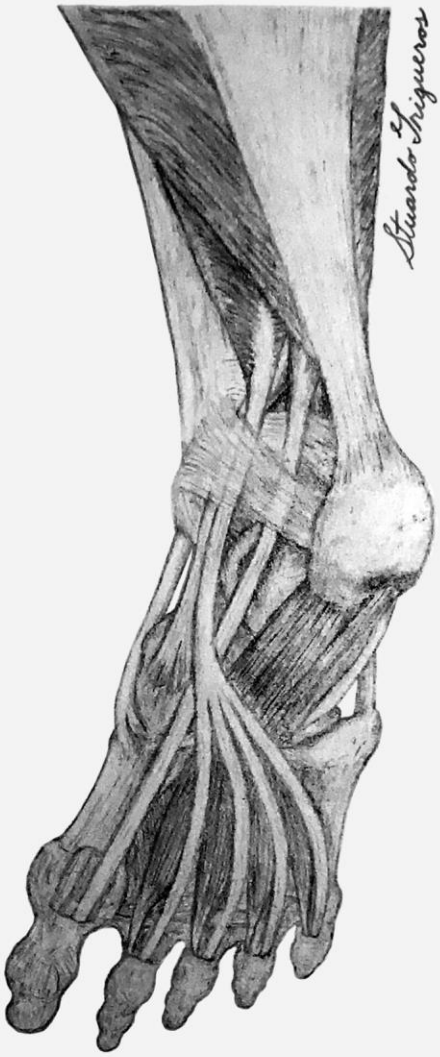
Volume 22
2019-2020

NFAR

National Foot & Ankle Review

The Academic Journal of Podiatric Medical Students



Published at the California School of Podiatric Medicine
at Samuel Merritt University

NATIONAL FOOT & ANKLE REVIEW

2019–2020
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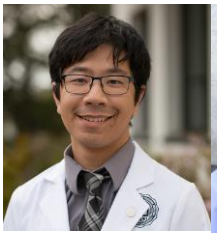
INQUIRIES:

Mailing address:
National Foot and Ankle Review
California School of Podiatric Medicine
c/o Editors-in-Chief
450 30th St. Suite 2860
Oakland, CA 94609

Email:
Direct to Editors-in-Chief
Phong.Ta@samuelmerritt.edu
Tamanna.Hoque@samuelmerritt.edu

California School of Podiatric Medicine
Samuel Merritt University
450 30th Street
Oakland, California
(510) 869 – 8727
(800) 607 – 6377
www.samuelmerritt.edu

Editors-In-Chief



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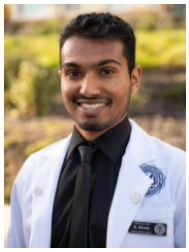

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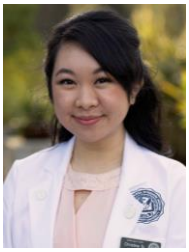

Christine Tu

A NOTE FROM THE EDITORIAL STAFF:

Welcome to the 22nd volume of the *National Foot and Ankle Review (NFAR)*, an academic journal produced by students at the California School of Podiatric Medicine (CSPM) at Samuel Merritt University. Each article is written by student authors and is peer-reviewed by student editors throughout the course of the academic school year.

As an editorial team, we thank all the student authors who submitted manuscripts for review. Even with the extra hardships caused by the COVID19 pandemic, the student authors meticulously learned and shared their research. We wish our fellow students success in their future endeavors and a rewarding lifetime of learning. It was a pleasure working with you all.

Next, the editorial staff would like to gratefully acknowledge our faculty advisor, Dr. Eric D. Stamps, for his invaluable guidance and keen editorial eye. We also thank Dr. Albert Burns, the founder of this journal, for his many years of dedication.

We dedicate this volume of the National Foot and Ankle Review to Dr. Chia-Ding Shih, an advocate for public health, who strives to improve students' learning by making scientific research education a vessel for acquiring knowledge and becoming better clinicians.

Finally, thank you for your support and readership of the *National Foot and Ankle Review*. We are proud to present the final product of our work this year.

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National Foot & Ankle Review

Effectiveness of Extracorporeal Shockwave Therapy in Chronic Achilles Tendinopathy: A Literature Review

Tamanna Hoque, B.S., M.S., Shalvi Prasad, B.S.

ABSTRACT

Extracorporeal Shockwave Therapy (ESWT) has been shown to relieve pain and improve function in patients with chronic Achilles tendinopathy (CAT) after failed or little improvement from conservative care such as physical therapy, orthotics, stretches, limiting mobility and impact activities, and nonsteroidal anti-inflammatory drugs. Augmenting ESWT with conservative treatment has also reduced pain, with some reporting no pain. ESWT treatment correlates with neovascularization and decreased calcification at the insertion site of Achilles tendon, which are indicative of a healing process. This treatment is effective for patients regardless of their age, presence, or absence of enthesophytes, and has lasting effects long after treatment has been completed. Therefore, ESWT can help avoid invasive procedures by safely and effectively improving outcomes for patients with CAT who have failed conservative treatments.

INTRODUCTION

Extracorporeal Shockwave Therapy

Extracorporeal Shockwave Therapy (ESWT) is a safe method that uses shock waves administered at various intensities to a metal plate target area. The shock waves that are transmitted to the target area are either focused or radial.[1] Focused shockwaves center around a specific area once the energy leaves the probe, while radial shockwaves are emitted directly to an area where the energy diverges outwards (see **Figure 1**).[2] ESWT has been historically used to help remove renal calculi and to treat erectile dysfunction.[3,4] Now, ESWT is also used for treating various musculoskeletal conditions including chronic plantar fasciitis and lower back pain. [5,6] The scope of ESWT as a treatment is still expanding. One expanded scope of treatment is for Morton's neuromas.[7] Furthermore, ESWT has shown promising results in treating chronic Achilles tendinopathy.[8]

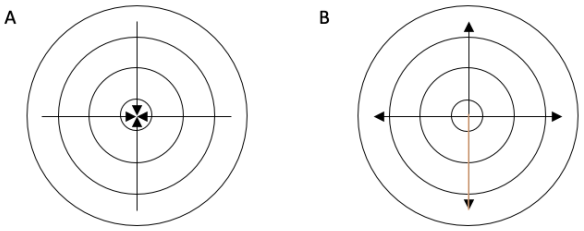

Figure 1. *Extracorporeal Shockwaves* (**A**) *Focused shockwave therapy with maximal energy generated at central location* (**B**) *Radial shockwave therapy with maximal energy dissipating*

The Achilles Tendon & Tendinopathy

The Achilles tendon transmits force from the gastrocnemius and soleus muscles to the calcaneus. This force, if excessive, can cause microscopic damage to the tendon. If the force applied to the tendon is limited to 4% or less of the total tendon load, the resulting microscopic damage can be healed. Inflammatory cells arrive at the injured site and initiate healing, which allows collagen to reform. If the force exceeds 8%, tendons can have macroscopic ruptures that are not easily repairable by the body.[8] Achilles tendinopathy can become a chronic issue because of poor healing processes and an absence of inflammatory cells.[8]

Chronic Achilles Tendinopathy (CAT) is more commonly seen among runners, likely caused by increased mechanical overload. However, people who participate in moderate to minimal activity can also suffer from CAT. In addition, multiple risk factors are associated with tendinopathy including advancing age, obesity, diabetes, hypercholesterolemia, hypertension, and genetic predisposition.[9,10] Thus, CAT is a condition that may limit activity.

The exact mechanism by which ESWT works to improve CAT is unclear. However, there are hypotheses as to why it is an effective treatment. One hypothe-

sis suggests that ESWT decreases the permeability of neuron cell membranes and induces an analgesic effect, which reduces pain reported by patients.[11] Another hypothesis is that ESWT promotes vascularization, bringing inflammatory cells to the treatment site to aid with the healing processes. Low-energy shockwaves introduce micro-traumas to the tendon, as opposed to macro-traumas (greater than 8% of mechanical force), which causes tendinopathy. Micro-traumas to the tendon recruit inflammatory cells, which promote tissue repair and regeneration.[11]

This article reviews recent studies demonstrating the effectiveness of ESWT in patients with CAT. The focus of this paper is to analyze the results of these studies to determine if ESWT should be considered before recommending more invasive treatments for CAT.

ESWT IN CHRONIC ACHILLES TENDINOPATHY

A Case Study

A 2018 case study by Nikolikj-Dimitrova et al. evaluated the effectiveness of radial ESWT in a 55-year-old, recreationally active male with CAT for 4 months.[12] A retrocalcaneal enthesophytes, a bony prominence or bone spur at the Achilles insertion site, was identified using conventional radiographs. Prior to receiving ESWT, the patient went through other forms of conservative treatment including activity modification, heel lifts, arch supports, stretching exercises, nonsteroidal anti-inflammatories (NSAIDs), and eccentric loading. The 11- point Numerical Rating Scale (NRS) was used to measure pain (a decrease in number indicates a decrease in pain) and the Roles-Maudsley Score (RMS) was used to measure function of the tendon (a decrease in number indicates an increase in tendon function, with 1 being excellent functionality and 4 being poor functionality). Prior to starting the ESWT treatment, the patient's NRS was 5 and RMS was 3 indicating pain with limited activities.[12]

The patient then received 2000 low energy radial extracorporeal shocks at a pressure of 2 Bar and frequency of 10 Hz at one-week intervals for 5 weeks.[12] In addition to ESWT, the patient was also advised to continue Achilles tendon stretches and exercises, decrease activity, refrain from performing high impact activity, and to wear comfortable, soft shoes. Results were recorded using NRS and RMS at immediate follow-up (1 week after treatment), short-term follow-up (3 and 6 months post-treatment), and long-term follow-up (12 and 18 months post-treatment).[12]

The patient reported an NRS score of 0, indicating no pain after the last ESWT treatment compared to a reported NRS score of 7 prior to starting treatment. At long-term follow up, the patient continued to report an NRS score of 0, indicating no pain. The RMS score also improved from 4 prior to receiving ESWT to 1, indicating no pain, full movement, and return to normal activity (see **Table 1**). This case study demonstrated the safety and efficacy of ESWT as a minimally invasive treatment for an older patient with CAT. Future studies need to expand this study with a larger sample size with a diverse cohort of subjects.[12]

A Retrospective Study

In a 2016 retrospective study, Wu Z et al. followed 67 patients with and without Haglund's deformity, who were treated with ESWT for insertional Achilles tendinopathy (IAT).[13] Haglund's deformity is a bony deformity of the posterosuperior calcaneus where the Achilles tendon inserts.[14] Thirty-seven subjects were categorized as having no deformity and 30 subjects had Haglund's deformity, confirmed via x-ray. All subjects had previously failed at least 6 months of conservative care: activity modification, physiotherapy, NSAIDs, and orthotics. Subjects received radial ESWT at 2000 pulses per session, once a week for a total of 5 sessions. Follow up was at 14.5±7.2 months and 15.3±6.7 months for the non-deformity and deformity groups, respectively (see **Table 1**).[13]

The Victorian Institute of Sport Assessment-Achilles (VISA-A) questionnaire score (0-100) was used to evaluate the severity of CAT and functionality of the Achilles tendon (a lower score indicates an increased number of symptoms with limited physical activity). The 6-point Likert scale was used to determine the success or failure of treatment. This grading scale was based on subjective assessments of the subjects. Scores of a 1 or a 2 indicate a successful treatment, and higher scores of 3-6 indicate treatment failure.[13]

In the non-deformity group, the VISA-A score increased from 49.57±9.98 at baseline to 83.86±8.59 at 14.5±7.2 months follow-up ($p<0.001$). In the deformity group, the score increased from 48.70±9.38 at baseline to 67.78±11.35 at 15.3±6.7 months follow-up ($p<0.001$). There was no significant difference in the 6-point Likert scale between the two groups ($p=0.062$), but there was a significant increase in VISA-A scores in both groups, indicating success of treatment whether the patient had Haglund's deformity or not (see **Table 1**).[13]

From this study, we can conclude that the presence of a spur does not change the effectiveness of ESWT to treat CAT. It can also be noted that the effects of ESWT are present long after the treatment has been performed. A shortcoming of this study was that patient follow-ups were not consistently taken at the same intervals from patient to patient. For future trials, each subject should return for follow up at equal intervals.[13]

Clinical Trials

Cheng Y et al. in a 2016 study used ultrasonography (US) to assess the effectiveness of ESWT in 42 patients with confirmed IAT.[15] All patients had an Achilles tendon that had areas of hypoechogenicity (appearing to have more lucent on the ultrasound than normal tendon) and more than half of the patients had some calcified plaque. Prior to participating, patients received non-invasive treatment for a minimum of 6 months, with no improvement in pain or function. Patients then received 2000 impulses at 6-8 Hz once a week, for 5 weeks. The severity of the CAT and functionality of the Achilles tendon were evaluated using the VISA-A questionnaire score at baseline, 4 weeks, and 12 weeks after the ESWT treatment.[15]

All patients had markedly improved VISA-A scores from 54±8.0 at baseline to 78.3± 5.6 at 4 weeks and 82.6±5.6 at 12 weeks.[15] This correlated with a decreased size of calcification from 8.5±8.4mm to 7.3±7.3mm at 4 weeks to 7.2±7.2mm at 12 week ($p=0.0$) evaluated using ultrasonography (see **Table 1**).[15] An increase in neovascularization was also seen using ultrasonography. This suggests the formation of new vessels improved blood flow to the inflamed tendon, leading to the repair and regeneration of the tendon.[15] The results of this study help demonstrate the underlying mechanism by which ESWT improves CAT. Future studies should incorporate a larger sample to strengthen the statistical significance.[15]

In a 2015 study, Carulli et al. studied the effectiveness of ESWT by evaluating results in three major tendon diseases: CAT, calcified tendonitis of the shoulder, and lateral epicondylitis of the elbow.[17] The study included 102 individuals with CAT who had tried and failed conservative treatment including NSAIDs, other analgesics, and physical therapy.[17]

Each patients received ESWT with 2400 shockwaves at an intensity of 0.08-0.33 mJ/mm^2 once a month for a total of 3 months.[17] A baseline Numeric Rating Scale (NRS) and ankle-hindfoot scale of the American Foot and Ankle Society (AOFAS) were obtained to assess pain and function, respectively. AOFAS score range from 0 to 100. An increase in AOFAS score represents a decrease in pain and increase in function. Follow up NRS and AOFAS scores were evaluated at 1, 6, and 12 months post-treatment.[17]

Before starting ESWT treatment, the patients' mean NRS score was 6.9±1.2.[17] The score improved to 5.3±1.1 ($p<0.001$) at 1 month, 1.7±0.8 ($p<0.001$) at 6 months, and 0.3±0.5 ($p<0.001$) at 12 months, indicating a correlation between ESWT treatment and decreased pain. The AOFAS score also showed significant improvement in function. The mean baseline score before starting the ESWT application was 71±5.6 ($p<0.001$), which then improved to 72±3.2 ($p<0.001$) at 1 month, 77±2.4 ($p<0.001$) at 6 months, and 86±1.9 ($p<0.001$) at 12 months (see **Table 1**). This study showed that ESWT provided long-term relief of pain and improved function in CAT patients. Although this study was double blind, adding a control group would help to illustrate the magnitude of decreased pain and increased functionality in patients who underwent the treatment compared to those who did not.[17]

In the study conducted by Pavone et al., 40 patients with chronic IAT were treated with low-energy ESWT after having persistent pain for 3 months with no improvement in pain after eccentric exercise.[18] Patients were assessed with the visual analog scale (VAS), ranging from 0 to 10, for pain evaluation (0 indicates no pain and 10 indicates worst pain possible) and AOFAS Hindfoot score for function and alignment. Prior to receiving ESWT treatment, all patients were treated with NSAIDs for 4-7 days and performed stretching and eccentric exercises for 50 minutes every day, four times a week.

Patients then started ESWT treatment in conjunction with eccentric exercises. Patients received 800 pulses of low-energy radial ESWT at a frequency of 4 Hz and 14 KeV every 2 weeks for 2 months.[18] Patients' mean VAS pain score was 7.6±0.6 before ESWT treatment, 3.8±0.7 at 2 months, 2.8±0.7 ($p<0.001$) at 6 months, and 1.9±1.2 ($p<0.001$) at 12 months post-treatment. The mean AOFAS score also improved from 71.4±4.6 before starting ESWT to 91.3±3.8 ($p<0.001$) after augmenting eccentric exercise treatments with ESWT. Having a larger sample size would increase the significance of the results, but overall, this study indicates that eccentric exercise treatment alone does not improve pain and function of Achilles tendinopathy as much as the combination treatment of ESWT and eccentric exercises (see **Table 1**).[18]

A Randomized Double-Blinded Trial

A double blind, randomized clinical trial conducted by Vahdatpour et al. in 2016 assessed the effectiveness of ESWT in 43 patients with CAT. Patients were randomly sorted into either the ESWT group (22 patients) or sham ESWT group (21 patients). The ESWT group received 1500 pulses of focused shockwaves (0.25–0.4 mJ/mm 2.3 Hz) and 3000 pulses of radial shockwaves (1.8–2.6 mJ/mm 2.21 Hz) every week for 4 weeks. The sham ESWT group did not receive shockwave therapy but were positioned to receive the therapy with ticking sounds mimicking a normal ESWT therapy session. Every individual who participated in the study concurrently received 4 weeks of physical therapy- consisting of stretches and exercises

Table 1. *Treatment Outcomes of ESWT on Chronic Achilles Tendinopathy*[12,13,15,17-19]

Studies	Measure of Effectiveness	Baseline Score	Post-ESWT Treatment Score	p-value
Vahdatpour et al.[19]	VAS	7.55±1.76	3.00±2.15	<0.001
	AOFAS	64.95±14.23	85.85±7.88	<0.001
Nikolikj-Dimitrova et al.[12]	NRS	Point 4, Pain	Point 1, No pain	---
	RMS	Limited activity	Full movement and activity	---
Wu Z et al.[13] No-deformity Group	VISA-A	49.57±9.98	83.86±8.59	<0.001
	6-point Likert Score	3.92±0.80	1.57±0.73	<0.001
Wu Z et al.[13] Deformity Group	VISA-A	48.70±9.38	67.78±11.35	<0.001
	6-point Likert Score	4.0±0.76	2.37±1.03	<0.001
Cheng et al.[15]	VISA-A	54±8.0	82.6±5.6	<0.01
	Neovascularization Score	1.3±1.1	0.6±0.9	<0.01
Carulli et al.[17]	NRS	6.5±1.4	1.2±0.8	<0.001
	AOFAS	71±5.6	86±1.9	<0.001
Pavone et al.[18]	VAS	7.6±0.6	1.9±1.2	<0.001
	AOFAS	71.4±4.6	91.3±3.8	<0.001

Abbreviations: ESWT, Extracorporal Shockwave Therapy; VAS, Visual Analog Scale, AOFAS, American Orthopedic Foot and Ankle Society; NRS, Numerical Rating Scale; RMS, Roles-Maudsley Score; VISA-A; Victorian Institute of Sports Assessment-Achilles.

and were also given 100 mg diclofenac sodium daily for 2 weeks.

The effectiveness of the ESWT was assessed using a VAS and the AOFAS scoring system to quantifying patients' pain and function, respectively. VAS and AOFAS scores were obtained before treatment, immediately after treatment, at 4 weeks, and at 16 weeks post-treatment. The mean VAS score decreased from 7.55±1.76 at baseline to 3.00±2.15 at 16 weeks post-treatment in the ESWT group compared to a decrease in baseline score of 7.70±1.34 to 4.30±1.84 in the sham ESWT group (p=0.047). Likewise, at 16 weeks post-treatment, the AOFAS score of the ESWT group increased from 64.95±14.23 at baseline to 85.85±7.88, when compared to an increase in baseline score from 64.40±11.96 to 79.50±7.53 in the sham ESWT group (p=0.013). Both VAS score and AOFAS score improved significantly more in the ESWT group compared to the sham ESWT group (see **Table 1**).[19]

Thus, this randomized, controlled, double-blinded study demonstrated the effectiveness of ESWT treatment in patients with CAT. Although this study has the highest level of evidence of the studies presented in this paper, it had a small sample size.

CONCLUSION

ESWT should be considered as a safe and effective treatment for patients with CAT who have failed other forms of conservative treatment. It should be noted that current studies have used varying numbers of shockwaves given per session and different modalities (focused and radial shockwaves) in a single treatment session. Having a more specific protocol with clearly defined shockwave intensities and the use of VAS and AOFAS scales to measure the effectiveness of ESWT in treating CAT would be helpful before adopting ESWT treatment as a conventional treatment for CAT. However, there is enough evidence that adding ESWT to conservative therapy should be considered in the treatment protocol for CAT.

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National Foot & Ankle Review

Risk of Statin-induced Tendon Injury in the Lower Extremity

James Diep, B.A., M.S., Daniel Kim, B.A., Raheel Majeed, B.S., M.A, Nicklaus Nishijima, B.S., Gautam Sowda, B.S.

ABSTRACT

Statins are widely used and considered safe for the treatment of high cholesterol. Over the years, case reports have illustrated a link between statin therapy and tendon injury, especially of the Achilles tendon. The findings of studies with higher levels of evidence have been controversial. Some studies have found a correlation between statin therapy and Achilles tendinopathy while others have not. Laboratory studies using mouse models have been the most conclusive in finding evidence of tendon injury due to statins. The histological similarity to tendon injury after statin therapy, the reduction in proteins needed to heal tendons, and the decreased migration of tendon cells to injury sites all point to the potential for statin-induced tendon injury. The mechanisms of statin-induced tendon injury and the confounding variable of hypercholesterolemia need to be addressed in future studies. In the meantime, awareness of the link between statins and tendon injury will help improve patient care.

INTRODUCTION

Statins have been used increasingly since 1987 to reduce hypercholesterolemia with the goal of preventing adverse cardiovascular events. The percentage of the population forty years of age and older using statins increased from 18 to 26% between the years 2003 and 2012.[1] In the United States in 2006, there were 157 million statin prescriptions issued grossing $16 billion.[2] Although statins have been studied and deemed safe to use, an increasing number of tendon rupture cases in the presence of statin therapy are being reported.[3] While physicians that treat tendon injury may not prescribe statins, those physicians should be alert to the potential link between statin use and tendon injury.

The link between statins and tendon injury may be questioned, as most of the published tendon studies were underpowered. None had a high enough level of evidence to confirm causation. This paper explores the current literature on statin-induced tendinopathies and discusses the possible pathophysiology attributed to statin-induced tendon injury.

STATINS BACKGROUND

Statins are a widely prescribed class of drugs used to reduce serum cholesterol and low-density lipoprotein (LDL). This effect is achieved through statins' property as a 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA Reductase) inhibitor, an enzyme in the cholesterol synthesis pathway. Large clinical trials have demonstrated the efficacy and safety of statins. Minor adverse drug reactions (ADRs) associated with statin therapy include headache, dyspepsia, constipation, and increase in transaminases. Major ADRs that have been reported with low incidence include myopathies, elevated creatine phosphokinase (CPK), elevated liver enzymes, and rhabdomyolysis.[3]

STATIN-INDUCED TENDINOPATHY

Few studies with high level of evidence illustrate or contradict the link between statins and tendon injury. Therefore, the association between statins and tendon injury remains inconclusive. Few controlled clinical trials and meta-analyses have been conducted to explore this relationship. Some studies have found a correlation, but none have found causation. There is, however, enough lower-level evidence to suggest that statins have a role in tendon injury. Most recent available data regarding this topic is presented below.

One case study raises concerns for Achilles tendon healing time when one or more statins are reinstated for lipid control. In this study, an active 40-year-old male, who was previously healthy other than hypertension and an elevated lipid profile, suffered an Achilles tendon rupture, which was surgically

repaired. After 18 weeks of physical therapy, the patient was pain-free and returned to activity. However, after resuming statin therapy (2.5 mg/day oral rosuvastatin for 7 weeks), the patient began experiencing Achilles' tendinopathy, which included swelling, redness, and joint stiffness. The symptoms disappeared when statin therapy was discontinued but returned with use of pravastatin at 20 mg/day orally. After reinstating pravastatin, the patient complained of debilitating tightness in the calf, so the statin therapy was discontinued again. Two months after the discontinuation of statins, the patient was able to walk with minimal discomfort.[4]

A retrospective study using data collected from 31 French Pharmacovigilance centers examined 96 patients reporting tendon injury after statin therapy between 1990 and 2005. The study found that 2.1% of all reported statin ADRs were tendon injury. Among those, 65.6% were tendinopathies and 34.4% were tendon ruptures. The Achilles tendon was the most frequent site of injury as it accounted for 52.1% of the cases.[3] Injury to the Achilles tendon was unilateral in 58.7% of cases. The mean time from starting statin therapy to injury was ten months. The researchers recognized major limitations of this retrospective study including the inability to control for confounding variables such as older age, pre-existing tendinopathies, and strenuous physical activity.[5] They acknowledged that a randomized controlled trial was needed to connect statins and tendon injury, but nevertheless recommended that physicians be aware of the risk.[3]

A Finnish case control study suggested the opposite, that there is no association between Achilles tendon ruptures and statin therapy. In this study, 1118 patients who ruptured their Achilles tendon between 1998 to 1999 were evaluated using data from historical Finnish hospital discharges.[6] Many drugs were assessed, but only fluoroquinolones were associated with tendon rupture (Odds ratio 2.20, 95% Confidence Interval 1.28-3.76, p=0.005). No significant increase in ruptures was found with lipid-modifying therapy such as simvastatin, fluvastatin, and lovastatin (Odds ratio 1.54, 95% Confidence Interval 0.96-2.48, p=0.465). However, this study only reviewed ruptures, not tendinopathies.[6]

Animal model research has demonstrated a link between statins and tendon injury. One such study evaluated the effects of simvastatin, atorvastatin, and rosuvastatin on the Achilles tendons of rats.[7] Forty-nine mice were divided equally into groups of 7. One group was designated as the control group. The other 6 groups were categorized by statin type and dosing as follows: atorvastatin 20mg/kg per day, atorvastatin 40 mg/kg per day, rosuvastatin 20mg/kg per day, rosuvastatin 40 mg/kg per day, simvastatin 20 mg/kg per day, and simvastatin 40 mg/kg per day. Statin treatments were administered for three weeks. After a week of discontinued treatment, the rats were euthanized, and their Achilles tendons were dissected. Researchers measured the force required to tear the tendon as well as the maximal force that did not tear the tendon but caused permanent injury. In the atorvastatin and rosuvastatin groups, a significantly lower force was needed to cause rupture and injury. The simvastatin group showed significantly lower force was needed for injury, but not for rupture. There was no significant difference between dosage groups. All statin treatments showed calcification of the tendon on histological examination.[7]

Another animal study used 50 rats and divided the sample into five groups (control, atorvastatin 20 mg/kg per day (A-20), atorvastatin 80 mg/kg per day (A-80), simvastatin 20 mg/kg per day (S-20), and simvastatin 80 mg/kg per day (S-80)). The study measured the extracellular protein and collagen degrading enzyme concentration in the Achilles tendon after treatment. The study found a trend towards reduction in extracellular proteins in the S-20 group and a significant increase in collagen degrading enzymes in both the S-20 and the A-80 groups. Glycosaminoglycans, an extracellular protein responsible for strength at the distal ends of tendons were reduced. In addition, researchers found that Matrix Metalloproteinase-9 (MMP-9), an enzyme that degrades collagen type I, was increased.[8] A follow-up study using the same experimental design found degenerative changes, histologically, in the collagen fibers in the A-20 and S-20 groups.[9]

A cell study evaluated the effect of statins on human tendon cells or tenocytes. Tenocytes were harvested from hamstring tendons. Sub-therapeutic, therapeutic, and supra-therapeutic concentrations of lovastatin were then administered. The study found a reduction in tenocyte migration, which is necessary for healing, with proportional increase in dose.[10]

The overall results of biomechanical, chemical, and histological examination show that statins adversely affect tendons, though it is not clear what dose is needed to have an adverse effect.

PROPOSED MECHANISMS

The exact mechanism by which statins may cause tendon injury is unknown. One leading hypothesis is that collagen remodeling after microtrauma is inhibited by statins through the dysregulation of matrix metalloproteinases. Specifically, MMP-9 levels h increased with simvastatin therapy.[8] The inability to remodel collagen after microtrauma makes tendons that are under constant stress, such as the Achilles tendon, prone to rupture.

Another effect seen in lovastatin, simvastatin, and atorvastatin therapy was decreased migration of tenocytes to sites of injury and an alteration of the extracellular matrix protein profile.[13] Again, this would affect healing of the Achilles tendon after microtrauma.

A third hypothesis is tied to the inherent purpose of statins which is to disrupt cholesterol synthesis.[11] In achieving this effect, statins may reduce cholesterol on the cell membrane which is necessary to maintain cell fluidity, including those of tendon cell membranes.

Two lesser hypotheses involve the reduction of isoprenoids and the ability of statins to induce apoptosis.[8] Isoprenoids are needed to modify substances present in muscle injury.[7] Inability to modify these substances can lead to further tendon injury.[5] Statins have also been found to induce apoptosis in some cancer cells. This same effect may occur on tendon cells.[1]

CONFOUNDING VARIABLES

Patients on statin therapy often have comorbidities and other factors than may also contribute to tendon degradation, including old age, strenuous exercise, and prior tendinopathy.[5] The largest confounding variable, however, may be hypercholesterolemia. In a post-Achilles tendon rupture study, 41 patients had operative repair of their Achilles tendon and blood levels of cholesterol were obtained. Eighty-three percent of patients had elevated levels (>200 mg/dl). The study did not indicate if these patients were using statins.[11] In a mouse model, apolipoprotein E knockout mice (high cholesterol levels) demonstrated reduced patellar tendon healing histologically compared to control mice ($p=0.02$).[12] These findings make it difficult to distinguish whether the effects of statins and hypercholesterolemia are synergistic or if only one contributes to tendon injury.

CONCLUSION

Statins are an effective and relatively safe medication for lowering cholesterol. Tendon rupture and tendinopathy are rare occurrences, but patients should be made aware of the risk. Current research remains inconclusive. Controlled studies have not been able to prove or disprove a correlation. The most important link has come from animal studies of the biomechanical, chemical, and histological properties of tendon cells after statin therapy. These studies have shown that statins do have an adverse effect on tendons. These findings should provide the basis for more clinical trials to better determine whether these effects are seen at a therapeutic level.

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National Foot & Ankle Review

Comparison of Cartilage of the Ankle and Knee Joint and Implications for Subchondroplasty

Ramez Sakkab, B.S., Melissa Lipari, B.S.

ABSTRACT

Osteochondral lesions of the talus (OLT) create significant morbidity among patients with ankle pathology. Several surgical interventions for OLTs have been proposed with varying levels of evidence for their use. Subchondroplasty (SCP) is a novel surgical technique in which a calcium phosphate material is arthroscopically inserted into bone marrow lesions. This technique is useful for lesions with mild-to-moderate cartilage damage and is considered minimally invasive. Recent promising evidence of its use in the knee suggests that this technique may be expanded to the ankle. As a non-direct cartilage intervention, SCP may not be constrained by the differences in knee and ankle cartilage. In particular, ankle cartilage is nearly 60% less thick, has a greater compressive capacity, a greater relative cellular regenerative function, and a greater uniformity when compared to knee cartilage. The increased capacity of ankle chondrocytes to heal, and positive results from recent studies indicate that SCP may have promising use in the talus.

INTRODUCTION

The progression of osteoarthritis (OA) has been correlated to lesions of subchondral bone and the chondral surface collectively called osteochondral defects (OCDs).[1-3] These OCDs can be present with or without deeper bone marrow lesions (BML) as seen on magnetic resonance imaging (MRI) as bone marrow edema.[4-6] Although more prevalent in the knee and hip, considerable morbidity and debilitation is associated with OCDs of the talus. The incidence rate of these lesions has been estimated at 27 per 100,000 person years among the active military population.[7] These osteochondral lesions of the talus (OLT) are a common cause of chronic ankle pain and disability with the potential to advance to symptomatic OA.[4,8,9] Incidence of articular cartilage injury has been reported in up to 50% of patients with ankle sprains and acute ankle fractures.[10,11] Despite its prevalence, standardized treatment for OLTs has not yet been established.[1,7,12] Historically, surgical treatment has been reserved for those who fail conservative regimens.[7] However, conservative treatment for OLTs, consisting of a combination of protected or modified weight-bearing, activity moderation, and cast immobilization, has exhibited mixed results.[12] The outcomes for those treated conservatively often involve only symptomatic relief.[12] For these reasons, along with the minimal healing potential of native articular cartilage, the majority of recent literature surrounding treatment to address OLTs is surgical.

Surgical treatment can be grouped loosely as reparative procedures, such as bone marrow stimulation (BMS), or replacement procedures, such as osteochondral allograft transplantation (OATS).[7,12-15] A novel reparative procedure, created in 2007 for BML or OCDs, is Subchondroplasty (SCP).[16,17] The SCP procedure comprises of an injection under fluoroscopy of synthetic, flowable calcium phosphate (CaP) into a bone to generate subchondral bone remodeling by augmenting structural integrity.[17,18] Nearly all research of SCP has been conducted in the knee joint.[19-21] To understand and project SCP viability in the ankle, the differences between knee and ankle cartilage as well as current SCP outcomes must be appreciated.

COMPARING KNEE AND ANKLE CARTILAGE

Cartilage tissue is avascular and aneural. However, cartilage of the ankle joint (distal tibia and talar dome) differs from that in the knee (femoral condyles and proximal tibia) in its biomechanical and biochemical properties.[22-25] Morphologically, the ankle is more congruous than the knee joint. The congruency of the ankle lends itself to thinner articular cartilage.[24] Specifically, mean cartilage thickness ranges from 1.0 to 1.62 mm in the ankle and 1.69 to 2.55 mm in the knee. This is made possible by the greater compressive modulus in the ankle joint.[24-26] The compressive modulus is the ratio of how much a material compresses

and the applied stress. In other words, it quantifies the resistance capability of a material.[26] Ankle cartilage features nearly twice the equilibrium modulus of knee and hip cartilage. Equilibrium modulus quantifies the reaction force that follows relaxation of applied stress.[23] There is also a decreased permeability and increased density within ankle cartilage.[27,28] This translates to increased resistance to shear forces in the talus, as necessitated by the rotary forces experienced by the ankle in contrast to the knee. The ankle thus maintains a superior inherent stiffness and compressive resistance compared to the knee.[26] These attributes explain why the most common etiology of arthritis in the ankle is post-traumatic, rather than from primary osteoarthritis as seen in the knee and hip.[25,29] This is further supported by the effects of aging (increased water content and decreased proteoglycan content of hyaline cartilage) which occur to a greater degree in the knee and hip than ankle.[30]

At the cellular level, ankle chondrocytes are more responsive to anabolic factors and less responsive to catabolic factors.[28] Additionally, the ankle contains increased synthesis markers and a relative lack of matrix metalloproteinases (MMP), compared to the level normally detected in the knee.[31] A decrease in MMPs allows greater longevity of cartilage extracellular matrix and proteins, while boosting chondrocyte reparative and compensatory processes.[32] The pattern of the chondrocyte arrangement also differs. The knee joint features predominantly single-cell patterns, while the ankle cartilage is arranged as paired cells.[33] In the ankle cartilage, there is also a smaller partition coefficient of solute transport due to a smaller effective pore size.[34] This is most likely secondary to a greater amount of proteoglycans and less water content.[30,34] This smaller partition coefficient benefits the ankle joint by causing an increased concentration of chondrocytes and growth factors.[30,34]

The aforementioned differences in ankle cartilage support its greater resistance to wear, and thus increased likelihood of developing post-traumatic OA rather than primary OA, as seen in the knee.[24,27] These biochemical attributes also demonstrate greater capacity for ankle joint repair after injury, making it more suitable for reparative rather than replacement procedures such as SCP. The data concerning SCP, reviewed next, has been conducted in the knee joint.

SUBCHONDROPLASTY RESULTS IN THE KNEE

The primary goal of SCP is restoration of natural osseous biology.[17,29] Since developing the procedure, Cohen and colleagues have published substantial data relating to its efficacy in the knee joint. Sharkey and Cohen exhibited favorable outcomes with SCP use in a case report in 2016. Their results demonstrated MRI resolution of bone marrow edema and a subjective reduction in pain from severe and activity limiting to minimal with an active lifestyle 31 months post-procedure. [16] This case report was the first to demonstrate a successful human outcome with SCP. From 2008-2012, Farr and Cohen performed a prospective study with 59 patients and mean follow-up of 14.7 months. In the study, 15 of 60 patients were recalcitrant to SCP treatment and electing for unicompartmental or total knee arthroplasty (TKA), which are joint replacement procedures for the knee.[18] Pain improvement was immediate and pronounced post-operatively but remained relatively unchanged 6 weeks after SCP. Cohen and Sharkey conducted a case series of 66 consecutive patients who underwent SCP. Thirty-four patients had at least 2 years of post-operative follow up, 29 of which had significant pain improvement ($p<0.001$).[17] Byrd et al. conducted a larger cohort study which included short to mid-term follow up of 133 SCP patients.[35] Pain scores decreased from 8.3 to 3.4 on VAS scale, and 32 patients (25%) progressed to TKA. Notably, the pain score (3.4) was maintained at mid-term follow-up. Of the 84 patients with mid-term results, 30 (41%) required injections to such pain. Lastly, 93% of all patients stated they would have the SCP procedure again. However, considerable cost and time is associated with the results given that one quarter of patients still underwent TKA after the initial index procedure.[35]

More recently, Astur et al. conducted a systematic review of 10 studies, totaling 164 patients who underwent SCP. The pooled data elucidated a 70% survival from TKA and improvement in Visual analog scale (VAS) pain scores and International Knee Documentation Committee (IKDC) functional scores. The VAS score quantifies subjective pain while the IKDC score quantifies objective functional measures such as swelling, locking, or difficulty with performing certain movements. However, 25% of patients stated they had "some type of pain" at their most recent follow-up. Of note, the use of fluoroscopic guidance and amount of CaP injectable was not uniform throughout the 10 studies.[36] The different amounts of CaP used for BML/OLTs in the studies is a major limitation of results.

Many of these same studies were used in a 2019 systematic review by Sundaram et al. of 163 total patients, reciprocating the findings. Overall, the five studies included demonstrated a drop in pain as seen in the decrease in VAS from initial presentation of 6.68 to 2.74 form initial present. At a mean follow-up of 18 months and post-operatively, complications secondary to the SCP occurred at a rate of 2.5%.[36]

Successful outcomes following SCP have not been ubiquitous. Conaway et al. reported a 54-year-old female patient whose symptoms and ability to bear

weight worsened post-operatively. A diffuse hyperintense T2 signal on MRI was seen at the site of the SCP. This patient also had a concurrent partial meniscectomy at the time of SCP.[37] Chatterjee et al. performed percutaneous CaP injections from 2012 to 2014 on 33 patients and measured outcomes via Tegner Lysholm Knee Score Scale. SCP resulted in only a 55% clinical success rate as defined by the aforementioned scale.[38]

Chatterjee and colleagues conducted all final follow-up data by telephone interview, without in-person physical examination as done in the aforementioned studies. Nevertheless, these results contrast with cotemporary publications that find SCP to be efficacious, as previously discussed. This means that there are other factors that influence the ability of success. Many knee studies did not analyze patient demographics, and that may be the reason for the conflicting conclusions. Specific patient demographics, such as BMI and socioeconomic status, should be measured in future studies for a more complete understanding of the potential predictors of SCPs failures and successes.

EXTRAPOLATING TO THE TALUS

Based on the differences between the ankle and knee joint cartilage, extrapolation of knee SCP outcomes to the talus may be imprudent. For example, MRI findings in the knee and in the talus have differing morphology and cartilage depth.[22] Therefore, a post-surgical MRI of the knee may look different than a similar successful outcome in the ankle.[22] However, pain may be translatable between joints. Osteoarthritis of the knee and ankle has demonstrated similar levels of patient debilitation and VAS, regardless of the cause.[1] One may be able to directly compare patient pain secondary to damaged cartilage or subchondral bone. Anatomically, cartilage is avascular and aneural.[8] One hypothesis is that pain is generated by reactions of the integrated subchondral bone, and to a far lesser extent from the synovium.[8] SCP acts to repair the damaged subchondral bone, a likely source of pain. Therefore, known VAS improvement post-SCP in the knee provides promise for similar ankle outcomes.

There are severe limitations of the literature encompassing SCP within the talus. One limitation is the small number of patients participating. However, the following positive results necessitate further investigation into SCP for OLT in future research. SCP is most commonly applied arthroscopically to the OLT to provide an osteoconductive void-filling substitute.[16,35] Miller and Hood published a case study of 2 patients who had undergone successful SCP with reduced pain in the ankle joint at 10-month follow up.[35] Both patients, males aged 42 and 28, returned to regular activities including athletics with minimal pain managed by nonsteroidal anti-inflammatories. Amount of SCP used for the lesions was not quantified. Chan et al. published what may be the largest cohort to date of SCP for OLTs with 11 patients.[41] The purpose of their report was to demonstrate safety and efficacy of the procedure in the talus. The authors measured OCD size, with a mean 1.3 x 1.4 cm, as well as CaP used with a mean of 1.7cc. At a follow-up of 52 weeks, mean weight-bearing VAS improved from 7.8 to 1.8, and mean Foot and Ankle Outcome Scores (FAOS) improved from 67.1 to 89.6, shifting from good to excellent on the scale.[41] The FAOS objectively measures ankle function and symptomatology through a questionnaire on function in daily living and sports/recreation, and ankle related quality of life. However, Chan et al. also encountered an adverse event, in which one patient suffered a talar neck fracture between postoperative weeks 5 and 6. The authors postulated that, along with visibly unstable cartilage, too large a CaP paste injection was given intraoperatively. To avoid this complication, surgeons should err on the side of too little CaP, rather than too much. Still, all patients in this cohort stated they would have the SCP surgery again given their original baseline. While these studies show that CaP injections are effective at reducing pain, the number of participants limits the data. Despite the current lack of literary evidence, the ankle is in theory a better candidate for SCP than the knee due to its robust and reparative chondrocytes. A recent study been published outcomes after utilizing SCP in other articular regions of the foot.[42] With substantial data supporting SCP in the knee, further research on the ankle is warranted.

CONCLUSION

Subchondroplasty as developed by Sharkey and Cohen uses a biphasic calcium phosphate injectable to treat a subchondral defect, originally performed in the knee.[16,17] Despite a deficiency of research on SCP in the talus, there are biochemical and biomechanical indications for the technique. The characteristics of ankle cartilage demonstrate its increased uniformity, resiliency, and chondrocyte reproducibility compared to knee cartilage.[22-25] As such, SCP hypothetically should be better at treating BML and OCD in the talus than in the knee. Because the mechanism of action of SCP is to resolve lesions of painful subchondral bone, one may be able to extrapolate pain reduction results observed in the knee cartilage to the ankle cartilage.

Nevertheless, the ability of bone to incorporate the CaP relies on many variables. Those variables are the host physiology, amount of CaP used, and the size of the lesion. Recent studies have shown good-to-excellent short-term results with SCP in the talus.[35,41] However, long-term safety and efficacy are not yet known as of this writing. Thus, adding SCP to the

standard armamentarium for OLTs may be precarious. Perhaps more importantly, the current literature and science of cartilage may provide the basis for higher-level studies for this intervention.

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National Foot & Ankle Review

Orthobiologics for the Treatment of Osteochondral Lesions of the Talus

Niyayesh Gorjikia, BS., Sunakshi Garg, BS., Phong H. Ta, BS., M.S.

ABSTRACT

Osteochondral lesions of the talus (OLT), which can vary from osteochondral fractures to osteochondritis dissecans, involve the talar articular cartilage and subchondral bone. Most OLTs manifest secondary to trauma, such as ankle sprains and ankle fractures. Up to 50% of ankle sprains and 73% of ankle fractures result in OLT, and there are over 2 million ankle sprains per year in the United States. Operative treatments for OLT consist of replacement or reparative strategies. Replacement strategy involves replacing the OLT with hyaline cartilage from a graft harvest. Reparative strategies allow bone marrow progenitor cells to infiltrate the lesion and create fibrocartilage to repair the defect. Recently, orthobiologics, a form of reparative therapy, are being used as adjuncts in the treatment of OLT. Two common orthobiologics are plasma rich protein (PRP) and bone marrow aspirate concentrate (BMAC). PRP is an autologous blood product that contains high concentrations of platelets, growth factors and cytokines. BMAC contains a combination of mesenchymal stem cells, hematopoietic stem cells, platelets, and cytokines. This article illustrates the benefits of using orthobiologics in the treatment of OLTs.

INTRODUCTION

Osteochondral lesions of the talus (OLTs) involve injury to the talar bone and its articular cartilage superiorly.[1] Pain is proposed to be caused by a rise in intraosseous fluid pressure on the weakest surface of the talus during ambulation. This can produce subchondral cysts and will aggravate the nerves associated with the subchondral bone.[2] OLTs are challenging to treat as there is poor vascular supply to the talus and poor regenerative capacity of the articular cartilage.[1]

Even though most OLT are caused secondary to trauma, OLTs progress slowly. The ankle joint has congruent joint surfaces and thin articular cartilage that enables the joint to tolerate the axial loading during gait. When the talus is injured, these same factors prolong the progression in creating subchondral cysts.[2] Seo et al. followed 142 patients with untreated OLT and measured the progression of osteoarthritis for an average of six years. These patients did not have any restriction in activities. The OLTs in all patients did not worsen, regardless of their size and location.[3]

Hannon et al. describes several treatments for both asymptomatic and symptomatic lesions. Patients with asymptomatic lesions were advised to use non-steroidal anti-inflammatory medication and to restrict athletic activities. For symptomatic lesions, two surgical approaches were considered. The first approach was reparative, such as microfracture and bone marrow stimulation. For microfracture procedures, a physician drills and creates holes in the subchondral plate. This induces mesenchymal cells and growth factors to start producing collagen. The second was replacement with fresh and frozen tissue allograft. The decision to perform the former or latter was primarily determined by size of the OLT. For example, if the OLT has a 15 mm diameter, the reparative microfracture approach is more favorable.[4] In a prospective study following 105 patients, Chuck-Paiwong et al. found that 73 patients with lesions less than 15 mm, who underwent microfracture repair, had "good to excellent results." However, 31 of the 32 patients with lesions over 15mm had "poor results."[5]

Biological augmentation of OLT's, including the use of BMAC and PRP, has recently been developed. PRP is an autologous blood product that contains a high concentration of platelets, growth factors and cytokines. BMAC contains a combination of mesenchymal stem cells (MSCs), hematopoietic stem cells, platelets, and cytokines. These are used as an adjunct to surgical treatments such as microfracturing and

autologous osteochondral transplantation. Their effectiveness has been well documented since 2014.[4] The objective of this article is to discuss current research and further illustrate benefits of using these orthobiologics in the treatment of OLTs.

PLASMA RICH PROTEIN

Plasma rich protein (PRP), an autologous blood product containing a high concentration of platelets, growth factors and cytokines, is useful for conservative treatment of OLT's. In a randomized study, Ahmet Guney et al. examined the effects of arthroscopic microfracture surgery alone or with combination of PRP in the treatment of OLTs.[6] A total of 35 patients were randomly divided into a control group who solely received treatment with microfracture surgery and an experimental group who were treated with microfracture surgery and PRP. Patients were then assessed using three different scoring measurements: American Orthopedic Foot and Ankle Society (AOFAS) score, Foot and Ankle Ability Measure (FAAM), and the visual analogue scale (VAS) for pain. After an average follow up of 16.2 months, the group of patients who were also treated with PRP showed an improvement in all three scoring instruments. AOFAS for the experimental group was 89.2±3.9 vs. 71.0±10.2 for the control group (p=0.001). FAAM overall pain domain was 1.0 (1.0–2.0) for the experimental group vs. 2.5 (1.0–4.0) for the control group (p=0.04). VAS also showed an improvement with the average for the experimental group being 2.2±0.8 vs. 3.8±1.2 for the control group (p=0.001). This study showed that combining PRP with arthroplasty micro fracture surgery significantly improved outcomes.[6]

In a prospective randomized study, Mei-Dan et al. examined the effectiveness of PRP vs. hyaluronic acid (HA) in the treatment of OLTs.[7] Thirty-two patients who had tried other treatment modalities with no improvement were selected and randomly assigned to receive either PRP or HA for treatment of OLTs. Patients were then assessed at weeks 4, 12, and 28 following the injection using five scales: the Ankle-Hind Foot scale (AHFS), the subjective global function, and the VAS for pain, stiffness, and function. AHFS scores showed improvement for both groups ($p<0.0001$). However, the PRP group's mean standard deviation at the 28th week was 92.5 vs. 78.3 for the HA group ($p<0.05$). VAS scores for stiffness for the PRP group at 28th week was 0.8 vs. 2.9 for the HA group ($p<0.05$). VAS scores for function for the PRP group at the 28th week was 0.8 vs. 3.5 for the HA group ($p<0.01$). Therefore, VAS scores for both stiffness and function also showed a significant improvement for PRP group over the HA group. Most importantly, VAS scores for pain for the PRP group at 28th week was 0.9 vs. 3.1 for the HA group ($p>0.05$); therefore, PRP's role in improving pain was inconclusive. Mean subjective global function also increased for both groups but similar to other scales, the PRP group yield improvement ($p<0.1$) with the PRP group at 28th week reporting 91 vs. the HA group reporting 73.[8] This study shows that PRP alone is an effective treatment for OLTs even in the patients who have failed other treatment modalities.[7]

In a retrospective cohort study, Akpancar et al. has compared PRP and prolotherapy (PrT) injections in the management of OLTs.[8] PrT is an injection that consist of a potential irritant such as dextrose and it is thought that it can trigger healing. The PrT solution that was used in this study consisted of 25% dextrose for intra articular injections and 15% dextrose. Forty-nine patients with chronic symptomatic OLT lasting more than six months and had received numerous conservative treatments without any improvements were selected and divided into two groups of PrT and PRP injections. Patients were given a total of 3 injections of 4ml solution into their ankle joint spaces and then evaluated using the VAS, AOFAS, and Ankle Osteoarthritis Scale (AOS) at 21, 90, 180 and 260 days. VAS score at 21st day for PrT was 129.37 vs. 137.41 for PRP, and at 260th day, it was 29.89 for PrT vs. 30.05 for PRP. AOFAS score at 21st day for PrT was 67.52 vs. 63.05 for PRP, and at 260th day, it was 89.44 for PrT vs. 87.77 for PRP. AOS score at 21st day for PrT was 75.15 vs. 86.45 for PRP, and for 260th day, it was 29.89 for PrT vs. 30.05 for PRP. Results showed that both PrT and PRP treatments resulted in improvement of both pain and function ($p<0.001$). In this study, 90.0% of the patients who received PRP and 88.8% of the patients who received PrT reported that they were happy with the outcome of their treatments. None of the patients reported any side effects from the injections such as fever, hematoma, or infection, which suggests that PRP is both effective and safe for treating OLTs.[8]

BONE MARROW ASPIRATE CONCENTRATE

Bone marrow aspirate concentrate (BMAC), also known as bone marrow concentrate (BMC), is another orthobiologic that is being used as an adjunct in the treatment of OLT. BMAC contains a combination of MSCs, hematopoietic stem cells, platelets, and cytokines.[9,10] While the amount of growth factors in BMAC is less than PRP, BMAC has higher concentration of MSCs and hematopoietic stem cells, allowing it to be a useful adjunct to both reparative and replacement therapies of OLT. The MSCs can facilitate the regeneration and enhance the quality of cartilage repair through their anti-inflammatory properties, immunomodulatory properties, and innate chondrogenicity, osteogenicity, and adipogenicity. Following the aspiration of the marrow (often from the iliac

crest), the MSCs in BMAC can be processed in two different ways: cultured and non-cultured. When BMAC is cultured, it undergoes a 2-step process that allows the MSCs in the BMAC to exponentially increase in cell numbers over the course of several weeks in vitro. This method, however, is currently prohibited in the United States of America. The non-cultured method is a 1-step process during which the BMSCs are centrifuged along with the rest of the BMAC and is used in same-day bedside therapy. While the lack of culturing limits the number of BMSCs, it does reduce potential patient risks, costs, and the need for a Good Manufacturing Practice Facility.[9] BMAC's ability to successfully augment the traditional treatment of chondral defects such as microtherapy has been have been illustrated in a goat model by Saw et al., and in an equine model by Frontier et al.[11, 12] These two studies have shown in animal models that the application of BMACs was able to improve the collagen orientation, collagen type II production, and hyaline cartilage repair.[10]

In a retrospective comparative study by Hannon et al., functional improvement and MRI evidence were compared for bone marrow stimulation (BMS) with and without BMAC to treat OLTs.[13] From a total of 34 patients, 22 received a combination of BMS and BMAC while 12 received the BMS alone. The outcomes were measured pre- and post-operatively with the Foot and Ankle Outcome Score pain subscale (FAOS), a general health questionnaire, and magnetic resonance observation of cartilage repair tissue score (MOCART). For the group with the combination treatment, the mean FAOS (from 60.6 to 77.6) and general health scores (from 42.6 to 61.7) improved significantly pre to post-operatively at mean follow up of 48.3 months ($p<0.01$). The group treated with BMS only showed that FAOS (from 54.8 to postoperatively 68.3) and general health scores (from 38.5 to 55.3) improved significantly pre to post-operatively at a mean follow up of 77.3 months ($p<0.01$). In terms of imaging, the MOCART score in the group with BMAC and BMS treatment was significantly higher than in the group with BMS only treatment ($p=0.023$). The MRI analysis showed that 77.3% of patients in the combination group (BMAC with BMS) had complete infill of the defect with repair tissue compared with only 25% of BMS-alone patients ($p=0.007$). Additionally, in the BMS-alone group, the repair tissue integrated poorly with the border zone in three quarters of patients while in the combination group, all but one patient had complete integration (95.5%, $p<0.001$). This study illustrated that combination of BMAC and BMS not only yield a similar result in terms of functional outcomes but also result in improved outcome in terms of imaging when compared to the BMS alone.[13]

In a prospective cohort study by Murphy et al., outcomes between BMS alone and BMS-BMAC combination were compared for the treatment of OLTs where the majority of the lesions were less than 1.5cm.[14] A total of 101 patients (91% of whom had lesions less than 1.5cm while 9% had lesions greater than 1.5cm) were followed for a minimum of 36 months. Fifty-two patients received the microfracture treatment and 49 patients were treated with BMS and BMAC. The outcomes were measured with pain scores (which are represented by VAS score), quality of life scores, participation in sport/daily activities, and revision rate. The VAS score in both groups was significantly reduced (3.04 points improvement in BMS group and 3.44 points improvement in the BMS and BMAC group). The revision rates were significantly higher ($p=0.0145$) in BMS alone group (28.8%) vs. BMS and BMAC group (12.2%). This study illustrated the safety and effectiveness of microfracture and BMAC for the treatment of OLTs.[14]

In a study placing an emphasis on surgical technique, Kennedy and Murawski presented the functional outcomes after an autologous osteochondral transplantation of talus with BMAC for the treatment of OLTs with lesions greater than 6mm in diameter.[15] A total of 72 patients (42 of which were athletes) were followed up for a mean of 28.02 months after they underwent the transplantation in which both the osteochondral autograft and the synthetic scaffold were soaked in BMAC. The outcomes were measured using the FAOS and the Short Form 12 (SF-12) general health questionnaire. The mean FAOS score improved from 52.67 points to 86.19 points while the SF-12 scores improved from 59.40 to 88.63 points. No surgical complications were reported. The mean time for return to athletic activities/sports was 13 weeks. This study illustrated that the autologous osteochondral transplantation soaked in BMAC is a viable primary treatment option for greater than 6mm OLTs.[15]

CONCLUSION

When surgical approaches are needed, OLTs are difficult to heal. Many existing treatments do not address the poor blood supply in the joint. This paper focused on biological augments such as PRP and BMAC for their regeneration properties in the treatment of these lesions.

In the literature reviewed, PRP and BMAC have been shown to be safe and effective in the treatment of OLTs. BMAC has safely been used an adjunct with both bone marrow stimulation and autologous osteochondral transplantation in order to improve collagen type II production, hyaline cartilage repair and repair tissue integration. However, the long-term efficacy of these treatments remains unproven. Moreover, future PRP research should be better controlled, standardiz-

ing the quantity of PRP plasma, growth factors and cytokines. It is also important to standardize the level of OLTs injuries.

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National Foot & Ankle Review

Pathogenesis, Diagnosis and Treatment of Infected Orthopedic Implants: A Literature Review

Andrew Rasiah, B.S., Varsha Salunkhe, B.S.

ABSTRACT

An infection in the presence of an orthopedic implant, especially in the lower extremity, is a treatment challenge. Bacterial resistance, biofilm production, and tenuous vascularity surrounding implants add to the complexity of medical management. Diagnosis is further complicated by differing clinical presentations. Typically, if bone is healed and stable, hardware may be removed followed by a course of culture-directed antibiotics. In the setting of a large bony defect, hardware may be removed with temporary fixation. Hardware retention or removal, specifically in the setting of bony instability with infection is controversial.

INTRODUCTION

Orthopedic implants are used to replace or support a damaged joint or bone or both. Implants include hardware for fracture fixation and prosthetic joints, which are both susceptible to bacterial growth and infection. Approximately 2 million fracture fixation implants are used in the United States annually and it is estimated that 100,000 of these become infected, with fixated ankle fracture involving the most infections.[1-3] Cure rates in orthopedic implant infections range from 14 to100%.[2,3] Major risk factors for implant infections diagnosed within 30 days postoperatively include the following: diabetes mellitus, American Society of Anesthesiology class 3+ (patient with a severe systemic disease that limits activity but is not incapacitating), and an unclean surgery (presence of purulence or devitalized tissue).[3] The most common infectious bacterial species in orthopedic implants are *Staphylococcus* and *Streptococcus*.[4] However, implant-associated infections are often polymicrobial, involving the combination of different species. Such bacteria can survive and grow through biofilm formation and quorum sensing.[7]

Treatment for implant infections varies from operative debridement, to prolonged antibiosis to invasive surgery, depending on the stage of osteosynthesis and the severity of infection. To diagnose an infection and to determine the course of treatment, several imaging modalities may be used. This review examines the complexity of implant-associated infections and their surgical and medical management.

PATHOGENESIS

Although *Staphylococci* are most often responsible for infecting patients with orthopedic implants, other microorganisms can also cause infection. The infectious species depends on factors such as the bacterial source, the procedure type, the implant type, and the patient's age.[1] The majority of infections that appear in open reduction and internal fixation (ORIF) procedures are contracted during the initial trauma or the procedure itself. Infections that present after implantation can be classified by the time of onset. Infections that occur within the first two weeks of surgical implantation are often caused by *Staphylococcus aureus*, aerobic gram-negative bacilli, and *Streptococcus pyogenes*.[5] Infections that occur within the postoperative time frame of 3 to 10 weeks are commonly associated with coagulase negative *Staphylococcus* and *S. aureus. Staphylococcus epidermidis* and *Pseudomonas aeruginosa* are often identified in infections that emerge 10 or more weeks of post-implantation.[5] Bonnevialle et al. determined that the order from the most common organisms to least is as follows: *S. aureus, S. epidermidis, Enterobacteria, Enterococci, P. aeruginosa* and *Streptococci*.[6]

The survival of these organisms is largely due to biofilm production. A biofilm is an association of microorganisms that adhere to one another and to the implant surface. Biofilm growth occurs through five stages: attachment, multiplication, colonization, maturation, and dispersal.[7] During the first stage, microbes adhere to biotic or abiotic surfaces, such as metal in implants. In the second stage, organisms begin to mul-

tiply, obtain nutrients, and recruit other microbes. The extracellular matrix, the architecture of the biofilm, is established during the third stage. The fourth stage involves the maturation of this matrix and matrix dispersal in the final stage. Dibartola et al. outlines several methods to examine orthopedic implant biofilms after implantation including direct culture in broth or agar, agar encasement culturing method, and immersion culture.[8] These techniques are employed to isolate species and visualize bacterial growth.[9]

The primary goal of biofilm production is for the bacteria to cross-communicate and create a defense system against the host. Microorganisms communicate through molecules known as a quorum-sensing system.[9] These molecules have the ability to activate genes that lead to increased structural integrity and virulence. Biofilms and quorum sensing play a crucial role in antibiotic resistance. The values of mean inhibitory concentration and mean bactericidal concentration of antibiotics are measurements of susceptibility and resistance. For biofilm growing bacteria, these values may be 100-1000-fold higher compared to those of free-living bacteria.[9] Two reasons for increased value of susceptibility and resistance are the production of molecules that confer antibiotic resistance, and the ability of the matrix to limit and/or prevent antibiotic binding and diffusion.[9] Therefore, these mechanisms permit bacterial infections to originate and progress in orthopedic implants.

Implant materials further influence the probability of implant infection. Titanium implants undergo osseointegration, the process by which bone forms an interface with the implant and does not involve soft tissue. This allows for a direct communication between the implant and bone while allowing for increased stability.[10] Stainless steel, on the other hand, produces fibrous tissue between implant and bone, therefore limiting blood supply to a potentially infected area. Overall, titanium implants are also shown to have decreased tissue reaction and reduced corrosion compared to stainless steel implants.[10]

DIAGNOSIS

Implant infection is classified by when the early, delayed, or late infection presentation begins.[10] Early presentation occurs during the first 2 weeks, either preoperatively during the traumatic incident, or intraoperatively. Delayed presentation occurs between 2-10 weeks, while late presentation occurs after 10 weeks. Although late and delayed infection can occur preoperatively, operatively, or during wound healing. Approximately one-third of implant infections occur within 12 weeks of implantation.[11]

Although there is no single blood test or imaging modality with high specificity, there are tests used to help guide clinicians. An acute phase reactant, C-reactive protein (CRP) is a non-specific marker of inflammation that has value for screening infections. CRP levels are typically elevated post-operatively, however a secondary increase in CRP is highly indicative of infection.[12]

A series of different imaging modalities must often be used to diagnose implant-associated infections. Radiography is usually the first choice to identify bone and soft tissue abnormalities. However, conventional radiography has 14% sensitivity and 70% specificity.[13] In addition, up to 50% of the radiographs of patients with implant-associated infections are normal.[13] Radiographically, implant infections typically show the presence of implant loosening with a surrounding radiolucency, which may indicate an unstable implant. This non-specific indication does not aid in decision making for implant retention or removal.[14] ^{99}mTc bone scintigraphy is 90-100% sensitive for bone remodeling and devascularization, with a 35% specificity for cases of orthopedic prosthetic implant. Thus, implant loosening, and infection may be difficult to discern.[13]

Magnetic resonance imaging (MRI) has been demonstrated to effectively assess soft-tissue involvement in trauma infections after internal fixation.[15] Specifically, MRI can identify the location and volume of osteolysis and how it affects the surrounding tissue structures.[16] Computed tomography (CT) scans are used for preoperative planning and infection evaluation. This modality is particularly valuable because it can analyze fracture pattern and implant loosening. In addition to these architectural features, CT scans can elucidate possible cortical bone reactions and abscess formations.[13] Ultrasound (US) can also identify abnormal fluid accumulation, in addition to synovitis and inflammation.

TREATMENT

In a patient with confirmed sepsis with an unknown source of infection, bacterial seeding to the implant is approximately 40%, thus, initial incision and drainage (I&D) is still warranted.[9] The decision to remove hardware is influenced by multiple conditions: infection duration, infection extent, location, structural stability/functionality, and patient preference. If an aggressive I&D results in a large bony defect, the implant is removed, as it is no longer useful for stabilization.[9] A 1-stage or 2-stage exchange may then be performed. A 1-stage, or direct, exchange is performed in aseptic nonunion or implant subsidence. All implant components are removed with reimplantation in 2-4 weeks with IV antibiotic administration during this interval.[9,12] If a direct exchange is contraindicated, a 2-stage approach is then attempted in cases of chronic infection and unstable or loose implants.[9] With a 2-stage approach, all infected implants are removed and replaced with antibiotic impregnated cement spacer or

beads, followed by a prolonged course of antibiotics for 4-6 weeks.[9,12]

In the case of a complete bony union and implant infection, the implant no longer serves a purpose in stability and may be removed. Berkes et al. studied 123 cases of patients who developed wound infections within 1-6 weeks after lower extremity, upper extremity or pelvic fracture ORIF with a positive wound culture.[17] Implants were retained and treated initially with I&D as well as a prolonged course of antibiotics. Success, defined by bony union with retained implant, was observed in 71% of cases, with 35.6% of those patients who had implant removal after bony union. Failure, defined by nonunion or implant removal prior to bony union, was observed in 29.2% of cases. Of the cases that failed, 19% had an amputation while 75% required a revision or arthrodesis.[17] Researchers also observed a higher implant infection risk with open fractures and intramedullary nail fixation. Several variables including smoking, Pseudomonas infection, and lower extremity ORIF trended towards a higher rate of failure. While these trends were not statistically significant, implant retention until bony union may be a viable option after risk assessment.

Although structural stability of the implant and bones is critical for functionality, soft tissue defect consideration is crucial for the dispersal of antibiotics. Guidelines issued by the Infectious Disease Society of America state that a positive probe to implant or exposed implant is highly indicative of infection, however recent findings suggest that exposed implants may still be salvageable. Major factors that influence surgical treatment of exposed implants include implant location, presence of infection versus colonization, duration of implant exposure, or implant loosening.[14] Shorter duration of infection and implant exposure, 2 weeks, will lead to implant salvage. [14] Soft tissue coverage with a free flap may decrease the time for implant, thus intervention by plastic surgery may be necessary to aid in coverage of the area.[12,14] In some cases, patients may elect lifelong suppressive oral antibiotic treatment to suppress clinical manifestations if surgery is either contraindicated or refused.[12]

CONCLUSION

Infection of an orthopedic implant is a treatment challenge. The type of microorganism and its ability to form a biofilm influences the complexity of the infection. In addition to a clinical diagnosis, multiple imaging modalities can be used to help detect the presence of an infection. Radiography, MRI, CT, and US each have unique strengths and weaknesses that need to be considered. These variables are important in guiding treatment and determining if surgical action needs to be taken. Antibiotic embedded implants have not shown great success due to the limited release of antibiotics and persistent biofilm formation.[18] I&D, prolonged antibiosis, implant removal with or without external fixation, and vascularized soft tissue coverage are used for limb salvage.[18] It is evident that orthopedic implant infection is an evolving complication that requires a systematic and methodical approach for resolution.

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National Foot & Ankle Review

Pilon Fractures: An Overview of its Classifications and Surgical Treatment Options

Paul Nguyen, B.S., M.S., Andrew Hu, B.S., Asad Sayeeduddin, B.A.

ABSTRACT

Pilon fractures are traumatic injuries that occur in the distal tibia. The approach to treatment is largely dependent on the degree of fracture as well as the health of the patient. Numerous classification systems for pilon fractures exist, with each system relying on a variety of factors such as location, relation to the articular surface, and soft tissue damage. Moreover, soft tissue preservation is a concern in pilon fractures as they present a risk for wound complications and deep infections.[1] Finally, treatment options can vary for individuals with pilon fractures, with a conservative and an operative approach. In this review, we will discuss the overview of the pilon fracture, the different classifications of the injury, and two treatment options, external fixation or open reduction internal fixation, that can be taken by physicians based upon these classifications.

INTRODUCTION

A pilon fracture occurs at the tibial plafond, a dome-shaped surface that articulates with the talus. Pilon fractures comprise approximately 3-10% of all tibial fractures.[1,2] These injuries can occur during falls or motor vehicle accidents that result in low-energy twisting or high-energy axial forces on the distal tibia.[3] The same forces can also damage the fibula, as the tibia and fibula are connected by ligaments and an interosseous membrane. Associated fibular fractures are common to both low energy twisting and high-energy axial forces.[4]

Along with bone fractures, clinicians should also consider the extent of soft tissue damage in open and closed fractures.[1] For example, a pilon fracture that does not break the skin surface and is non-comminuted can heal with conservative treatment. On the other hand, an open, comminuted pilon fracture with exposed soft tissue down to bone may require a more aggressive surgical approach. The purpose of this literature review is to expand upon the different classification systems used to diagnose a pilon fracture and the surgical treatments available for repair.

CLASSIFICATION SYSTEM

Pilon fractures are classified according to several factors including location of articular surface involvement of the distal tibia and soft tissue impairment. The first widely used classification system is the Ruedi-Allgower classification, which classifies the fracture into 3 different types. A Type I fracture is a cleavage fracture of the distal tibia with a non-displaced articular joint. Type II fractures have a simple displacement with incongruous joints. Finally, a Type III fracture involves impaction and comminution of the distal tibia.[5]

Another classification system was developed by the Orthopedic Trauma Association (OTA). Each section of the body is assigned a number. For the purposes of pilon fractures, the tibia is assigned the number 4. The bone is then further divided into proximal, diaphyseal, and distal sections, denoted by 1, 2, and 3, respectively. A proximal tibia fracture would thus start with the notation “41”. The number 4 indicates the tibia bone, and the number 1 indicates the proximal portion of that bone. Fractures are further classified into classes A, B, and C. Type A fractures are extra articular with sub types of simple (A1), comminuted (A2), and severely comminuted (A3). Type B fractures are partial intra-articular fractures with subtypes of a pure split (B1), split with depression (B2), and multifragmenting splits (B3). Type C fractures are complete intra-articular type fractures with subtypes consisting of metaphyseal complex association (C1), multiple depression fragments (C2), and multiple articular fragments (C3).[6,7]

For example, a fracture with a classification of “43-A1” indicates a simple, distal tibial fracture that

is extra-articular. The number "1" next to letter "A" denotes the severity of the fracture, in this case a simple fracture. If this number were either "2" or "3," it would refer to a comminuted or severely comminuted fracture.

Finally, the Gustillo-Anderson system is based entirely on soft tissue impairment in open fractures, using 4 grades. Grade 0 is a simple fracture pattern with minimal tissue damage. Grade 1 is a fracture with superficial abrasion or contusion to soft tissue. Grade 2 fractures have deeper abrasions on the skin or muscle contusions. Grade 3 indicates extensive skin and muscle damage, seen in crush injuries, subcutaneous avulsions, and compartment syndrome.[8]

Commonly used classification systems, such as those developed by the Ruedi-Allgower, OTA, and Gustillo-Anderson are useful because they allow surgeons to quickly categorize and communicate the severity of the injury and plan accordingly. Based upon the classification, surgeons can decide whether an injury needs to be treated more conservatively or more aggressively.[5,6]

TREATMENT

Pilon fractures are high impact injuries that require a great deal of management. A systematic physical examination should be performed to identify associated injuries involving the ipsilateral foot, knee, or other locations in cases of polytrauma.[9]

The severity of injury needs to be ascertained before creating a treatment plan. Othman et al. have analyzed whether conservative care is an appropriate option for individuals with Type I, II, and III Ruedi-Allgower fractures. According to their findings, conservative treatment is an appropriate method of treatment in cases of Type I and Type II fractures, but not a Type III fracture, which indicates a comminuted fracture. The minimal amount of commination made the destruction of articular surfaces not a concern and patients recovered with casting treatment.[10]

Some pilon fractures, if traumatic enough, will involve destruction of bones and articular surfaces.[2] Three approaches are used in these cases, which are external fixation, open reduction internal fixation (ORIF), and hybrid fixation (a combination of both mentioned).

External Fixation

External fixation is the method of aligning or realigning bones using a combination of pins, wires, clamps, bars, and rings. Pins and wires connect the sidebars and clamps to bone. Transfixion wires and pins go from one clamp or side bar, through the bone, and out to the opposite clamp or sidebar. The scaffolding creates a rigid construct producing bilateral and circular fixation.[11]

Pin-bar fixators, which are a type of external fixation, provide an advantage compared to ORIF in specific cases. Injuries that involve large open wounds and comminuted fragments can benefit from external fixation because they are easy to apply and allow access to soft tissue to continue wound care.[11]

In general, fractures with metaphyseal comminution and large articular fragments are reducible by ligamentotaxis. Ligamentotaxis involves longitudinal distraction of the fracture in order for the soft tissue surrounding it to mold the bony fragments into their anatomical position.[11] External fixation on large, non-comminuted fragments can provide enough reduction for bone fragments to heal as there is enough bone to bone surface and compression from intact soft tissue to allow adequate union between fractures. Small, intra-articular, comminuted fragments are difficult to reduce with ligamentotaxis. External fixation exclusively will not provide adequate compression for bone healing with intra-articular comminuted fractures due to the nature of attempting to wire or pin every fragment back to its anatomical position. Therefore, more severe cases may require a hybrid approach. An ORIF localized to the most severe comminuted portions of the fracture would allow for sufficient reduction and compression followed by external fixation for larger metaphyseal fragments in the tibia and fibula.

OPEN REDUCTION INTERNAL FIXATION

An ORIF procedure involves making an incision at the site of injury, reducing the fractured bone to its anatomical position, and internally fixating with a combination of plates and screws, as necessary. The incision site is then closed. ORIF procedures can be done in stages. A two-stage approach is used to compress pilon fractures. The first stage involves using both open reduction and external fixation. When proper reduction and soft tissue swelling improves, ORIF can be performed at the second stage.[12]

Reduction and fixation of the articular surface of the tibia is also an option if soft tissue damage such as edema is minimal. If the articular surface needs to be restored, an anterior incision to the articular surface can be made to visualize the central and posterior fragments. Individual fragments are then reduced in a posterior to anterior manner. [13] Other modalities that minimize incision sizes include percutaneous placement of screws and the usage of an extraosseous tunnel to fixate the plate.

HYBRID TECHNIQUES OF FIXATION

Several procedures are available to treat pilon fractures. Recent literature has shown a shift away from standard procedures, such as the ORIF, to a combination of multiple procedures in order to treat

pilon fractures. These examples include soft tissue preservation and repair using staged reconstruction, transosseous tunnels for plate fixation, and the consideration of closed reduction external. For instance, Gunmann et al. have concluded that surgical approaches to pilon fractures have evolved to keep soft tissue damage at a minimum and reduce complications such as infections.[19] This is a paramount issue according to a study done by Sirkin and Sander as well as the studies previously mentioned. Therefore, surgical approaches aim to reduce incision size, reduce physical probing, and reduce the shifting of soft tissue, all to reduce the risk of infection.[18]

While there are some concerns about the effectiveness and complications with hybrid internal and external fixation techniques in place of ORIF, there are studies that have shown there is no difference in outcomes. A meta-analysis of 9 studies that included 498 fractures by Wang et al. found no significant differences between the hybrid internal/external fixation group and ORIF group in bone healing complications (p=0.58), non-union (p=0.82), malunion and delayed union (p=0.59), deep infections and arthritic symptoms (p=0.18), or chronic osteomyelitis (p=0.2). The occurrence of bone healing complications was 5.6% in hybrid groups and 4.7% in ORIF groups.[20]

Wang et al. emphasized that while one treatment option may be non-traditional, there was no increased risk of adverse effects such as non-union, superficial and deep tissue infection, and osteomyelitis.[20] Even though both procedures are statistically insignificant for healing complications, the hybrid internal and external fixation would reduce soft tissue damage.

SOFT TISSUE COMPLICATIONS

Soft tissue injury is an important factor involving both open and closed pilon fractures. Minimizing the risk that these injuries pose can be dealt with by avoiding delays in fracture reduction. [2,4,14] This is achieved through a combination of reducing the fracture, aggressive debridement of nonviable tissue in the case of open fractures, and the use of antibiotics to decrease infection risks. In large open fractures where the bone pierces the skin and leaves a gaping wound, the skin is closed with either a graft once debridement has been performed and the wound margins are clean and well perfused.[15]

As with all invasive procedures, there are associated surgical risks. For example, superficial skin necrosis as well as cellulitis along the proximal or distal margins of the surgical site can occur. Skin necrosis can be remedied with wound care while cellulitis can be treated with oral or intravenous antibiotics, depending on the severity. Wound dehiscence can lead to contamination of the hardware and eventual bone infection.[16] Moreover, the wound care application choices can also have a significant difference in preventing the spread of infection. For example, using negative pressure wound therapy in lieu of standard post-operative dressings may reduce the infection rate by almost half.[17]

In 2001, Sirkin and Sanders found that pilon fracture fixation using large fragment screws and large spoon plates resulted in a higher rate of wound complications to the soft tissue. Switching to a two-stage procedure (delaying definitive surgery 10-14 days after the incident) reduced wound healing complications by 5.3% in all fractures and 2.9% in closed fractures. [18] Shifting from ORIF to a combination of both external and internal fixation reduced the need to intensively dissect soft tissue in order to fit the large screws and plates. Hybrid external fixators also allow for greater ankle range of motion and lessen the need for extensive internal fixation.

CONCLUSION

Multiple classification systems such as the Reudi-Algower or OTA can tell the surgeon the extent of damage in a concise and descriptive manner. This allows the surgeon to decide a more conservative or aggressive approach. Minor injuries that do not damage the articular surface and joints can be treated conservatively with casting. However, more severe cases that result in severe joint displacement and extensive damage to the articular surface will need to be treated surgically. High-energy injuries that result in comminuted fractures spanning the entirety of the articular surface can be approached with a combination of both external fixation and localized open reduction internal fixation. Along with bone damage, healthcare providers should consider the severe soft tissue damage associated with open and closed pilon fractures.[1] More innovative surgical techniques are starting to be employed with the goal of reducing incision sizes in addition to physical probing and shifting of soft tissue.[18] A smaller incision size as well as less invasive soft tissue probing would reduce the chances of infection. This in turn, reduces the probability of trauma and healing complications. More research is needed regarding the long- term effects of non-traditional Pilon fracture procedures in order to heal the fracture completely while keeping soft tissue preservation in mind.

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National Foot & Ankle Review

Primary Deltoid Ligament Repair in Acute Ankle Fractures: A Literature Review

Stuardo Trigueros, B.S., Varsha S. Salunkhe, B.S.

ABSTRACT

The deltoid ligament is the primary stabilizer of the ankle joint. Ankle fractures may present with deltoid ligament rupture if the medial malleolus remains intact, as seen in bimalleolar equivalent fractures. Medial ankle injury may be present especially in supination-external rotation and pronation-external rotation patterns of the Lauge-Hansen classification. Because of limitations in current literature, there is still debate on whether to surgically repair the deltoid ligament in the setting of acute ankle fractures. Based on the studies examined in this literature review, primary deltoid ligament repair is not indicated unless there is persistent medial clear space widening after proper open reduction and internal fixation of the fibula, or if there is deltoid ligament entrapment in the medial gutter of the ankle mortise.

INTRODUCTION

With ankle fractures, the deltoid ligament may rupture if the medial malleolus remains intact, as seen in bimalleolar equivalent fractures.[1] In 2000, an arthroscopic study of 288 ankles by Hintermann et al. revealed 39.6% of ankle fractures were associated with deltoid ligament injury.[2] There are reports that ankle fractures with deltoid ligament rupture can cause persistent medial ankle pain, instability, and post-traumatic arthritis if not surgically treated.[1,3] These poor outcomes are believed to be related to the deltoid ligament not healing in anatomical position.[1]

Studies since the 1980's have evaluated whether deltoid ligament repair is required in the setting of ankle fractures.[4-10] Until the 1990's, the general consensus in published literature advised against the repair of the deltoid ligament, however, the majority of these studies are underpowered.[3] The lack of consistency in sample sizes, control groups, and standardized scoring systems brings into question the validity of these published conclusions.[3]

The deltoid ligament is suggested to be the primary stabilizer of the axially loaded ankle.[11] In regards to ankle fractures with deltoid ligament rupture, there has been speculation on whether repair is indicated.[1] The goal of this literature review is to discuss the importance of the deltoid ligament, recent literature and potential indications for primary deltoid ligament repair in the setting of acute ankle fractures.

ANATOMY & FUNCTION

The deltoid ligament is a complex structure that provides medial ankle stability.[12] The components are separated into a superficial and deep layer. The superficial layer originates from the anterior colliculus and intercollicular groove of the medial malleolus, crossing both the ankle and subtalar joint.[12-14] In contrast, the deep layer originates from the anterior colliculus, intercollicular groove and posterior colliculus, crossing the ankle joint only.[12-14] The deltoid ligament is composed of six separate ligamentous bands.[12] The superficial layer of the deltoid ligament, which primarily resists eversion of the hindfoot, includes the tibionavicular, tibiospring, tibiocalcaneal, and superficial posterior tibiotalar ligaments.[12,15] The deep layer, which primarily stabilizes external rotation of the talus, includes the deep anterior tibiotalar ligament and the deep posterior tibiotalar ligament, the strongest and largest component of the deltoid ligament.[12,13,15] In a cadaveric study, Milner et al. evaluated 40 cadaveric feet and found only the tibiospring and tibionavicular ligaments to be constants anatomically in the superficial layer, while only the deep anterior tibiotalar ligament was constant in the deep layer.[16] The ligamentous bands that make up this complex are most vulnerable to injury in a plantarflexed, externally rotated, and everted foot.[17]

If the integrity of the deltoid ligament is compromised, the ankle joint becomes unstable leading to a valgus talar tilt.[18] According to an early cadaveric

study, Earll et al. found the greatest changes in ankle biomechanics occurs after sectioning of the tibiocalcaneal ligament, with 26-43% decrease contact area and a 20-30% increase in peak pressures.[17] With both layers of the deltoid ligament transected, Michelson et al. found a lateral talar shift ≥2 mm and valgus tilt ≥15º when performing a stress test.[19] Primary deltoid repair may be considered with a positive intraoperative stress test after ankle fracture fixation.

ANKLE FRACTURE FIXATION PRINCIPLES

Injury to the deltoid ligament complex usually occurs in association with a fracture of the fibula as seen in transsyndesmotic (Weber B) and suprasyndesmotic (Weber C) fibular fractures.[5] Especially in supination-external rotation and pronation-external rotation patterns of the Lauge-Hansen classification system. The force of injury causes a spiral or oblique fracture through the lateral malleolus and may result in deltoid ligament rupture.[20] Rupture of the ligament results in lateral talar shift, widening of the medial clear space (MCS), and leads to an unstable ankle joint.[21]

Stress radiographs are the gold standard in evaluating the integrity of the deltoid ligament.[22] Relying solely on clinical signs such as ecchymosis, swelling, medial ankle tenderness, and initial injury radiographs are no longer acceptable.[22,23] In the intraoperative setting, an external rotation stress test under fluoroscopy may be performed to assess MCS widening after open reduction and internal fixation (ORIF) of the fibula.[1] With or without stress radiographs, the MCS is considered widened in the ankle mortise view if the distance between the medial aspect of the talus and the articular surface of the medial malleolus is >4 mm and at least 1 mm more than the superior tibiotalar clear space.[1]

In 1977, Yablon et al. concluded that with bimalleolar fractures, the talus can be anatomically repositioned only if the integrity of the lateral malleolus is restored.[24] With persistent MCS widening or lateral talar subluxation, the ruptured deltoid ligament is likely to be entrapped in the medial gutter.[25]

OUTCOMES

Previous literature from 1987-1999 are predominantly low level of evidence.[4-7,9,10] The majority are small retrospective case series and primarily suggest no deltoid ligament repair.[4-7,9,10] However, several studies lacked a comparison group in their design.[5-7,10] The only randomized controlled trial to our knowledge is from 1995 by Stromsoe et al., which advocated for no repair of the ligament due to a lack of significant difference in outcomes.[8] These studies are summarized in **Table 1**.

In 2015, Yu et al. published a 5-year retrospective cohort study of 106 patients, evaluating indications for deltoid ligament repair in the setting of ankle fractures.[25] Repair indications included a preoperative MCS >5 mm or persistent medial ankle instability after ORIF (MCS was >1 mm) with external rotation stress. Persistent medial ankle instability was considered indicative of entrapment of the medial soft tissue structures. Syndesmotic fixation was performed if necessary. Functional outcomes were measured using the American Orthopaedic Foot and Ankle Society (AOFAS) ankle-hindfoot scale and Medical Outcomes Short Form 36-item questionnaire (SF-36) while clinical outcomes were measured with the Visual Analog

Table 1. *Early studies evaluating primary deltoid ligament repair in ankle fractures*[4-10]

Study	Level of Evidence	Total Patients (repair/no repair)	Conclusions
Baird & Jackson (1987)[4]	4	24 (3/21)	Repair DL if MCS widened post fibula fracture ORIF
Johnson & Hill (1988)[5]	4	29 (0/29)	Unrepaired DL results in prolonged pain and disability
Harper et al. (1988)[6]	4	36 (0/36)	DL heals and prevents valgus instability provided MCS reduction is maintained post fibular fracture ORIF
Zeegers & van der Werken (1989)[7]	4	28 (0/28)	With anatomical reconstruction of ankle mortise, DL can be left unrepaired
Stromsoe et al. (1995)[8]	2	50 (25/25)	No significant difference, DL can be left unrepaired
Maynou et al. (1997)[9]	3	35 (18/17)	Repair DL if MSC widened post fibular fracture ORIF
Tourne et al. (1999)[10]	4	33 (0/33)	Excellent clinical and radiographic results with no DL repair

Abbreviations: DL, deltoid ligament; MCS, medial clear space; ORIF, open reduction and internal fixation.

Scale (VAS) for pain. Average follow-up for the study was 27 months (range 12 to 72 months). At the last follow-up visit, results indicated significant improvements in all 3 outcome measures from baseline ($p<0.05$). There were no cases of clinical or radiographic ankle instability on final follow-up. The authors concluded that repair of deltoid ligament ruptures was indicated in patients with unstable medial ankle after ORIF and as a prevention of complications associated with ankle instability (**Table 2**). However, this multicenter study lacked a control group that did not receive deltoid ligament repairs, for comparison.[25]

In the same year of 2015, Hsu et al. published a 10-year retrospective case series evaluating the outcomes and complications of acute superficial deltoid complex avulsion repair after ORIF of the fibula and syndesmotic fixation in 14 National Football League (NFL) players.[26] Repair indications were based on clinical exam including a medial dimple sign as evidence of deltoid ligament complex being invaginated into medial gutter. Preoperative radiographs showed increased MCS and syndesmotic widening under fluoroscopy with stress. Outcomes were determined per physical therapy evaluations, NFL game data and players playing experience. The results for the 14 patients who underwent ligamentous repair revealed no significant difference in playing experience before and after surgery. Mean final follow-up time was 1.8±0.6 years (about 21.6 months). During final follow-up, there was neither clinical evidence of medial pain or instability nor evidence of MCS widening and ankle arthritis radiographically. This study concluded that surgical repair of the deltoid ligament in professional athletes may prevent persistent medial ankle symptoms and complications. The authors recommended deltoid ligament repair in the presence of instability after fibula and syndesmotic fixation (**Table 2**). This small study lacked established clinical outcome measures in addition to a comparison group for no deltoid ligament repair.[26]

In 2017, Zhao et al. published a 6-year retrospective cohort study evaluating the need for deltoid ligament repair in ankle fractures.[27] A total of 74 patients were included in the study in which deltoid ligament repair was performed in 20 patients and were compared to 54 patients in which no repair was performed. A total of 49 Weber B (12 for repair group, 37 for non-repair group) and 25 Weber C (8 for repair group, 17 for non-repair group) type of ankle fractures were evaluated. Repair indications included a pre-operative MCS ≥5 mm. However, no stress tests or intraoperative radiographs were taken for this study. A postoperative MCS ≥5 mm was defined as malreduction. Outcomes were measured using AOFAS ankle-hindfoot scale and VAS for pain. Average follow-up was 53.7 months. At the last follow-up visit, results indicated that there was no significant difference in outcome scores ($p>0.05$). However, the non-repair group had a 20.4% malreduction rate versus 0% for the repair group primarily in Weber C type ankle fractures. Mean post-operative MCS was significantly smaller in the repair group ($p=0.03$). The study concluded deltoid ligament repair helps decrease post-operative MCS and malreduction rate especially in Weber C type ankle fractures (**Table 2**). There was no significant difference in Weber B type ankle fractures in terms of malreduction between the two groups.[27]

More recently in 2018, Woo et al. published a 15-year retrospective study evaluating radiologic and clinical outcomes of deltoid ligament repair post ORIF compared to non-repair.[21] A total of 78 patients were evaluated out of which 41 patients had their deltoid ligament repaired and 37 patients did not. A total of 62 Weber B (30 for repair group, 32 for non-repair group) and 16 Weber C (11 for repair group, 5 for non-repair group) type of ankle fractures were evaluated. Repair was performed if intraoperative stress radiographs revealed an MCS >4 mm or at least 1 mm more than the superior tibiotalar clear space post fracture or syndesmotic fixation. Functional and clinical outcomes were measured per AOFAS, Foot Function Index, and VAS for pain. Average follow-up time was 17 months. Despite the MCS being significantly smaller at final follow up with deltoid ligament repair ($p<0.01$), there was no significant difference in functional and clinical outcomes between the two groups ($p>0.05$). However, when comparing the ankle fractures, which had syndesmotic fixation in both groups, results indicated a smaller MCS ($p=0.02$) and better outcome scores with deltoid ligament repair ($p<0.05$). In both groups, no post-operative complications were reported. The study concluded that in the absence of syndesmotic injury, there is no indication for the repair of the deltoid ligament as there were no clinical benefits or significant radiographic findings to support it (**Table 2**).[21]

CONCLUSION

Despite the available published literature, there is still no clear consensus.[14] The literature available is limited and generally of low level of evidence. The authors of this literature review conclude that randomized and large sample size studies with comparison groups are needed. Based on the literature examined, deltoid ligament repair is indicated if increased MCS persist post ORIF and considered in Weber C type of ankle fractures with syndesmotic injury. [4-10,21,25-27] In light of these indications, a surgeon must consider ligamentous repair in a case-by-case basis. Additional operation time as well as patient comorbidities that increase risk for incisional complications must be considered when deciding the candidacy of a patient.[3,15]

Table 2. *Recent studies evaluating primary deltoid ligament repair in ankle fractures*[21,25-27]

Study	Level of Evidence	Total Patients (repair/no repair)	Complications[a]	Conclusions
Yu et al. (2015)[25]	3	106 (106/0)	Repair: 0/106	Repair DL if medial ankle is unstable after ORIF
Hsu et al. (2015)[26]	4	14 (14/0)	Repair: 0/14	Repair if unstable after fibula and syndesmotic fixation
Zhao et al. (2017)[27]	3	74 (20/54)	Repair: 0/20 No repair: 11/54	DL repair decreases MCS and malreduction rate especially with Weber C ankle fractures
Woo et al. (2018)[21]	3	78 (41/37)	Repair: 0/41 No repair: 0/37	Repair DL in concurrent syndesmotic injury

Abbreviations: DL, deltoid ligament; MCS, medial clear space; ORIF, open reduction and internal fixation.
[a]Based on patients with ankle instability, post-traumatic arthritis, malreduction, or failure.

Primary deltoid ligament rupture repair is not indicated unless there is persistent medial clear space widening in the setting that ORIF of the fibula was performed adequately or if there is deltoid ligament entrapment in the medial gutter of the ankle mortise.

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National Foot & Ankle Review

Spring Ligament Rupture: A Review of Etiology, Diagnosis, and Surgical Treatment

Jae Yoon Kim, B.A., Paul Nguyen, B.S., M.S., Chris Zimmer, B.S.

ABSTRACT

The spring ligament supports the medial longitudinal arch and is frequently defined as consisting of two distinct bundles. The rupture of this ligament is typically seen with a flat foot deformity and results in excessive plantarflexion of the talus. This review explores different descriptions of the spring ligament, causes of spring ligament rupture, techniques for diagnosing spring ligament rupture, and techniques for surgical repair of a ruptured spring ligament, including internal bracing and the use of a double bundle posterior tibial tendon.

INTRODUCTION

The spring ligament, otherwise known as the plantar calcaneonavicular ligament, is a complex structure connecting the calcaneus to the navicular. It is comprised of the superomedial calcaneonavicular ligament (SMCNL) and the inferior calcaneonavicular ligament (ICNL). The SMCNL is the medial component of the band, which originates from the sustentaculum tali and inserts onto the superomedial side of the navicular tuberosity. In contrast, the inferior calcaneonavicular ligament is the lateral section of the spring ligament complex, which originates from the anterior and middle facets of the calcaneus and inserts on to the navicular beak.

According to Taniguchi et al., however, there is also a third bundle of spring ligament fibers, independent of the SMCNL and the ICNL that runs deep to the fibrocartilaginous surface. These fibers run from a notch between the anterior and middle facets of the calcaneus to the navicular tuberosity.[1]

MECHANISM OF INJURY

Posterior tibial tendon dysfunction (PTTD) is often accompanied by injury to the spring ligament, much more frequently than other nearby ligaments such as the plantar metatarsal ligaments or the plantar naviculocuneiform ligament.[2] Spring ligament failure can result in a collapsed medial longitudinal arch and has been implicated in acquired "flatfoot" deformity.[2] In a review of magnetic resonance imaging (MRI) for spring ligament tears by Toye et al., the SMCNL plays an important role in ankle stability and is often the most torn.[3] Alongside the spring ligament, the posterior tibial tendon (PTT) is one of the main tendons supporting the medial arch of the foot. The PTT originates from the upper half of the tibia, fibula and interosseous membrane and inserts on the navicular, spring ligament, and 2nd, 3rd, and 4th metatarsals. Tension on the PTT allows the foot to invert and plantarflex. With PTT degradation, the force normally placed on the PTT to invert and plantarflex the foot is transferred to the spring ligament.[2] This weakening of the PTT eventually ruptures the SMCNL and collapses the medial longitudinal arch. Unrecognized or untreated PTTD can cause secondary injury to the spring ligament and to the deltoid ligament.[4]According to Ribbans and Garde, both exclusive attenuation and rupture of the spring ligament can degrade the stability of the medial longitudinal arch. Furthermore, the principal force behind the rupture of the spring ligament is excessive pronation and usually involves the SMCNL.[4]

Some acute injuries do occur but are uncommon. A complete rupture of all three sections of the spring ligament complex can occur and is typically associated with talonavicular dislocation. The study by Ribbans and Garde goes on to summarize that acute injuries in athletes are usually due to an excessive pronation force. However, progressive weakening of the spring ligament can also be seen in individuals who have excessive body weight.[4]

DIAGNOSING SPRING LIGAMENT INJURIES

A majority of spring ligament tears are identified using MRI. Rule et al. state that the plantar portion of the ligament is best seen on oblique sagittal images

along the axis of the calcaneus with the ankle in a neutral position. Axial views allow better visualization of the plantar medial aspect of the spring ligament. The medial segment of the ligament can be seen as a black sliver through the talonavicular articulation on axial and oblique axial images.[4] A healthy ligament on MRI displays minimal to no changes in signal while damage to a ligament causes increased signal on fluid sensitive sequences. In addition, acute SMCNL injuries exhibit soft tissue and osseous edema, early hematoma formation, and gapping of the ligament. In contrast, chronic injuries of the SMCNL are associated with tibialis posterior tendinopathy (TPT).[4]

SURGICAL TREATMENT

The deltoid ligament is commonly damaged along with the spring ligament in adult-acquired flat foot, however, most often, only one of these two ligaments is reconstructed.[1,4] Nery et al. introduced a new method of reconstructing both the deltoid and spring ligament using an internal brace. The internal brace concept consists of 3 anchors and a strand of suture. The 1st anchor is inserted into the medial aspect of the calcaneus, directly inferior to the sustentaculum tali, the 2nd anchor is inserted into the dorsolateral aspect of the navicular, and the 3rd anchor sits on the most medial point of the navicular. The resulting 3-point brace resembles a standard 3-point seat belt in an automobile and runs in the same direction as the ligaments it emulates. This allows the strands to share the eversion forces that the deltoid ligament would have beared.[6] A total of ten patients were studied with a mean age of 64. Among the inclusion criteria were adults with progressive pain and medial arch collapse despite nonoperative treatment, radiological signs of medial longitudinal arch collapse, progressive subluxation of the talonavicular joint in both coronal and sagittal planes, and degenerative MRI changes of the PTT, spring ligament, and deltoid ligament. Postoperative weightbearing radiographs showed angular correction of both the spring ligament and deltoid ligament in all 10 patients, indicating adequate correction achieved by the procedure. All ten patients returned to normal activities and could perform single heel rises 9 months after surgery.[6]

The surgical technique described in Mousavian et al. reconstructs both the spring ligament and the PTT. This reconstruction technique uses a simultaneous double bundled PTT, which gives more tensile strength than a traditional single bundle technique. The double bundled reconstruction technique involves bisecting the PTT, of which the medial bundle of PTT is used to repair the spring ligament while the lateral bundle of PTT is transferred to the flexor digitorum longus (FDL).[7] This technique is novel because it pairs a double bundled PTT reconstruction with a spring ligament reconstruction. The cases that the authors reviewed indicated that this procedure achieves a more functional PTT compared to the more conventional single bundle technique.[8] The study did not investigate the limitations of this procedure when treating a patient with severe PTT degeneration.

A study by Ryssman and Jeng in 2016 illustrated a newer technique that can recreate the function of the spring ligament. In patients with adult-acquired flat foot deformity, the PTT and spring ligament are not strong enough to resist flattening of the medial longitudinal arch. This causes peri-talar subluxation as well as valgus heel misalignment. This study presents a novel procedure in which the original PTT, if viable, is used to reconstruct a spring ligament in flat foot patients--giving the spring ligament more structural integrity. An FDL tendon transfer to the PTT is done prior to cutting the PTT. The PTT is released proximally, and the distal attachment is left intact. The proximal stump is then passed through a surgically drilled tunnel through the sustentaculum tali and tensioned to recreate the spring ligament. Cadaveric studies have shown good correction on radiographs. Early clinical results seem to recreate the sling function of the spring ligament.[8]

The technique described by Ryssman and Jeng, which involved reconstructing the spring ligament using the PTT autograft, may not be suitable for patients who have severe PTT destruction or lack one altogether. Drilling multiple holes into an ankle with weakened tendons increases the possibility of intraoperative complications including tendon laceration and weakening of the bone where the unhealthy tendons attach. By drilling one tunnel instead of two into the sustentaculum tali, this technique decreases the potential for complications during drilling and fixation of the tendon. This procedure is unique because it uses the diseased PTT as the autograft while keeping intact its broad distal insertion. Preliminary results of this technique demonstrated functional repair of the spring ligament; however, longer follow up is needed, as is a direct comparison of single versus two-hole drilling techniques.[8]

The spring ligament can also be repaired endoscopically using the superficial deltoid ligament to stabilize the medial longitudinal arch. This can be performed with both posterior tibial tendoscopy and reconstruction of the PTT with the assistance of an endoscope.[9] Similar endoscopic procedures, such as talonavicular arthroplasty, may be performed alongside the spring ligament repair.[10] These endoscopic techniques provide minimal soft tissue destruction and can be used with other types of endoscopic procedures that require similar incision sites. However, these procedures have a risk of damaging the medial plantar nerve and therefore, require a lot of experience.[10, 11]

CONCLUSION

The spring ligament complex is commonly described in the literature as being comprised of the SMCNL and the inferior calcaneonavicular ligament. The spring ligament is injured when the PTT weakens and passes on the brunt of eversion and dorsiflexion forces onto the spring ligament. Injury to the PTT and spring ligament may result in an acquired flat foot deformity.[3]

A few innovative surgeries use an internal brace as well as a deltoid and spring ligament reconstruction simultaneously.[6] Other surgical procedures can strengthen the integrity of the spring ligament by reconstructing the ligament in conjunction with a double bundled PTT.[7] Care should be taken when using innovative approaches. Many of these techniques require additional evidence of their long-term viability.

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Surgical Technique in Achilles Tendon Repair Augmentation with Stravix: A Case Series

Mackenzie Luke Chesworth, B.S., Kayla C. DeBlauw, B.S.

ABSTRACT

Many surgical techniques are available to repair a torn Achilles tendon. Tendon repair augmented with tissue substitutes have shown to improve post-operative pain and accelerate return to activity. This article presents a series of cases to highlight surgical techniques used in the repair of the Achilles tendon with Stravix® [Osiris Therapeutics, Inc., Columbia, MD].

INTRODUCTION

The musculoskeletal anatomy of the lower extremity is a complex series of pulley systems of muscles attached to bones via tendons. The contraction of muscles allows tendons to pull on bones that articulate at joints, which allows the body to move. Many tendons have the propensity to tear with forceful contractions or lengthening. Most tears in the Achilles tendon appear 3-6 cm proximal to the insertion at the calcaneus in a location referred to as the watershed area, an anatomical location with reduced vascularity.[1] Surgery is often indicated to repair tendon ruptures to restore normal function. Many surgical techniques have been described for repairing different tendons in the lower extremities. Re-rupture rates of the Achilles tendon have been reported to occur after surgical intervention in 1.7–5.6% of cases, as compared to 11.7–20.8% after conservative treatment.[2] To help reduce post-operative re-rupture rates even further, a tissue substitute or graft may be used to augment the surgical repair.

Many types of grafts have been used to augment tendon repair, including autogenous, allogeneic, xenograft, and synthetic. An autogenous tendon has the same donor and recipient. The plantaris tendon is the most commonly used and accessible autograft for Achilles tendon repair. One substantial benefit is that the plantaris tendon is usually accessible through the same surgical wound created for the Achilles tendon repair. The plantaris tendon is cut from its calcaneal insertion, stretched or "fanned out," and sutured over the rupture site with absorbable sutures.[3]

An allogeneic graft is taken from another donor. An example is GraftJacket® [Wright Medical Technology, Inc., Arlington, TN], an acellular human dermal matrix that has suture-retention properties. This type of allograft material eliminates the need for an additional donor tendon surgical site. Lee et al. used GraftJacket in 9 patients for Achilles tendon repair and found no re-ruptures or recurrent pain at twenty to thirty months.[4]

A xenograft is obtained from a different species. OrthADAPT™ [Synovis Orthopedic and Woundcare Inc., Irvine, CA], for example, is an acellular collagen scaffold derived from equine pericardium that has been used in tendon augmentation. Xenografts have been found to have some success when utilized, however graft rejection is often reported.[5]

Finally, synthetic grafts are typically composed of polypropylene mesh such as Marlex® [ConocoPhillips Co., Houston, Tx]. Synthetic grafts often integrate poorly and may limit normal gliding motion of the tendon.[5]

Stravix® [Osiris Therapeutics Inc., Columbia, MD], an allograft, was used in the case studies to be discussed. It is made from cryopreserved placental tissue called viable cryopreserved umbilical tissue (vCUT). vCUT is placental tissue composed of Wharton's Jelly, which is a gelatinous substance made of an outer amnion layer and inner stromal layer possessing a native collagen and hyaluronic acid-rich extracellular matrix containing growth factors, cytokines, fibroblasts, mesenchymal stem cells and viable epithelial cells. vCUT is a soft, flexible, 1-3-mm-thick durable graft that is useful in augmenting Achilles tendon repair, as well as covering large complex wounds.[6] The mesenchymal stem cells and growth factors in the

GraftJacket® Wright Medical Technology, Inc., Arlington, TN
OrthADAPT™ [ynovis Orthopedic and Woundcare Inc., Irvine, CA
Marlex® ConocoPhillips Co., Houston, Tx
Stravix® Osiris Therapeutics Inc., Columbia, MD

Stravix allograft are found to help with angiogenesis, providing antioxidants, chemoattraction, and antimicrobial peptides. It can also reduce postoperative inflammation, adhesions, and fibrosis.[7-10]

Neglected Achilles tendon ruptures are considered chronic injuries due to alterations in fiber structure, fiber arrangement, cellular morphology, cellular proliferation, and vascularity.[4] Many chronic wound studies have revealed that chronic wound exudates have higher levels of anti-angiogenic proteins, which correlates with reduced tubular formation (a quality of angiogenesis) when compared to acute wounds. Therefore, stimulating angiogenesis with growth factors can be a key component of wound care therapies.[7] Fresh and processed devitalized placental membranes, as seen in Stravix, can promote micro-vessel formation by recruiting hematopoietic progenitor cells, therefore giving Stravix angiogenic properties which prove beneficial for wound treatment, including tendon repair.[11] Duan-Arnold et al. demonstrated that the preservation of human amniotic membrane (hAM), including endogenous viable cells, can potentially protect fibroblasts from oxidative damage and stimulate cell migration, which is essential for wound healing.[8] Clinical outcomes of a case study done by Brandeisky et al. support the use of vCUT for augmenting the surgical repair of an Achilles tendon tear. According to the study, Stravix ancillary use resulted in a quicker postoperative recovery time as well as a faster return to work and baseline activities preinjury as opposed to patients who received only the standard of care treatment.[10] This paper explores a series of cases using Stravix augmentation in Achilles tendon repair.

CASE PRESENTATION

Patient #1:

A fifty year old female with chronic right heel pain for the past four months reported falling at her home. She was initially treated by her primary care physician with a Controlled Ankle Motion (CAM) boot for two months. Due to increased discomfort in her right knee, she discontinued using the CAM boot and returned to her normal footwear. On presentation, her pain, described as 7/10, was localized to the posterior plantar aspect of the right heel. She had a past medical history of hypercholesterolemia for which she was taking daily statin. On exam, she had a positive Thompson test to her right lower extremity, a 3 cm palpable dell in her right Achilles tendon 4 cm proximal to the tendon's insertion, and diminished plantarflexion strength in her right lower extremity. An Achilles tendon rupture was suspected and confirmed by MRI, which showed a partial tear measuring about 3 cm on the T1 image and 6 cm on the T2 (**Figure 1**). Based on the clinical and radiological findings, the patient elected an open repair with Stravix augmentation.

The patient consented and was prepared for the operating room. She was placed in prone position and intubated for the procedure. The right lower extremity was anesthetized using 10cc of 0.5% marcaine plain proximal to the Achilles tendon in a V-like distribution. The surgical site was prepared and draped, during which time the Stravix was removed from its packaging and thawed in saline. A 6cm linear incision was made centrally over the Achilles tendon. Meticulous dissection was carried out in layers, avoiding all neurovascular structures. An incision was made into the Achilles tendon sheath which revealed significant fibrous adhesions on the tendon. The adhesions were freed using blunt dissection. The surgeon noted that a portion of the Achilles tendon was still preserved. At this point, the Stravix graft, which was soaked for fifteen minutes prior, was applied. The "ribbed" side of the graft was placed on the tendon and folded over in a burrito fashion. The graft was tubularized around the tendon using 3-0 Vicryl® [Ethicon, Inc., Somerville, NJ]. The graft was then repositioned to place the sutured edges facing anteriorly and was sutured superiorly and inferiorly to the tendon using 3-0 Vicryl. The surgical site was flushed with copious amounts of saline and closure was obtained by layers.

The paratenon, a loose areolar tissue around the Achilles tendon, was noted to be frayed and an attempt to partially reapproximate was accomplished using 4-0 Vicryl. The subcutaneous layer was closed using 4-0 Vicryl and skin was then closed with 4-0 Nylon. The surgical site was dressed with betadine-soaked Adaptic and dry sterile dressings. The patient was then placed in a posterior splint with approximately fifteen degrees of plantar flexion. The patient was discharged shortly after recovery from surgery and instructed to be non-weight bearing to right leg and to ambulate with crutches. Sutures were removed two weeks postoperatively without incident.

Patient #2:

A thirty-seven year old male presented to the clinic complaining of marked pain in his right Achilles tendon after sustaining an injury while playing basketball a month prior. The patient was initially treated in the emergency department with a posterior splint. Two weeks later, the patient discontinued the splint and crutches on his own and returned to regular walking shoes. His past medical history included methamphetamine addiction and fifteen years of tobacco use. He stated that he stopped all recreational drugs for over two months during his initial visit. A right lower extremity exam was significant for a positive Thompson

Vicryl® Ethicon, Inc., Somerville, NJ
Adaptic™ Kinetic Concepts, Inc., San Antonio, TX

test, diminished plantarflexion strength, marked pain to palpation to the posterior ankle and Achilles tendon. The patient was diagnosed with an Achilles tendon rupture, placed in a CAM boot with a heel lift and consented for open repair with Stravix augmentation.

In the operating room, the patient was intubated and was positioned prone. The Stravix was thawed and prepped as described previously. The leg was draped, prepped, and anesthetized with 10cc of 0.5% marcaine plain in a V-like distribution superior to the Achilles tendon rupture. A 10cm linear incision was made over the Achilles and dissection down to fascia was carried about by layers. Blunt dissection was employed to visualize the paratenon followed by a linear incision over the paratenon. The paratenon was reflected medially and laterally, and a 3 cm complete rupture was identified in the midsubstance of the Achilles tendon. There was a considerable amount of scar formation noted at the rupture site and proximal to the rupture site. The scar tissue was released and the area was then irrigated with saline. The foot was placed in plantarflexion and the tendon edges were reapproximated. Using the Kessler technique, a #2 FiberWire suture was used to maintain tendon approximation, passing first through the proximal end of the Achilles then subsequently through the distal stump. The suture was tied off laterally. The paratenon was closed using a 3-0 Vicryl in a running fashion. Stravix allograft was placed over the posterior aspect of the Achilles and redundancy to graft was removed. The graft was sutured on all edges into the posterior tendon using 3-0 Monocryl as shown in **Figure 2**. Subcutaneous tissue was approximated with 3-0 Vicryl in a buried interrupted configuration and the skin was closed with 4-0 nylon using interrupted horizontal mattress stitches. The incision site was dressed with betadine-soaked Adaptic™ [Kinetic Concepts, Inc., San Antonio, TX] and dry sterile dressings. The patient was then splinted with 15 degrees of plantarflexion.

The patient was later discharged after recovery and instructed to be non-weight bearing to the right leg. Because the patient has a history of substance abuse, he opted to avoid opioid pain medication and agreed to take tramadol and gabapentin as needed for his pain. He also received a popliteal block in the recovery room. Upon follow-up one week later, the patient reported having his pain adequately controlled with gabapentin.

DISCUSSION

Approximately one in four Achilles tendon ruptures are misdiagnosed. Inglis and Colleagues attribute the 22% incidence of misdiagnosis seen in their case series to patients and physicians being misled by the underreporting or inconsequential perception of trauma, the lack of significant pain the patient experiences, and the patient's ability to weakly plantar flex the ankle on exam.[13] Ankle swelling can make a palpable dell difficult to appreciate on exam and action of the flexor hallucis longus may provide enough strength to deceive a physician that only a partial rupture is present.[3]

Once a tendon rupture has been diagnosed and classified, treatment should be selected with respect to the patient's comorbidities and their overall goals. The criteria for using tissue substitutes is surgeon dependent. However, with chronic tendon injuries, a tissue substitute may provide additional support in postoperative healing. The determining factor for using augmentation in this case series was chronic injury greater than one month. Augmentation of the tendon repair has been shown to not only increase the repair strength preventing re-rupture, but also allows for early active mobilization.[5] In addition to these attributes, Stravix has been shown to have antifibrotic, antimicrobial, and anti-inflammatory properties that benefit surgical outcomes, especially when used in tendon repair augmentation. These properties contribute to the reduction of postoperative pain and decrease transition time to ambulation in regular footwear without an assisted device.[12] Stravix is also very robust and easily manipulated intraoperatively.

In these two cases, we demonstrated the ease in technique associated with applying Stravix. The major difference between the two surgical cases noted by the surgeons was the use of "burrito wrapping" in Patient One versus posterior overlying in Patient Two. The former may provide more ease for the tendon to glide after closure and possibly prevent adhesions anteriorly. In addition, this method provides circumferential coverage, which increases the surface area of the applied tissue substitute on the surgical repair. There are no comparative studies to our knowledge between the two techniques, which could be further explored. A limitation of both studies includes the lack of long-term postoperative follow-up. Although this paper does not review the potential economic impact, it could be argued that the economic impact of augmenting the tendon repair with a tissue substitute may pose a burden. On the other hand, the reduction in pain and the potential decrease in re-rupture rate and possible repeat surgery may decrease the overall financial impact.

CONCLUSION

As described above, the surgical techniques for Stravix allograft are easy to perform, and the patients in the two cases were satisfied. However, the criteria

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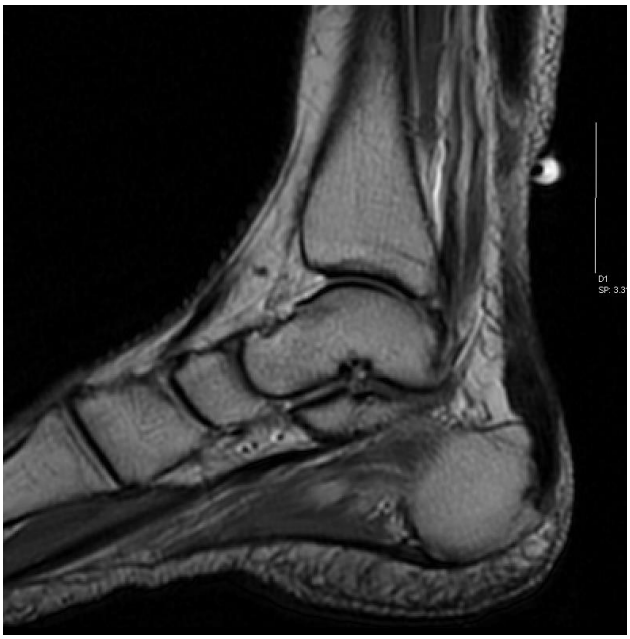
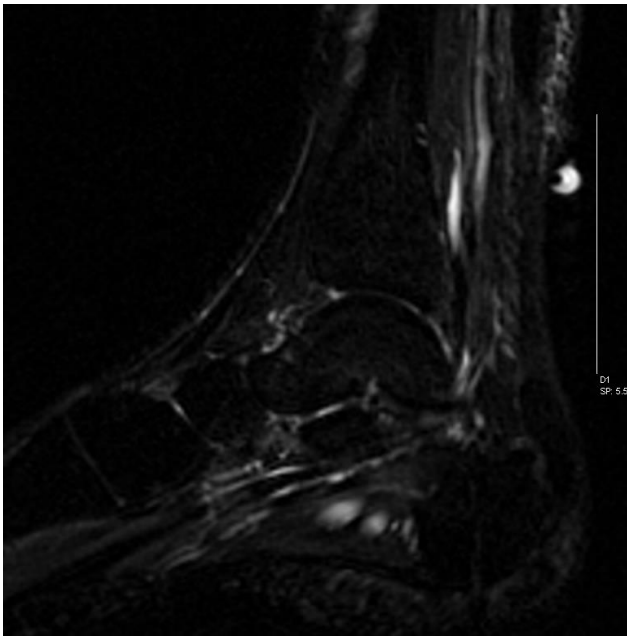
for using augmented tendon repair is still not established as long term outcomes and cost effectiveness are unknown.

ACKNOWLEDGMENTS
A special thank you was given to Dr. Samuel Caine, DPM, Dr. Janelle Maravelias, DPM and Jillian Nunes, Osiris for patient information and figures.



A.



B.

Figure 1: T1 (A) and Fluid Sensitive (B) Sagittal MRI images of large partial Achilles tendon rupture.

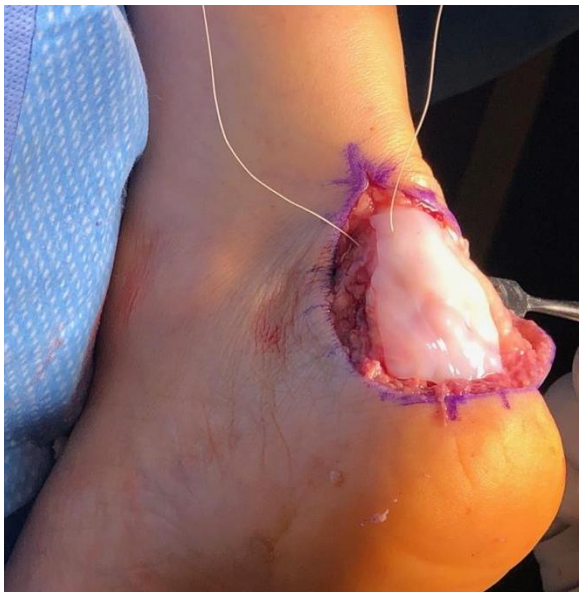


Figure 2: Stravix overlying posterior Achilles tendon.

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