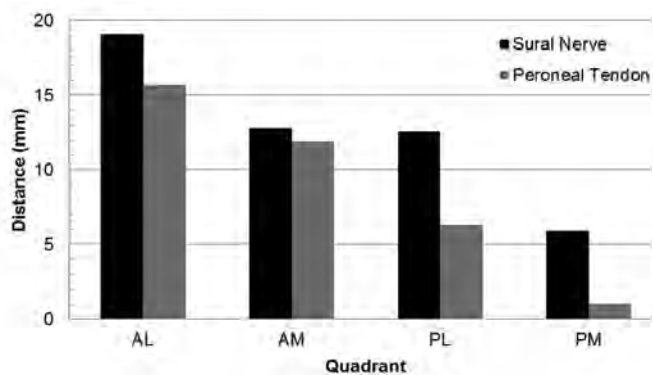
Table 2. Distances and Injury to Peroneal Tendon After K-wire Placement into Four Quadrants of Distal Fibula

Quadrant	Avg.	Min–Max	SD	Variance	# Pierced or Abutted	% Injured
Anterolateral	15.7	9.5–23.1	4.4	19.1	0	0
Anteromedial	11.9	3.2–21.7	5.2	27.0	0	0
Posterolateral	6.3	0.1–14.4	3.9	15.5	1	10
Posteromedial	1.0	0–5.6	1.6	2.6	7	70

Distances are in millimeters.

The anterolateral quadrant (AL-Q) K-wires were the furthest from the sural nerve with an average distance of 19.1 mm (range, 5.1–35.5 mm; SD 8.95). Distances measured in this quadrant exhibited the greatest variability among quadrants. Similarly, no tendons were abutted or pierced when K-wires were inserted in this quadrant (average distance, 15.65 mm; range, 9.5–23.1 mm; SD 4.37).

Figure 5. Average Distance from K-Wire in Each Quadrant of Distal Fibula to Sural Nerve and Nearest Peroneal Tendon



AL = anterolateral, AM = anteromedial, PL = posterolateral, PM = posteromedial.

Discussion

The fundamental advantage of fibula fixation in certain isolated fibula fractures and in combined distal tibia-fibula fractures is well established.¹⁰ Intramedullary fibula fixation is a successful surgical option in patients with potential for poor wound healing, soft tissue damage, osteoporotic bone, segmental or fragility fractures, open fractures and elderly patients.⁵ Percutaneous pinning of the fibula is a more minimally invasive option than open reduction internal fixation, with limited incisions and less prominent implants. Pub-

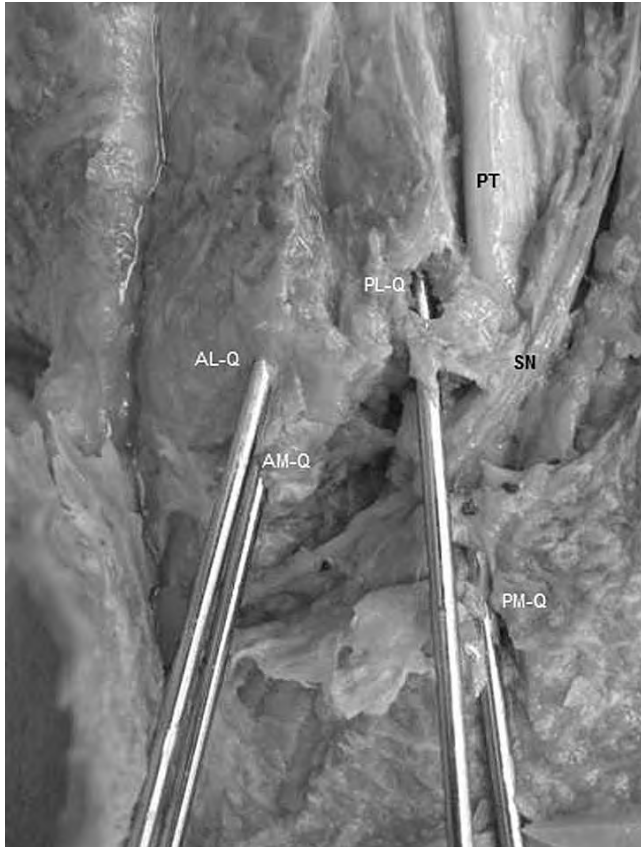


Figure 6. Dissected cadaver specimen with K-wires in each quadrant and identification of SN and PT.

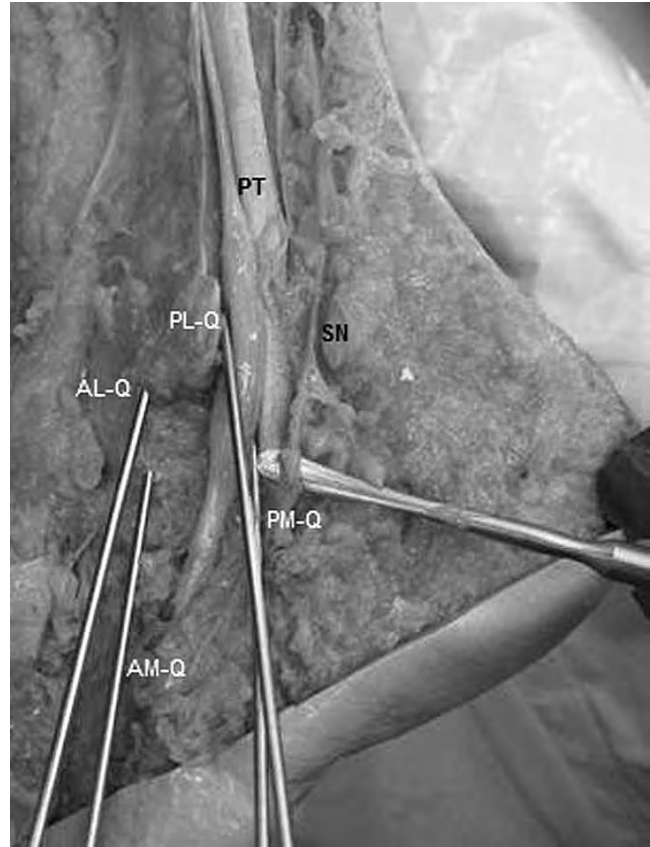


Figure 7. Dissected specimen with K-wires in all four quadrants and identification of SN and PT. Note proximity of posterolateral and posteromedial K-wires to nerve and tendon.

lished studies for intramedullary fibular fracture fixation describes the starting point to be at the distal tip of the lateral malleolus or 2 mm medial to the distal tip.^{1,4-6,11} However, the starting point in relation to anatomic structures has not been described. The rate and morbidity of sural nerve and peroneal tendon injury and irritation from intramedullary fibula fixation has also not been previously reported.

Indications for intramedullary fibula fixation include segmental or axially stable fractures, open fractures, fragility fractures, patients with potential healing problems or soft tissue damage and any displaced ankle fracture that involves the lateral malleolus.³⁻⁶

Our cadaveric study looked at pin placement starting at the distal tip of the lateral malleolus in four different quadrants — anteromedial, anterolateral, posteromedial and posterolateral. The posteromedial quadrant starting point was the most dangerous with regard to injury of the peroneal tendons and/or sural nerve. Twenty percent (2/10) of cadavers had pins that abutted the sural nerve and 70 percent (7/10) cadavers had pins that pierced or abutted the peroneal tendons. The posterolateral quadrant was the second riskiest location for intramedullary wire placement. Ten percent (1/10) of cadavers had pin placement next to the peroneal tendon and there was no injury to the sural nerve with an average distance of 12.6 mm.

Our anatomic study found the safe zone for the starting point in percutaneous pinning of the distal fibula to be in the anterolateral quadrant of the lateral malleolus. The ideal pin orientation is parallel to the medullary canal. No cadavers had damage to the sural nerve or peroneal tendons in this group. The sural nerve was as close as 5.1 mm from the pin insertion point with an average distance of 19.1 mm. The peroneal tendons were as close as 9.5 mm from instrumentation with an average proximity of 15.7 mm.

Open fibular plating can be complicated by wound complications, particularly in high energy injuries, as well as by late complaints of painful implants. Wound complications from closed distal fibula fractures treated with open reduction internal fixation occur at a rate as high as 17.5%.^{12,13} Lee et al. compared pinning of the fibula with a Knowles pin to open reduction internal fixation. No patients treated with the pin had wound complications. The tubular plate fixation group had a wound complication rate of 13.3%.¹¹ There was no statistical difference in the rate of elective implant removal. No patients with the pin complained of pain due to the instrumentation; however 24 out of 45 patients opted for removal. Forty percent (12 out of 30 patients) of the plate fixation group complained of painful screws or plates and 18 of them elected for removal.¹¹ Brown et al. had a symptomatic plate/screw rate of 31% in 126 patients treated by open

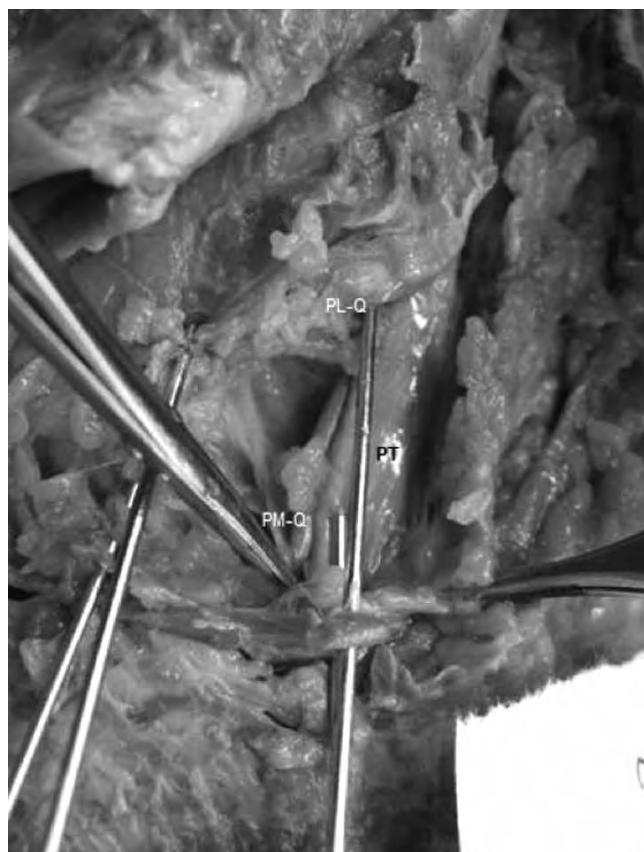


Figure 8. Dissected cadaver ankle specimen with pins in four quadrants and identification of SN and PT. Posteromedial quadrant pin is piercing peroneal tendons and abutting the sural nerve. Posterolateral quadrant pin is abutting the peroneal tendon.

plating.¹⁴ Bugler et al. reviewed 105 unstable ankle fractures treated with the Acumed fibular nail. The average patient age was 64.8 years and 76% had significant medical comorbidities. The lateral wound infection rate was 4.7% (five patients) and 15% (16 patients) required removal of the nail or screws.⁴ The locking screws were removed in nine patients and the fibular nail in seven patients.⁴ Appleton et al. treated 37 patients with unstable ankle fractures with a fibula intramedullary nail. The average patient age was 67 years and all of them had a medical comorbidity that compromised the skin on the lateral ankle; such as diabetes or chronic steroid use. One patient had a post-operative superficial infection of the lateral ankle that required irrigation and debridement in the operating room and a week of antibiotics.⁵ The patients average Olerud and Molander score was 87 out of 100 and 85% had ankle range of motion that was within 90% of the uninjured ankle at final follow-up.⁵

Rajeev et al. performed a retrospective review of 24 patients aged 71 to 91 years with fragility fractures and treated with intramedullary fibula fixation reported no wound complications, no non-unions or deep infections.⁶ The average union rate for fibula intramedullary fixation was 8.7 weeks.⁶ Pritchett studied functional outcome in Rush rods vs. plate osteosynthesis. The study had good to fair

functional outcomes in 88% of patients that underwent rush rods fixation compared to 76% of patients treated with open reduction internal fixation.⁷ The Rush rod group reached full weight bearing six weeks earlier than the open reduction internal fixation group.⁷

Although these several studies cited above indicate the utility of intramedullary fibular pinning as a treatment option for certain fractures, very little mention is made of the risks of nerve or tendon injury in their series. The clinical significance of smooth pin penetration of the sural nerve or peroneal tendons is not well described, but we believe that it is safe to assume that this could contribute to unexplained pain postoperatively. Larger diameter implants such as locked intramedullary nails marketed for distal fibular fixation do not provide any surgical technique suggestions for avoiding nerve or tendon injury. It is possible that careful evaluation in unexplained complaints of pain or limited motion postoperatively could possibly point to inadvertent injury as an etiology.

Weaknesses of our study involve the limitations with fixed (not fresh) cadaveric specimens. The ankles were in a fixed equinus position and unable to be manipulated during the percutaneous pinning. Therefore, our study was limited in observing what ankle position, in regards to the degree of plantarflexion and inversion, puts the anatomic structures furthest from the starting point. Another weakness of our study is the smaller instrumentation size. We used smaller diameter K-wires (1.1 and 2.0 mm) than the cannulated drills and reamers (range from 3.1–6.1 mm) used in the Acumed and Biomet fibular nail technique.^{4, 6, 8} Therefore, the safety zone for percutaneous pinning with a K-wire is theoretically larger than the safety zone for a 4.5 mm diameter rod. Furthermore, our cadaver study has no clinical follow-up. The possible complications of Kirschner wire migration, pin site infection and loss of reduction could not be addressed.

Percutaneous pinning of distal fibula fractures is a successful treatment option with minimal complications. Our anatomical study found the safe zone of percutaneous pin placement to be in the anterolateral quadrant. The sural nerve can be as close as 5.1 mm and the peroneal tendons as near as 15.7 mm.

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Does Intraoperative Fluoroscopy Improve Component Position During Anterior Hip Arthroplasty?

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Abstract

Objective: The goal of this retrospective review is to determine if fluoroscopic guidance improves acetabular cup abduction and anteversion alignment during anterior total hip arthroplasty.

Method: A single-center, case-control study of 199 patients (fluoroscopy group = 98, non-fluoroscopy group = 101) undergoing anterior hip arthroplasty. Acetabular cup abduction and anteversion angles were measured and compared between groups.

Results: The fluoroscopy group had mean abduction and anteversion angles of 43 and 23 degrees, respectively. The non-fluoroscopy group had mean abduction and anteversion angles of 46 and 23 degrees, respectively. Difference in acetabular abduction angle between groups was significant but radiographic anteversion was not significantly different.

Conclusions: A significantly higher percentage of acetabular cup abduction angles were in the safe zone in the fluoroscopy group. The percentage of cups in combined anteversion and abduction safe zones was higher in the fluoroscopy group. Use of fluoroscopy is not required for proper anteversion placement of acetabular components but may increase combined safe zone placement.

Introduction

In 1947, Robert Judet performed the first hip arthroplasty through an anterior approach at Hospital Raymond Poincare outside Paris. He originally named this the “Hueter” approach, which may have been a reference to Hueter Volkmann’s method for drainage of a hip infected with tuberculosis.²⁰ Today, it is commonly referred to as the Smith-Peterson approach. Over the years, this technique has been modified to allow exposure of the femur and pelvis with less soft trauma by avoiding release of any of the surrounding muscles from their bony attachments.

The direct anterior approach to total hip arthroplasty (THA) is a less invasive technique with the advantages of reduced soft tissue trauma, lower dislocation rate, and earlier improvement in function as compared to the posterior and anterolateral approaches.²² This can be performed with or without C-arm fluoroscopic guidance, but potential benefits

of an image intensifier include improved component positioning, longer implant survival, less wear, and better range of motion.²⁵

Acetabular orientation is critically important in the outcome of hip arthroplasty. Component positioning is related to impingement, stability, wear rates, and survivorship.²³ Poor cup positioning results in limited hip range of motion and undesired impingement. Kummer et al. suggest acetabular inclination between 35° and 45° and anteversion less than 20° for optimal hip range of motion.¹³ Increases in linear polyethylene wear of 40% occur with abduction angles of ≥45°. ²⁸ Avoiding malposition of components is crucial in reducing the occurrence of aseptic loosening and the incidence of THA revisions which is expected to double in the next 20 years, reaching an estimated 96,700.²³

In 1978, Lewinnek et al. described a safe zone for acetabular cup positioning of 15 ± 10° of anteversion and 40 ± 10° of abduction.¹⁴ In their review of 300 THA patients, the difference in dislocation rate was statistically less for subjects within the safe zones versus those outside of the defined safe zones (1.5% vs. 6%). Further studies have supported the importance of proper placement despite the varied consensus on safe zone parameters. In 1990, McCollum and Gray performed a prospective study of 441 THAs and reported a dislocation rate of 1.14%.²¹ They concluded that 30–50° of abduction and 20–40° of anteversion prevents dislocation and impingement. Safe zone recommendations vary from little or no anteversion to 40° and depend on method of THA fixation.^{6, 10, 14, 21, 24} Presently, it is accepted that ≤45° of acetabular abduction provides optimal stability and wear rates.¹⁸

To our knowledge, no studies have compared postoperative acetabular component positioning after anterior THA with and without fluoroscopy. Proposed disadvantages of fluoroscopy are increased operative times, radiation exposure to both the surgeon and patient, and field contamination.^{4, 29, 34} The goal of this retrospective review is to determine if fluoroscopic guidance improves acetabular cup abduction and anteversion, thus prompting the question, is fluoroscopy necessary?

Methods

A single-center, case-control study of 199 patients who underwent primary THA at a single institution were ran-

domly selected from the primary surgeon's case log. All patients were operated on by a single surgeon (A.S.). Patients for the non-fluoroscopy (NF) group were selected from the 2008 surgical log because the primary surgeon was not yet using fluoroscopy consistently during this time. Subjects for the fluoroscopy (FL) group were selected from the 2011 surgical log because fluoroscopy was routinely used for patients during that year. Fluoroscopy was used intraoperatively during reaming of the acetabulum and socket impaction with adjustments made until components were fully seated in the pelvis. Imaging was not used live to guide insertion. Components were adjusted if determined to be outside the safe zones and the same fluoroscopy procedure was repeated until the surgeon was satisfied with positioning. Safe zones were defined as an anteversion of $15 \pm 10^\circ$ and an abduction angle of $40 \pm 10^\circ$ as described by Lewinnek et al.¹⁴

Types of implants used in the FL group (n = 98) include Corail Total Hip Systems (n = 5, 5.4%) and Trilock Bone Preservation Systems (n = 87, 94.6%) (DePuy Synthes; Warsaw, IN). In the NF group (n = 101), Corail (n = 53, n = 54.1%), Summit Cementless Hip System (n = 4, 4.1%), and Trilock products (n = 41, 41.8%) were used (DePuy Synthes).

One researcher (a senior-level resident) measured acetabular cup abduction and anteversion angles on six-month postoperative anteroposterior (AP) pelvic radiographs. This was performed using the method described by Widmer and Ing which allows for obtaining angles from an AP pelvic x-ray (Figure 1).³⁵ Acetabular inclination was determined by drawing a line parallel to the tear drop and another line through the long axis of the acetabular ellipse. Anteversion was measured by dividing the short axis of the ellipse which reflects the cup opening by the total length of the cup and corresponding the ratio to the table or graph in Widmer and Ing's article.

Exclusion criteria were revision arthroplasty, periprosthetic fracture, metal-on-metal prostheses, and insufficient postoperative radiographs that would preclude proper acetabular measurements. After exclusion, 101 NF and 92 FL replacements were included in the study. Demographic data including age, body mass index (BMI), and gender were collected.

Data was combined to provide a mean, range, standard deviation, and p-value for each variable. Analysis of variance (ANOVA) was used to determine differences between variables. A p-value of ≤ 0.05 was used for statistical significance.

Results

Demographic data is displayed in Table 1. A significant difference ($p \leq 0.05$) in acetabular cup abduction between the FL and NF groups was found (Figure 2). The difference in anteversion angle between the two groups was not significant ($p = 0.875$). The FL group (n = 98) had mean abduction

and anteversion angles of 43.4 and 23.1 degrees, respectively. The NF group's (n = 101) mean abduction and anteversion angles were 45.9 and 23.1 degrees, respectively. Eighty-eight percent (n = 86) of acetabular cup abduction angles in the FL group fell within the safe zone ($30\text{--}50^\circ$) versus 72% (n = 73) in the NF group. Eight-six percent (n = 85) of anteversion angles in the FL group fell within the safe zone ($15 \pm 10^\circ$) versus 79% (n = 101) in the NF group.

The number of patients with components in safe zones for both anteversion and abduction were 78 (80%) in the FL group and 64 (63%) in the NF group. There was a trend toward greater combined safe zone placement in patients undergoing anterior THA with intraoperative image guidance.

Discussion

THA is one of the most successful procedures performed by orthopaedic surgeons. Anterior THA is the only approach that uses an internervous plane, which is between the superior and inferior gluteal nerves and the femoral nerve. The goal of this approach is to obtain immediate stability by sparing posterior muscle attachments. Surgical approaches and component positioning affect postoperative stability and function with the anterior approach being associated with earlier return to function, shorter hospital stay, and better perioperative outcome in some studies.^{1, 19, 23} Another benefit of the anterior approach is preservation of gluteal muscles in cases of future revision surgery that tend to be more difficult and invasive than primary arthroplasty.³

Acetabular component positioning affects patient outcomes after THA. Impingement, pelvic osteolysis, and bearing wear are all associated with suboptimal placement.^{7, 12, 23, 33} Patient-related outcomes are also affected by cup positioning. One example is leg length discrepancy (LLD). LLD after THA is a cause of postoperative morbidity due to limping, muscle strain, sciatic nerve palsy, and aseptic loosening.³² Additionally, it is a common cause of litigation in the United States.²⁷ Roder compared 478 cases of lengthening and 275 cases of shortening after THA with matched controls.³² Outcomes were ability to walk greater than 60 minutes, hip pain, limping, and patient satisfaction. Compared to controls, patients with lengthened extremities were more likely to not be able to walk for more than one hour, more likely to limp at follow-up, and more likely to not achieve excellent patient satisfaction scores (OR 1.70, 95% CI 1.28–2.26; OR 2.08, 95% CI 1.55–2.8; and OR 1.67, 95% CI 1.23–2.38; respectively). In the shortened group, the odds ratios for these same parameters were 1.23 (95% CI 0.84–1.81), 2.61 (95% CI 1.78–3.21), and 2.15 (95% CI 1.44–3.21), respectively. LLD is associated with significant patient dissatisfaction and is largely preventable by surgeon technique.

Leg length differences from our patient cohort are not reported although LLD in patients after anterior THA have been reported in the literature. Matta's series of 437 patients

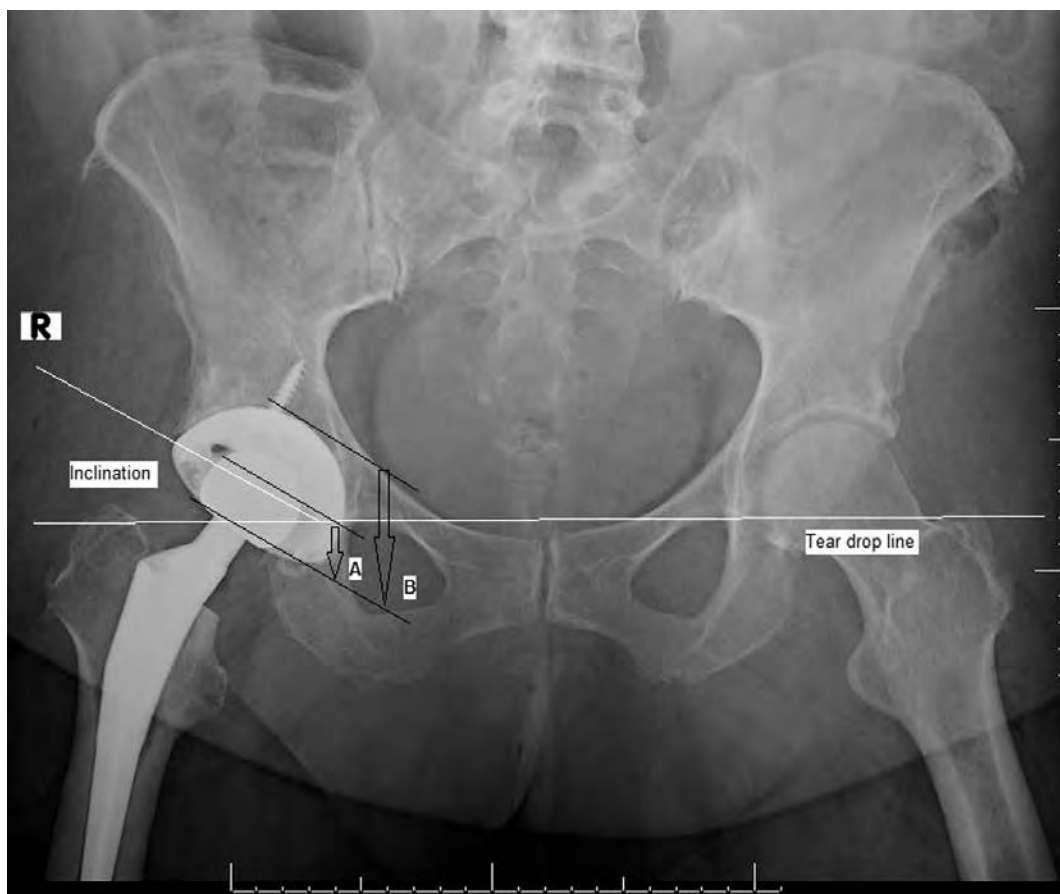


Figure 1. Technique for measuring inclination and anteversion. Inclination is the angle formed by a line parallel to the tear drop and a line running through the long axis of the ellipse. Anteversion is measured by dividing the width of the ellipse (A) by the total length of the cup (B).

Table 1. Comparison of Demographic Data and Radiographic Measurements for Anterior THA

	Fluoroscopy (n = 98)	Non Fluoroscopy (n = 101)	p-value
Age			0.017
Mean	69	66	
Range	40–91	45–86	
Std. Dev.	9.4	10.3	
BMI			0.005
Mean	28.1	25.8	
Range	18.8–43.2	20.1–42.8	
Std. Dev.	4.9	4.5	
Abduction			0.002
Mean	43.4	45.9	
Range	31–59.9	32.7–61.6	
Std. Dev.	4.9	6.3	
Anteversion			0.876
Mean	23.1	23.1	
Range	17–28	18–29	
Std. Dev.	4.9	2.24	

(494 hips) undergoing fluoroscopic-guided, primary anterior THA showed an average postoperative LLD of 3 ± 2 mm (range, 0–26 mm) and the author reported enhanced accuracy of leg lengths with the help of imaging.¹⁹ Fifty-eight percent (n = 287) of the hips had LLD between 0–2 mm and all four of the patients with greater than 11 mm postopera-

tive leg length inequality had preoperative LLD greater than 15 mm and hip dysplasia. To our knowledge, no studies comparing postoperative LLD between patients receiving anterior THA with and without fluoroscopy exist.

A serious concern is component positioning outside of safe zones. Malpositioning results in impingement and edge loading thereby accelerating polyethylene wear rates in metal-on-polyethylene THAs and increasing serum levels of metal ions after metal-on-metal THA.⁷ The clinical implications of wear debris are numerous despite absence of long-term clinical data. Wear debris are thought to be involved in the development of pseudotumors, iliopsoas bursal cystic lesions, vascular compression, loosening, and fractures.^{2, 18} Polyzois reviewed several animal studies and found adverse effects of metal ions released from joint arthroplasty materials on several organs including liver, kidney, heart, and nervous systems.³¹ Necropsy results from animals showed hepatic necrosis, acute tubular necrosis, impaired bone remodeling after fracture, testicular toxicity, and retinal degeneration. However, the long-term effects in humans are still unclear.

Wear rates in THA are significantly greater with acetabular inclination angles greater than 45°. Little et al. prospectively followed 43 patients after uncemented THA for a

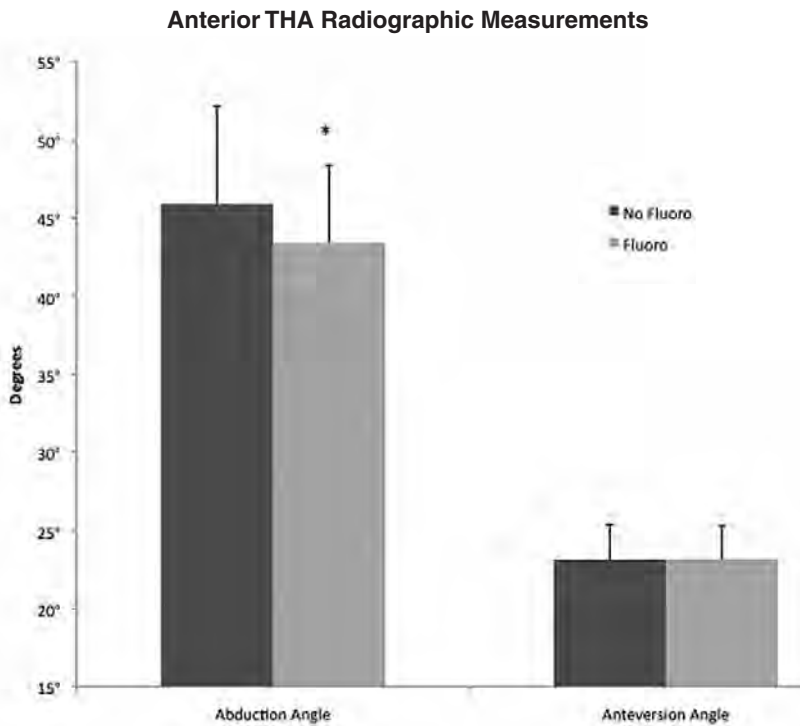


Figure 2. Mean acetabular cup abduction and anteversion angles with and without fluoroscopic guidance. Acetabular cup abduction angles are significantly different (*) between the two groups ($p < 0.05$).

mean of 64 months and found a significantly greater mean wear rate (50%) in those with less than 45° versus greater than 45° of inclination (0.12 mm/year vs. 0.18 mm/year, $p = 0.012$).¹⁵ Volumetric wear in the group with more than 45° inclination was 44% greater and approached statistical significance ($p = 0.17$). Patil and colleagues computed contact stresses during a normal gait cycle using a finite element model and validated their results by comparison with findings from hip wear simulator studies in which acetabular cups were positioned at 45° or 55° of inclination.²⁸ Forces on the hip joint were scaled to represent loads produced by a 75 kg patient. The authors concluded greater abduction angles result in increased contact stresses and linear wear rates likely due to reduced contact area of the femoral head and increased anteversion decreases contact stresses and wear rates due to greater contact (17.2 vs. 21.7 mg/million cycles; $p < 0.01$). In the clinical arm of the study, 56 patients (60 THAs) were followed for up to five years and linear wear rates were measured on AP radiographs by a technique described by Livermore et al. Cups with greater than 45° inclination had 40% greater mean linear wear than those with less than 45° inclination ($p < 0.0001$).¹⁶

Acetabular components are involved in greater than 50% of THA revisions.⁸ Dislocation after anterior approach to THA is a less likely cause of revision surgery due to its lower dislocation rates as compared to other approaches. Dislocation rates after anterior THA have been reported as low as 0.61% while rates after posterior THA vary from roughly 1% to 11%.¹⁹ In contrast, bone loss remains a common reason for implant failure and results from osteolysis and stress

shielding, creating technical difficulties in revision surgery. Schmalzried reviewed 93 patients (113 hips) with an average follow-up of 64 months and found pelvic osteolysis in 17% (19 hips).³³ Osteolysis was significantly associated with cup abduction in excess of 50° ($p < 0.0001$). Kennedy et al. compared a group of patients with mean acetabular inclination of 61.9° against a group with an average of 49.7° and found significantly higher percentage of patients with pelvic osteolysis in the former group (24% vs. 13%).¹² They concluded that a more horizontal cup position reduces osteolysis.

The anterior approach to THA has seen advancements since its inception by Judet in 1947. Over the years, it has been modified to allow exposure of the femur and pelvis with less soft trauma by avoiding release of any of the surrounding muscles from their bony attachments. In recent years, the use of an image intensifier has become popular because it provides intraoperative assessment of cup and femoral stem positioning and potentially reduces error despite use of alignment rods and patient experience. Surgeon assessment of component positioning may be incorrect. Hassan et al. prospectively

measured cup abduction and anteversion in 50 consecutive THAs intraoperatively via alignment guide and postoperatively on radiographs.¹¹ Goal cup placement was 30 – 50° of abduction and 5 – 25° of anteversion. Four surgeons recorded their intraoperative inclination and version values after the alignment guide was fitted into the component. Cup abduction was measured directly from x-rays and version was calculated according to the equation in their study. The authors concluded a 5° (range, 0 – 20°) and 9° (range, 0 – 24°) mean error of cup abduction and version, respectively.

Disadvantages include radiation exposure and risk of contamination from the intensifier. In a study by Schuler evaluating fluoroscopy of the hip, knee, and ankle, the hip produced the greatest amount of scatter secondary to tissue density. Reduction in radiation was most affected by reducing fluoroscopy time rather than standing at a distance or using laser targeting.³⁴ C-arm contamination of the surgical field during anterior THA is largely theoretical as there is a paucity of studies on this topic. Biswas et al. studied sterility of C-arm drapes after spine surgery cases and found that although some degree of contamination was found on all areas of the drape after surgery, the upper portions exhibited the greatest rates of contamination.⁴ Another study investigating the timing of C-arm drape contamination found 50% contamination at 20 minutes and a large correlation with lateral position changes.²⁹

There are several limitations to our study. First, this is a retrospective analysis in which a single rater was not blinded to the variable of fluoroscopy. Second, the non-fluoroscopic guided THAs were performed earlier in the surgeon's career

when he was less familiar with the anterior approach. The high percentage of acetabular components in safe zones may reflect the surgeon's experience and high case volume. Anterior THA is technically demanding and there is a substantial learning curve which may have accounted for the greater number of cup abduction angles and combined anteversion-abduction angles outside safe zones in the NF group. Since patients were randomly selected, the first several patients may have been included in our analysis at a time when complications are known to reflect the learning curve.^{9,30}

A third limitation is that measurement of cup anteversion is not always precise. In the method described by Widmer and Ing, the anteversion is measured on a plain radiograph of the pelvis centered on the tear drop.³⁵ Unfortunately, precise determination of component landmarks is obscured by implant materials and the quality of postoperative radiographs is not always optimal. Pelvic tilt may have also affected our measurements.

A fourth limitation of our study is the non-uniform demographics between the FL and NF groups. The two groups were significantly different in age and BMI and it is unclear whether these differences affected our results. A study by Paterno et al. found no correlation between age and BMI and dislocation rates after primary THA.²⁶ Another study found BMI greater than 30, surgical approach (specifically, minimally-invasive surgery), and surgeon volume to be independent predictors of malpositioned cups.⁵ However, this study did not specifically address the anterior approach nor did they discuss fluoroscopy. Matta reported accurate and reproducible component positioning using an anterior approach and fluoroscopy for THA in patients with an average age of 64 years regardless of body habitus.¹⁹

In summary, the anterior approach to THA may be performed with and without fluoroscopy. The advantages of fluoroscopy include intraoperative assessment of component positioning and, according to the results of our study, a significantly higher percentage of acetabular cup abduction angles in the safe zone. Our results also show a trend toward a larger proportion of components in combined abduction and anteversion safe zones when using image guidance. This may reduce wear and increase longevity of the arthroplasty. Our results also support accurate cup anteversion without imaging and this may avoid the drawbacks of fluoroscopy which include radiation exposure and possible field contamination. In the future, we would like to determine the differences in postoperative complications between our groups. Prospective studies investigating component positioning during anterior THA with and without fluoroscopy are still needed.

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Medical Student Research Project

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Incidence of Fracture Displacement and Hemorrhage from Stable Pelvic Injuries Treated Nonoperatively with Early Weight Bearing

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Abstract

Mechanical stability of pelvic ring injuries frequently determines the ability to mobilize a trauma patient safely and comfortably. The assessment of stability can be made on static imaging, dynamic imaging, and clinical examination. With dynamic imaging often difficult in acute trauma patients, we have instituted a pelvic fracture management protocol at our institution that involves repeat static radiographs after weightbearing of presumably stable injuries as well as serial hemoglobin checks to rule out pelvic instability and hemorrhage. We performed a retrospective analysis of our data over 18 months. Nearly half of the patients with presumably stable injuries did not have followup radiographs and were excluded, and one patient did not have followup hemoglobin checks. Of the remaining patients, 26 were evaluated which consisted of LC-1, APC-1, and isolated pubic ramus fractures. Radiographs were assessed for displacement using a previously described method, which demonstrated a maximal displacement of 5.7 mm. No patients required any surgical treatment or change in their nonoperative treatment course. Eight patients required packed red blood cell transfusions, although several of these patients also had other injuries. In conclusion, routine followup weight bearing radiographs may not be required in cases of stable fracture patterns, although serial hemoglobin checks might be helpful, particularly in patients with additional injuries.

Introduction

Most orthopaedic surgeons agree that decision making with pelvic ring injuries centers on an assessment of the stability of the injury. This includes both hemodynamic stability as well as mechanical stability. Although percutaneous treatment of the posterior and anterior pelvic ring has become more popular, there are clearly still a large group of patients who are treated nonoperatively because their injury is assessed to be mechanically stable. But how does a sur-

geon decide that a pelvic fracture will be stable? Predictions can be made based on static radiographic imaging, dynamic standing radiographs, or dynamic fluoroscopic stress images in the operating room. Mechanical instability of a fracture on a stress view, however, does not necessarily indicate that surgical repair is indicated. Loss of alignment on interval static views, however, is arguably more concerning and indicative of the need for improved mechanical stability (i.e., surgical intervention).

Another concern with pelvic fractures is the potential for hemorrhage and its sequelae. Although fractures with more severe, unstable fracture patterns are more likely to incur clinically significant blood loss requiring intervention, minimally displaced fractures are also reported to cause hemorrhage in certain circumstances, particularly related to non-compliant vasculature in the elderly. Therefore, most surgeons have a heightened clinical suspicion for hemorrhage in patients with pelvic fractures, often requiring admission to the hospital and hemoglobin checks.

At most institutions, pelvic fractures that are stable and without significant associated hemorrhage are typically treated nonoperatively. At our institution, a clinical protocol was established to ensure that, amongst other things, serial hemoglobin tests were checked over the first 24 hours and repeat pelvic radiographs were done after weightbearing on fractures deemed to be nonoperative. There are differing opinions regarding the degree of scrutiny required for these matters, particularly in lateral compression type 1 fractures. The aim of this study is to retrospectively evaluate the incidence of clinically significant hemorrhage and fracture displacement after immediate weightbearing of stable pelvic fractures to help determine the appropriate level of surveillance warranted for stable fracture patterns treated nonoperatively.

Methods

Our Level 1 trauma center instituted a pelvic fracture management protocol in October 2010. All patients with pelvic fractures from blunt and penetrating trauma with the exception of Tile type A avulsion fracture were admitted,

and had serial hemoglobin (every eight hours) checked for 24 hours. Fracture types were grouped into stable pelvic ring fractures, unstable pelvic ring fractures, and unstable sacral fractures. Details for proper initial evaluation and management of the pelvic fracture patient were outlined, the details of which are not given here. Ongoing management guidelines were also provided, which included repeat neurological examination as determined by initial findings, serial hemoglobin checks, serial lactate level assessment until normalized in multiple trauma patients and patients with known pelvic hemorrhage, and repeat radiographic examination after the patient is ambulatory to check for interval displacement. IRB approval was obtained for this particular study. Our orthopaedic database as well as the trauma surgery database (Pennsylvania Trauma Systems Foundation registry) were retrospectively reviewed for all patients treated nonoperatively for a pelvic fracture between October 2010 and April 2012. Inclusion criteria included all patients, 18 years or older, who presented within that timeframe with stable pelvic fractures, including lateral compression type 1, APC type 1, Tile type A, and isolated pubic ramus injuries. Any patient with unstable fracture patterns, including lateral compression types 2 and 3 or APC types 2 and 3, gunshot injuries, or pathologic fractures from tumors were excluded. Pelvic fracture patterns were classified according to the Tile classification system and Young and Burgess classification system.^{1,2} The initial search identified 55 patients. Of these 55 patients, 26 patients had AP pelvic radiographs available at both initial presentation and following advancement to weightbearing status. Serial hemoglobin levels were reviewed for the initial value upon admission and the value following 24 hours.

In order to evaluate fracture displacement using radiographic interpretation, a novel method developed by Soles et al. was applied to AP radiographs both at the time of presentation and following weightbearing.³ Measurements taken on the initial radiographs were compared to measurements taken on radiographs following advancement to weightbearing status to determine interval fracture displacement.

On the AP radiograph, a plumb line drawn through the midline of the spine and sacrum served as a reference for perpendicular lines drawn from points of interest on either hemipelvis. These points of interest included iliac wing height, sacral height, ischial height, sacral width, and pelvic ring width (Fig. 1). The difference between left and right hemipelvis was recorded as a positive value and taken as a measurement of vertical displacement. These measurements were repeated for all AP radiographs. Interval displacement was determined by comparing values from time of admission to those following weightbearing.

Results

The final analysis included 26 patients admitted between the months of October 2010 and April 2012. The mean age

at the time of injury was 55 years, with a range of 20–88 years.

All fractures consisted of stable patterns, including lateral compression type 1, APC type 1, Tile type A, and isolated ramus injuries according to both the Tile as well as the Young and Burgess classification systems.^{1,2} Of the 26 patients included in the study, nine (35%) had unilateral ramus fractures, two (8%) had bilateral rami fractures, five (19%) had intraarticular (acetabular) extension, one (4%) had a pubic symphysis diastasis, and eight (31%) had incomplete sacral fractures.

The mean interval displacements recorded on AP radiographs following advancement to weightbearing status were as follows: iliac wing height, 0.17 ± 2.01 ; sacral height, 0.02 ± 1.61 ; ischial height, 0.08 ± 1.40 ; sacral width, 0.89 ± 2.14 ; pelvic ring width 0.04 ± 2.67 . Interval displacement results were calculated as absolute values. The greatest displacement was observed in pelvic right width, with three patients found to have 5.2, 5.5, and 5.7 mm of additional displacement on early radiographs. However, no patients were determined to require surgical intervention and all patients progressed to clinical union of their pelvic fractures.

Of the 26 patients included in this study, two were found to have pelvic hematomas and eight patients ultimately required transfusion of packed red blood cells. The mean interval change in hemoglobin levels over the first 24 hours of admission for the eight patients that required transfusion was 2.05 ± 2.99 . The mean interval change in hemoglobin levels for the 17 patients that did not require a transfusion (one patient did not have follow-up hemoglobin levels available) was 1.68 ± 1.43 . Of the two patients found to have pelvic hematomas, one patient had an admitting hemoglobin level of 6.6 and required two units of packed red blood cells. The second patient did not require transfusion.

Among the eight patients requiring transfusion, six (75%) also presented with a non-pelvic fracture, two (25%) presented with an abdominal hematoma, three (38%) presented with an abdominal organ laceration, and one (13%) presented with a pelvic hematoma. Among the 18 patients that did not require a transfusion, six (33%) presented with a non-pelvic fracture, two (11%) presented with an abdominal organ laceration, and one (6%) presented with a pelvic hematoma.

Discussion

Stable pelvic fracture patterns are commonly treated nonoperatively with early weightbearing. Soles et al.³ reported on 118 patients with LC 1 pattern pelvic fractures that presented at a single Level I Trauma Center. These patients were treated nonoperatively with immediate mobilization and repeat radiographs to monitor for further displacement. Of the 118 patients, only one patient failed nonoperative management and presented radiographically with 5 mm of additional displacement, while the other 117 patients healed



Figure 1. AP pelvis radiograph demonstrating measurement technique. A vertical plumb line was drawn through the midline of the spine and sacrum with perpendicular lines at the level of the iliac wing height, sacral height, ischial tuberosity height, sacral width, and pelvic ring width. The difference in height was recorded.

Table 1. Interval Fracture Displacement

Measurement of Interest	Interval Displacement (mm)
Iliac wing displacement	0.17 ± 2.01
Sacral displacement	0.02 ± 1.61
Ischial displacement	0.08 ± 1.40
Sacral width difference	0.89 ± 2.14
Pelvic ring width difference	0.04 ± 2.67

Table 2. Associated Injuries

Injury	Transfusion	No Transfusion
Non-pelvic fracture	75%	33%
Abdominal hematoma	25%	0%
Abdominal organ laceration	38%	11%

26 patients (eight transfusion, 18 no transfusion)

with minimal additional displacement. The investigators concluded that minimally displaced LC sacral fractures could be treated safely nonoperatively with immediate weightbearing. A similar study by Bruce et al.⁴ consisted of 117 patients who presented to two Level I trauma centers with an LC pelvic fracture with less than 5 mm of initial displacement. The patients were treated nonoperatively with mobilization and monitored with serial radiographs. Of the 117 patients, 23 presented radiographically with more than 5 mm of additional displacement. However, none of these 23 patients included incomplete LC sacral fractures with ipsilateral rami fractures, and the investigators concluded that such fracture patterns could be treated nonoperatively. These studies support nonoperative management of minimally dis-

placed LC fractures, but there is still a question of what degree of scrutiny is required with early serial radiographs and hemoglobin checks.

In our study, the majority of our patients showed less than 5 mm additional displacement in all parameters on early radiographs. Only three patients were found to have greater than 5 mm additional displacement in a single parameter, but still went on to clinical union without requiring surgical intervention. Our results suggest that clinically significant displacement does not occur with nonoperative treatment and immediate weightbearing of these stable fracture patterns, as evidenced by early radiographs.

Catastrophic hemorrhage is a concern with pelvic fractures and serial hemoglobin checks are employed by our institution to monitor for such incidences. Two patients were found to have pelvic hematomas, and only one of these patients required transfusion. However, eight patients ultimately required transfusion, suggesting that the majority of hemorrhage seen in these patients is due to associated injuries rather than their pelvic fractures. This is further supported by the higher rates of associated injuries seen among these eight patients. This suggests that the overall clinical picture of the presenting patient taken into consideration with serial hemoglobin checks may provide the best predictive tool for incidences of hemorrhage.

One of the challenges in assessing interval fracture displacement was determining a methodology for radiographic interpretation. Lefavre et al.⁵ determined that a lack of standardization exists in the measurement of radiographic outcomes. In an effort to establish a level of consistency, we chose to model our measurements from a novel method developed by Soles et al.,³ a technique similar to one used by Bruce et al.,⁴ which utilizes a vertical plumb line for reference and multiple points of interest. We have detailed the radiographic measurement technique used in our study to present a reproducible method. However, we acknowledge the variability in radiographic quality and technique as well as the inevitable human error in attempting to standardize each measurement. As Lefavre et al.⁵ have discussed, further investigation in the area of radiographic interpretation is needed to establish a standardized method that is both reproducible and reliable.

Conclusion

In our retrospective analysis of 26 patients with stable pelvic injuries, we found minimal displacement following early weightbearing and a single incidence of pelvic hemorrhage that required transfusion of 2 units of packed red blood cells. This suggests that stable pelvic fracture patterns do not result in significant interval displacement or catastrophic hemorrhage.

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Medical Student Research Project

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The Role of Pharmacological Agents in the Management of Post and Chronic Concussion Syndrome: A Systematic Literature Review

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Introduction

Concussion, or minor traumatic brain injury (mTBI), is a common neurologic problem that has received increasing attention in recent years. The Center for Disease Control and Prevention (CDC) has estimated that 1.7 million patients present each year to the emergency departments with traumatic brain injury (TBI).¹ About 75% of TBIs that occur each year are concussions or other forms of mild traumatic brain injury (mTBI).¹

The terms concussion and mTBI are used interchangeably and is the most common form of TBI.² mTBI is defined by the World Health Organization (WHO) as:

- One or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery.

- Glasgow Coma Score (GCS) of 13–15, 30 minutes post-injury or later upon presentation for healthcare.³

Previous review articles discussed pharmacological agents in treating traumatic brain injuries, but the results were either inconclusive or not specific to mild traumatic brain injuries. Comper et al.³ performed a systematic review for treatments, but they did not find any significant evidence on the efficacy of drug interventions for treating the symptoms of mTBIs. Other review articles covered more severe forms of TBI, but did not report findings specific to mild traumatic brain injuries.^{4–6} Therefore, this systematic literature review aims to investigate the use of drug therapies in treating mild traumatic brain injuries.

Methods

Search Strategy

Relevant studies were identified using PubMed. The search strategy included terms related to concussions, mild traumatic brain injuries, and pharmaceuticals. Variations of

these terms were included in the search as both free text and Mesh terms. The complete search strategy was as follows:

PubMed

#1 Concussion* or mild traumatic brain injury or mild TBI or mTBI or "Brain Concussion" [Mesh] (8,465 results)

#2 Traumatic Brain Injury or "Brain Injuries" [Mesh] (61,893 results)

#3 Drug Therapy or "Drug Therapy" [Mesh] or pharmacological agent* or pharmaceutical agent* (2,196,844 results)

(#1 or #2) and #3 (6,452 results)

The search was last performed on 6/22/2012.

Reference lists of identified articles were also checked for relevant publications in order to identify additional articles that were not found by the search strategy. There were no restrictions on the year of publication; however, the search was limited to articles in English.

Selection of Studies and Data Extraction

Articles were screened and selected if they included studies that treated concussed patients or patients with mTBI using pharmaceutical agents. The articles were screened and reviewed based on the following inclusion criteria: (1) study must include patients with a concussion or mTBI; (2) patients being studied must have a GCS \geq 13.

Study design methodology information was extracted, such as the study design type, study size, pre-treatment GCS, symptom of concussion, study drug, follow-up time, and study results. The study's population demographics were also collected, such as cohort size, mean age, and the number of mTBI patients in the study.

Results

The search strategy identified 6,581 citations with an additional nine studies identified from the hand search of review articles. From the 6,590 citations, the full text of 338 articles was retrieved for further review. Of the 338 articles, 23 studies met the inclusion criteria to be reported in the review. The flow diagram is shown in Figure 1.

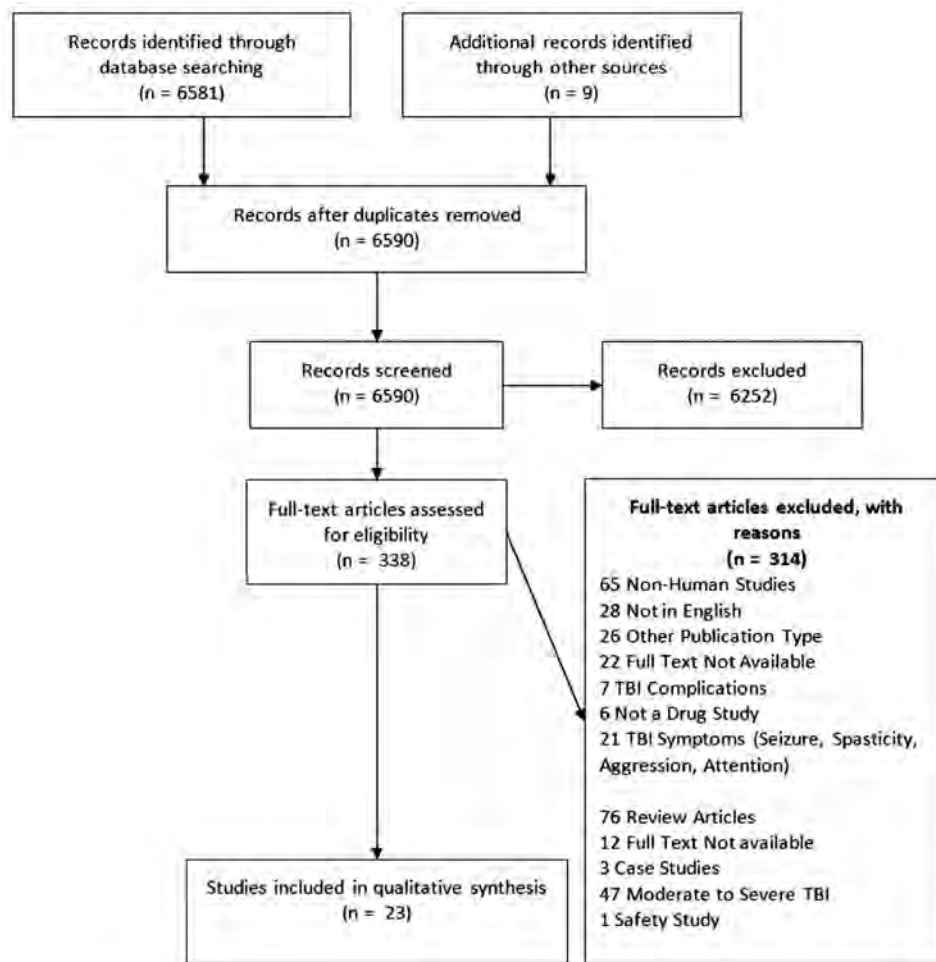


Figure 1. Flow Chart for Identifying Studies

Attention, Cognition, and Memory

Of the identified articles, 14 articles described pharmaceutical treatments with outcomes of attention, cognition, and memory.⁷⁻²⁰ The population characteristics of the studies are described in Table 1. The sample sizes in these studies were small, ranging from 10 to 182 patients. The number of patients with mild TBI is also shown in Table 1, with most studies having only a fraction of their total patients with mTBI. The mean ages of patients from these studies ranged from 11.9 to 51.7, indicating that most of the patients were young. The pre-treatment GCS was not available for all studies, since some studies used different methods to distinguish between mild to moderate TBIs.^{11, 13, 17, 20} The length of time from injury to treatment initiation varied from hours to months, with most studies initiating the intervention months after the initial traumatic insult.

Table 2 describes the study design, study drug, the outcome measure, and the results. Eight studies utilized a randomized, double-blind, placebo-controlled trial, while the other six studies used other study designs. The outcomes

used to measure the effects of the drug interventions were heterogeneous between the studies. The Controlled Oral Word Association Test (COWAT) and the Paced Auditory Serial Addition Test (PASAT) were used in several studies,^{11, 12, 15, 16, 20} however, many studies used different outcomes to measure the patient's attention, memory, and cognition.

Dopaminergic Agents

Methylphenidate was investigated in five studies for its effects on attention and cognition in patients with brain injury. Plenger PM et al.⁷ showed that there were improvements in attention ($p < 0.03$) and motor performance ($p < 0.05$) when compared to placebo. However, only four patients out of 23 had a mild TBI. Mahalick DM et al.⁸ studied children and showed that performance on all tasks of attention and concentration was statistically significant when compared to placebo ($p < 0.04$ to $p < 0.005$), but only two patients in this study had a mTBI. Kaelin DL et al.⁹ found a significant improvement in attention with patients using methyl-

Table 1. Population Characteristics of Studies with Outcomes in Attention, Cognition and Memory

Author	Sample Size/ mTBI Sample Size	Mean Age of Population	Pre-treatment GCS	Time Since Injury to Study Treatment
Dopaminergic Agents				
Plenger PM et al., 1996 ⁷	23/4	Acute phase placebo 26.6 (8.7), acute phase methylphenidate 31.4 (17), 30-day follow-up placebo 22.2 (5.2), 30-day follow-up methylphenidate 28.6 (13.9), 90-day follow-up placebo 21.5 (6.5), 90-day follow-up methylphenidate 25.8 (13.4)	6–15	Enrolled from hospital
Mahalick DM et al., 1998 ⁸	14/2	10.67	3–15	14.14 Months (mean)
Kaelin DL et al., 1996 ⁹	10/2	51.7	3–13	19.8 Days (mean)
Whyte J et al., 1997 ¹⁰	19/1	30.8	3–14	514.1 Days (mean)
Kraus MF et al., 2005 ¹¹	22/6	TBI patients 36.0 (11.8 (SD)), TBI patients undergoing PET 33.2	GCS not reported (mild, moderate or severe closed head TBI)	63.2 (6–240) Months (mean, range)
Serotonergic Agents				
Fann JR et al., 2001 ¹²	15/15	41.9 (SD 8.5)	13–15	10.6 Months (mean)
Dopaminergic and Serotonergic Agents				
Lee H et al., 2005 ¹³	30/Not reported	Methylphenidate group 35.3 (SD 8.0), sertraline group 33.6 (SD 12.3), placebo group 35.5 (SD 7.2)	GCS not Reported (mild to moderate TBI)	Methylphenidate: 34.8 days (mean) Sertraline: 31.9 days (mean) Placebo: 30.0 days (mean)
NMDA Antagonists				
Merchant RE et al., 1999 ¹⁴	45/19	14–75 (range)	9–14	<12 Hours
Phospholipid Intermediates				
Levin HS, 1991 ¹⁵	14/14	CDP-choline median 25, placebo median 20	15	Recruited bedside once out of post-traumatic amnesia
Cholinergic Agents				
Zhang L et al., 2004 ¹⁶	18/Not reported	Group A 33 ± 2 Group B 31 ± 2	Group A: 9.3±1.1 (mean ± SD) Group B: 8.9±1.0 (mean ± SD) 3–15	Group A: 4.6 ± 0.7 months (mean ± SD) Group B: 3.9 ± 0.5 months (mean ± SD)
Kaye NS et al., 2003 ¹⁷	10/6	41	GCS not reported (mild to severe TBI)	1.2 Years (mean)
Tenovuo O et al., 2005 ¹⁸	111/64	All patients 40 ± 1.3	13–15	71 ± 6.7 Months
Peptide Treatments				
Alvarez XA et al., 2003 ¹⁹	20/3	30.1 ± 2.15	3–15	23–1107 Days (range)
Filipova M et al., 1989 ²⁰	17/17	DDAVP mean 41, placebo mean 28	Minor head injury patients	Within 16–40 hours

phenidate, when compared to a natural recovery of rehabilitation. However, due to the small sample size of 10 patients, the study was unable to find statistical significance in many of the tests. Additionally, only two patients included in this study had a mTBI. In the study by Whyte J et al.,¹⁰ methylphenidate had statistically significant differences in the variables of speed and mental processing ($p < 0.001$), but did not have statistically significance in the overall effect over all the variables ($p = 0.46$). In this study, there was only one patient with a mild TBI. Lee H et al.¹³ found that methylphenidate improved cognitive function in nine out of 10 cognitive tests ($p < 0.05$ to $p < 0.001$). Methylphenidate was also found to improve daytime sleepiness ($p < 0.01$). In this study, it was unclear how many patients with mild TBI were included, but the patients in the study ranged from mild to moderate TBI.

The use of amantadine was investigated for its effects on attention, memory and behavior. In an open-label trial, Kraus MF et al.¹¹ found that there was improvement in executive function ($p = 0.02$) with amantadine. However, no significant improvements were found in attention ($p = 0.10$) or memory ($p = 0.44$). Furthermore, only six out of 22 study patients had a mild TBI.

Serotonergic Agents

Sertraline was investigated for its use in cognition and memory. Fann JR et al.¹² found improvements in cognitive function such as cognitive efficiency, psychomotor speed, and flexible thinking ($p < 0.01$ to $p < 0.05$). They also found improvement in recent memory ($p < 0.001$ to $p < 0.002$).

Table 2. Attention, Cognition, and Memory Outcomes of Identified Studies

Author	Study Design	Drug	Measure	Main Result
Dopaminergic Agents				
Plenger PM, et al., 1996 ⁷	Randomized, double-blind, placebo-controlled study	Methylphenidate	Disability Rating Scale (DRS) and tests of attention, memory, and vigilance	The methylphenidate group was significantly better at 30 days on the DRS ($p < 0.02$), and on tests of attention ($p < 0.03$) and motor performance ($p < 0.05$). No significant differences were noted between groups at 90 days.
Mahalick DM, et al., 1998 ⁸	Randomized, double-blind, placebo-controlled, cross-over experimental design	Methylphenidate	Measures of attention and concentration: The Gordon Diagnostic System (Model III); the Woodcock-Johnson Psychoeducational Test Battery-Revised	Performance on all tasks of attention and concentration was statistically significant when compared to placebo ($p < 0.04$ to $p < 0.005$) for all analyses.
Kaelin DL, et al., 1996 ⁹	Prospective multiple baseline design (A-A-B-A) utilized on a consecutive sample of patients.	Methylphenidate	Neuropsychological battery of tests to assess attention: Digit Span Sub-Test of the Wechsler Adult Intelligent Test — Revised; the Mental Control Sub-Test of the Wechsler Memory Test-Revised; Trail Making Parts A and B; the Symbol Search Sub-Test (Part A) of the WISC-III; the Mesulam Verbal Cancellation Test	Use of methylphenidate in acutely brain-injured adults was well tolerated and demonstrated a significant improvement in attention compared to natural recovery in a rehabilitation setting. Methylphenidate also correlated with faster functional recovery as measured by the Disability Rating Scale although the improvement did not achieve statistical significance. Total digit span score, mental control, and symbol search was improved significantly ($p < 0.05$). There were not enough data points to perform a statistical analysis for the other tests.
Whyte J, et al., 1997 ¹⁰	Randomized, double-blind, placebo-controlled, repeated crossover design	Methylphenidate	Measures of attention: Sustained arousal task, phasic arousal task, distraction task, choice reaction-time task, behavioral inattention task	Methylphenidate had no significant overall effect across the 22 performance variables ($p = 0.46$). Methylphenidate did have different effects on individual performance variables ($p < 0.001$), specifically to variables of speed and mental processing. Methylphenidate appeared to affect the arousal and speed of mental processing. Methylphenidate appears to increase mental processing speed.
Kraus MF, et al., 2005 ¹¹	Open-label trial	Amantadine	Executive domain: Trail Making Test Part B, Controlled Oral Word Association Test (COWAT) Attention domain: Trail Making Test Part A, Digit Span (from WAIS-R) Memory domain: California Verbal Learning Test (CVLT), Rey Osterreith Complex Figure-immediate and delayed recall	Significant improvements on tests of executive function were observed with treatment ($p = 0.02$). No significant improvements found in attention ($p = 0.10$) or memory ($p = 0.44$).
Serotonergic Agents				
Fann JR, et al., 2001 ¹²	Non-randomized, single-blind, placebo run-in trial	Sertraline	Depression: HAM-D Neurological tests (cognition and attentional): Digit Span; Digit symbol; Vocabulary; Finger Tapping Test; Trailmaking Test, Parts A and B; Controlled Oral Word Association Test (COWAT); Logical Memory I and II; Visual Reproduction I and II; Buschke Selective Reminding Test (SRT); Benton Visual Retention Test (BVRT); Self-Perception of TBI Severity	Depression scores changed significantly with sertraline, from the baseline mean SD HAM-D score of 25.0 ± 4.36 to a mean of 7.2 ± 5.30 at Week 8 ($P < 0.001$). Vocabulary was unchanged compared to baseline. Simple auditory attention was not significantly different. Digit symbol scores changed significantly ($p < 0.01$), indicating improvement in general cognitive efficiency. Psychomotor efficiency and attention improved on Trailmaking Test Part A ($p < 0.05$). Speed and flexible thinking skills were improved on Trailmaking Test Part B ($p < 0.04$). Recent memory ability was improved as seen in the verbal recent memory tests, as well as the WMS-R Logical Memory Tests ($p < 0.001$ to $p < 0.002$). There were significant improvements in cognitive function, especially in psychomotor speed, cognitive efficiency, flexible thinking, and recent memory ability. Vocabulary unchanged, some improvement in psychomotor speed, improvements in memory ability.

(continued on next page)

Table 2. Attention, Cognition, and Memory Outcomes of Identified Studies (Continued)

Author	Study Design	Drug	Measure	Main Result
Dopaminergic and Serotogenic Agents				
Lee H et al., 2005 ¹³	Randomized, prospective, double-blind, placebo-controlled, comparative drug trial	Methylphenidate, sertraline	<p>Depression: Hamilton Rating Scale for Depression (HAM-D); Beck Depression Inventory (BDI)</p> <p>Rivermead Postconcussion Symptoms Questionnaire (RPQ) for postconcussional symptoms; SmithKline Beecham Quality of Life Scale (SBQoL) for quality of life</p> <p>Seven performance tests: Critical Flicker Fusion Threshold (CFFT), Choice Reaction Time (CRT), Continuous Tracking Task (CTT), Mental Arithmetic Test (MAT), Sternberg Memory Scanning Task (STM), Digit Symbol Substitution Test (DSST) and Mini-Mental State Examination (MMSE)</p> <p>Subjective measures of sleep: Leeds Sleep Evaluation Questionnaire (LSEQ) and daytime sleepiness (Chonnam Epworth Sleepiness Scale (CESS))</p>	<p>Both methylphenidate and sertraline improved depressive symptoms compared to placebo. However, methylphenidate improves cognitive function and maintains daytime alertness.</p> <p>Methylphenidate and sertraline were significantly superior to placebo, as measured by the HAM-D ($p = 0.005$), no significant differences were found by the BDI.</p> <p>Postconcussional symptoms (as measured by the RPQ) were significantly improved in the methylphenidate ($p < 0.001$) and placebo ($p < 0.05$) groups compared to baseline. Postconcussional symptoms for sertraline were not significantly improved.</p> <p>Methylphenidate significantly improved cognitive function in nine out of 10 cognitive tests ($p < 0.05$ to $p < 0.001$) compared to baseline; placebo significantly improved cognitive function in seven out of 10 cognitive tests ($p < 0.05$ to $p < 0.001$); sertraline significantly improved cognitive function in only two out of 10 cognitive tests ($p < 0.05$ to $p < 0.01$).</p> <p>Methylphenidate ($p < 0.01$) and placebo ($p < 0.05$) both significantly reduced daytime sleepiness as measured by the CESS, while sertraline did not.</p> <p>Quality of life was improved for all three drug treatments when compared to baseline (methylphenidate ($p < 0.01$), sertraline ($p < 0.05$), placebo ($p < 0.05$)).</p>
NMDA Antagonists				
Merchant RE et al., 1999 ¹⁴	Randomized, double-blind, placebo-controlled study	CP-101,606 (Traxoprodil)	<p>10-item Neurobehavioral Rating Scale; Kurtzke Neurologic Status Evaluation; Galveston Orientation and Amnesia Test (GOAT); National Institutes of Health (NIH) Stroke Scale; a battery of nine neuropsychological tests</p>	<p>CP-101,606 had no psychotropic effects and was well-tolerated in patients who had sustained either a mild or moderate TBI or an atraumatic hemorrhagic stroke.</p> <p>The GCS score showed no statistical significance in the speed of recovery between cohorts.</p> <p>Neurobehavioral rating scale showed improvement in all groups but was not statistically significant between groups.</p> <p>The Kurtzke Neurologic Status Evaluation was not statistically different between groups.</p> <p>No statistical difference was seen with the GOAT, NIH stroke scale, and the battery of nine neuropsychological tests.</p>
Phospholipid Intermediates				
Levin HS, 1999 ¹⁵	Randomized, double-blind, placebo-controlled study	Cytidine diphosphoryl choline (CDP-choline)	<p>Memory: verbal recall, spatial memory, recognition memory test</p> <p>Fluency: verbal and design tests</p> <p>Attention: Continuous Performance Test, Paced Auditory Serial Addition Test (PASAT)</p>	<p>Results showed that CDP-Choline produced a greater reduction in post-concussional symptoms than placebo ($p < 0.005$). Analysis of the neuropsychological findings revealed a significantly greater improvement in recognition memory for the CDP-Choline group ($p < 0.02$) whereas the other changes in test performance did not differ between the two groups.</p>

Table 2. Attention, Cognition, and Memory Outcomes of Identified Studies (Continued)

Author	Study Design	Drug	Measure	Main Result
Cholinergic Agents				
Zhang L, et al., 2004 ¹⁶	Randomized, placebo-controlled, double-blind crossover trial	Donepezil	Memory: Auditory Immediate Index [AII], Visual Immediate Index [VII] from the Wechsler Memory Scale–III Cognition: Paced Auditory Serial Addition Test (PASAT) (measures sustained attention, working memory, and information processing speed)	At week 10, group A taking donepezil had statistically significant benefits to memory when compared to group B taking placebo (AII score $p = 0.002$, VII score $p < 0.001$). After cross-over, scores at week 24 were not statistically significant, indicating that donepezil's effects were carried over. At week 10, the cognition scores were also statistically significant for group A taking donepezil compared to group B taking placebo ($p \leq 0.001$ for all PASAT scores). After cross-over, scores at week 24 were not statistically significant, indicating that donepezil's effects were carried over. Donepezil increased neuropsychologic testing scores in short-term memory and sustained attention in postacute TBI patients.
Kaye NS, et al., 2003 ¹⁷	Open-label trial	Donepezil	Clinical Global Improvement (CGI) ratings; symptom focused neuropsychological test battery Global memory scale (GCS); Memory Assessment Scale (MCS)	Overall impression of improved focus, attention, clarity, and thought while on medication. CGI showed improvement. Global memory scale (GCS) and Memory Assessment Scale (MCS) did not improve.
Tenovuo O, et al., 2005 ¹⁸	Randomized trial	Donepezil, galantamine and rivastigmine	Subjective description of drug effect	Higher vigilance, better attention and raised general functioning seem to be the most constant and expected effects.
Peptide Treatments				
Alvarez XA, et al., 2003 ¹⁹	Open exploratory clinical trial, without a control group	Cerebrolysin	Syndrome Kurztest test (SKT, cognitive improvement test) Glasgow Outcome Scale (GOS)	Significant improvement in cognitive performance was seen, only evident during the first year of brain trauma. A significant improvement in SKT performance was observed after treatment with Cerebrolysin ($p < 0.01$). A significant improvement in GOS scores was observed ($p < 0.05$).
Filipova M, et al., 1989 ²⁰	Randomized, double-blind, placebo-controlled	1-desamino-8-D-arginine-vasopressin (DDAVP)	Mika's Tactile Memory Test; Dichotic Listening; Postcard Recognition Test; Story Memory; Rhythm Pursuing; the Paced Auditory Serial Addition Test (PASAT)	The first and second series of PASAT (an information processing test) was statistically significant ($p < 0.05$ and $p < 0.01$ respectively) compared to placebo. The Story Memory (a test of verbal logical memory) DDAVP was significantly ($p < 0.05$) superior to placebo.

However, Lee H et al.¹³ found that sertraline was not as effective as methylphenidate in treating postconcussional symptoms and cognitive function.

NMDA Antagonists

The use of Traxoprodil (CP-101,606) was investigated by Merchant RE et al.¹⁴ in patients with mild to moderate traumatic brain injury. There were no statistically significant differences in the speed of recovery and neurobehavior when compared to placebo.

Phospholipid Intermediates

Levin HS¹⁵ investigated the use of Cytidine diphosphoryl choline (CDP-choline) in 14 patients with mild TBI. Their results showed that there was a greater reduction in post-

concussional symptoms when compared to placebo ($p < 0.005$). They also found that improvement in recognition memory ($p < 0.02$). They found no other statistically significant differences in the other tests evaluated in the study.

Cholinergic Agents

Zhang et al.¹⁶ investigated the use of donepezil in patients from mild to severe TBI. This study found that the patients taking donepezil had statistically significant improvements in memory ($p < 0.001$) when compared to placebo after 10 weeks, with effects that carried over even during the cross-over period. Additionally, cognition scores were also statistically significant for patients taking donepezil ($p \leq 0.001$) when compared to placebo, as measured by the Paced Auditory Serial Addition Test (PASAT). Similar to the memory

analysis, the effects of cognitive improvements were carried over during the cross-over period. However, only 18 patients were included in this study, and it was unclear how many of those patients had a milder TBI.

In an open-label trial, Kaye NS et al.¹⁷ investigated the use of donepezil in 10 patients, six of whom had mild TBI. They reported that there was an impression of improved focus, attention, clarity, and thought while on donepezil. The Clinical Global Improvement Ratings in this study showed an improvement. However, there was no statistical analysis to indicate any statistical significance.

Tenovuo et al.¹⁸ also investigated the use of donepezil, along with galantamine and rivastigmine. The outcome used in this trial was the personal subjective experience with one of the study drugs. There was an apparent higher vigilance, attention, and increased functioning of the patients.

Peptide Treatments

Alvarez XA et al.¹⁹ investigated the use of cerebrolysin in 20 patients, three of whom had mild TBI. A significant improvement in cognitive performance was seen by the Syndrome Kurztest Test ($p < 0.01$). Filipova M et al.²⁰ assessed the effects of 1-desamino-8-D-arginine-vasopressin (DDAVP) on memory in patients with mild TBI. The Paced Auditory Serial Addition Test (PASAT) was found to be statistically significant in both the first and second series of tests ($p < 0.05$ and $p < 0.01$ respectively) compared to placebo. The Story Memory Test was also found to be statistically significant ($p < 0.05$) when compared to placebo.

Depression

From the identified articles, six studies were found that studied the effects of a pharmaceutical agent to treat depression after a TBI.^{12, 13, 21–24} The pharmaceutical agents that were investigated to treat depression were dopaminergic or serotonergic agents. All six studies used the Hamilton Rating Scale for Depression (HAM-D) as a measure for depression.

Lee H et al.¹³ found both methylphenidate and sertraline improves the HAM-D score ($p = 0.005$) of depressed patients, when compared to placebo. In two articles, Fann JR et al.,^{12, 21} described the treatment of sertraline in improving the HAM-D scores ($p < 0.001$) in patients with mild TBIs when compared to baseline scores. However, Ashman TA et al.²² found no statistically significant improvements in HAM-D scores when comparing sertraline to placebo.

Dinan TG et al.²³ compared the use of amitriptyline in functionally depressed patients to patients who developed symptoms of depression following a mild TBI. It was found that the patients that were functionally depressed responded better to amitriptyline when compared to patients with depression following mTBI (HAM-D, $p < 0.01$).

The use of milnacipran was investigated by Kanetani et al.²⁴ in 10 patients, seven of whom had mild TBI. In this open label study, it was found that milnacipran statistically significantly improved HAM-D scores when compared to

baseline at two weeks ($p = 0.0044$), four weeks ($p = 0.005$), and six weeks ($p = 0.0002$), when compared to baseline.

Amnesia

Two articles were identified that investigated the use of pharmaceutical agents and its effects on post-concussive amnesia symptoms. The use of rosuvastatin was investigated by Tapia-Perez et al.,²⁵ in which it was reported that there was a reduction in amnesia time with a hazard ratio of 53.76 (95% confidence interval (CI), 1.58–1824.64) when compared to placebo. However, it was unclear how many of the 21 patients had an initial GCS of at least 13. In a retrospective medical record review, Mysiw JW et al.²⁶ found that neuroleptic use during the acute stage of recovery can increase post-traumatic amnesia by almost seven days ($p = 0.00$).

Fatigue

The use of modafinil to treat post-concussive fatigue was investigated by Jha A et al.²⁷ in 51 patients, with 13 patients who had mild TBI. It was found that there was no significant difference in treatment with modafinil when compared to placebo over a 10-week period.

Corticosteroids

The death and disability from the use of methylprednisolone in treating patients with TBI was investigated in the Corticosteroid Randomisation After Significant Head Injury (CRASH) Trials.^{28, 29} Overall, the study reported a higher relative risk of death within two weeks when treated with corticosteroids, when compared to placebo (RR = 1.18; 95% CI 1.09 to 1.27; $p = 0.0001$).²⁸ When the endpoint was extended to death after six months of treatment, the relative risk of death was still higher when treated with corticosteroids compared to placebo (RR = 1.15; 95% CI 1.07–1.24; $p = 0.0001$).²⁹

In the CRASH trial, 10,008 patients were enrolled, where 3,002 patients reported with a GCS of 13 or above. In this mTBI group, the relative risk of death within two weeks was not statistically significant when compared to placebo (RR = 1.032; 95% CI 0.7322 to 1.4546; $p = 0.8573$).²⁸ Additionally, the relative risk after six months of treatment was not statistically different when compared to placebo (RR = 1.0808; 95% CI 0.8109 to 1.4405; $p = 0.5961$).²⁹

Discussion

The number of studies which investigated the use of drug therapies in patients with mild traumatic brain injuries was limited. Studies which included patients with mild TBI were usually only a fraction of the total sample size, and there usually was no separate analysis for this subgroup population. Most studies investigated the use of drugs in patients with more severe TBI patients. However, this present systematic review shows that there may be promising results if more studies were to be conducted on patients with milder traumatic brain injuries.