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Journal of Lower Limb Medicine

WESTERN UNIVERSITY OF HEALTH SCIENCES

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Vol.6 May 2019

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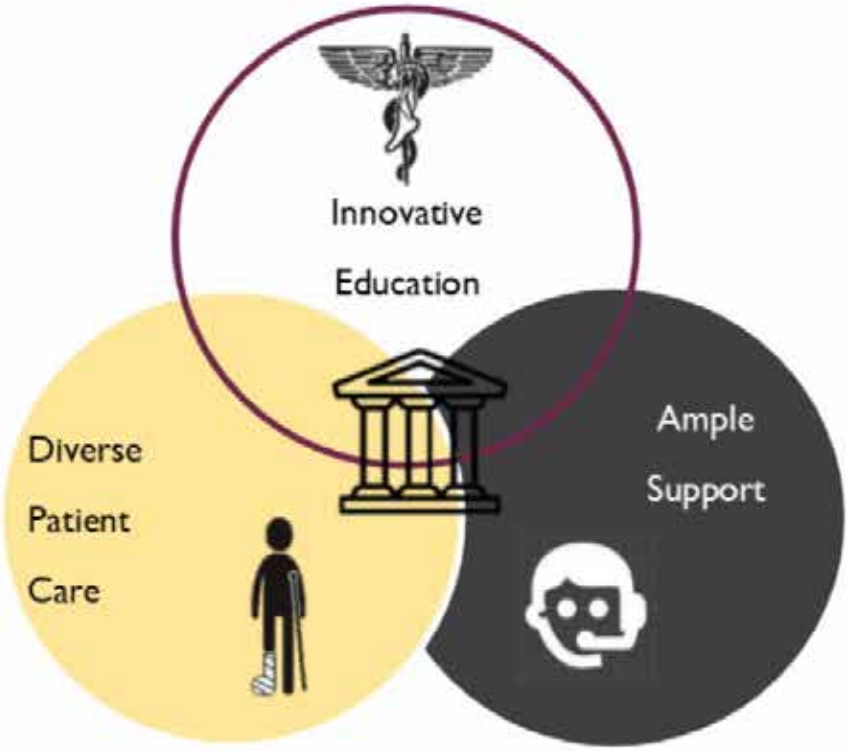

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Dear Reader,

Since the genesis of *Extremitas Journal of Lower Limb Medicine*, it has been the mission of Western University and WesternU's College of Podiatric Medicine to promote student research and propel conversations to ultimately provide enhanced, evidenced-based care we will give to others. As the years have gone by, it is my belief that this mission has not only been reached, but every year, the expectations have spanned further, pushing the boundaries of what our future health care providers are capable of.

In your hands, you hold the exceptional efforts of over fifty of WesternU's student body to research, craft, and revise a series of journal articles for the sole purpose of sharing knowledge. The discipline, compassion, and time commitment it takes to publish is no easy feat. This issue is a testament to the very fabric of what grit and multidisciplinary team work can produce. It has been a humbling experience to witness the talent that walks on our campus grounds, and to have the privilege to work in unison with students across the different colleges WesternU offers.

As a student run journal, the costs for printing and distribution are 100% dependent on the generosity of our sponsors who also echo the importance of student research and evidenced-based medicine. To that degree, I'd like to extend my deepest gratitude to our sponsors as well as the mentors, faculty, and administration that have supported this publication.

Special mentions are due to WesternU's current president, Dr. Daniel R. Wilson, recently retired interim Dean of WesternU's College of Podiatric Medicine, Dr. Lester Jones, current Dean of WesternU's College of Podiatric Medicine, Dr. Katherine Satterfield, and amazing faculty advisor for all editions of *Extremitas Journal of Lower Limb Medicine*, Dr. Jarrod Shapiro - Thank you all for the guidance, support, and encouragement throughout the journey of creating *Extremitas Journal of Lower Limb Medicine*. The memories, experience, and lessons have been priceless, and something I will carry with me always.

Last, but certainly not least, thank you Reader for supporting our journal through your viewership. Thank you for taking the time to digest our articles regarding current literature and pathologies of the lower limb. Furthermore, thank you for going beyond the doors of the lecture halls to understand and learn. As Brian Herbert perfectly said, "The capacity to learn is a gift; the ability to learn is a skill; the willingness to learn is a choice."

It is my distinct honor and pleasure to present to you the 6th annual edition of *Extremitas Journal of Lower Limb Medicine*. I hope you enjoy!

Sincerely,

Elizabeth Oh
Editor-In-Chief

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Dear Readers,

It is with great pleasure that we present the 6th edition of *Extremitas: Journal of Lower Limb Medicine*. Throughout the past six years, *Extremitas* has grown tremendously with the help of our student authors, faculty advisor, and sponsors. *Extremitas* represents the hard work and dedication of Western University students as we present the latest research in the field of lower limb medicine. This issue of *Extremitas* delves into a variety of topics such as biomechanics of the lower limb, diabetic complications, pain management, as well as recent advancements in surgical and conservative treatment.

Extremitas would not be possible without the continued support of Western University of Health Sciences and the College of Podiatric Medicine. We would like to extend our deepest gratitude to our sponsors: Western University's College of Podiatric Medicine, California's Podiatric Medical Association, PICA insurance Group, American Board of Podiatric Medicine, and Bako Diagnostic. We would also like to thank our cover designer, Kira Cramer, and all of our authors, who decided to use our journal as a platform to share their talents and passion for lower limb medicine. We appreciate your continued support and look forward to continuing the tradition of student research and excellence set forth by WesternU and *Extremitas*.

Sincerely,
The *Extremitas* Staff

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Biomechanics of Cycling and Ballet Footwear: A Review

Andrew Y. Lee, B.S.

ABSTRACT

Objective: To review the biomechanical advantages and limitations of cycling and ballet footwear on the lower extremity.

Methods: Peer-reviewed articles compiled from the online journal database, PubMed, were included in this narrative literature review.

Results: Cycling shoes feature cleats, wedges, and stiff midsoles to maximize smooth transfer of energy from shoe to pedal. Incorrectly fitted cycling shoes can result in neurovascular compression and increased localized forefoot pressure. Ballet pointe shoes emphasize solid toe boxes and rigid shanks to help stabilize the foot and ankle in order to support en pointe movements. Over-worn pointe shoes tend to express compliant shanks and increased frictional forces, consequently leading to significantly greater plantarflexion and midfoot flexion.

Conclusion: Cycling and ballet are two different examples of exercises that have varying demands on the lower extremity, which require shoes that address specific biomechanical needs and provide compensatory functions. The most prevalent injuries to the lower extremity for both sports are due to overuse-- 41.7% of cycling injuries and 53.6% to 85% of ballet injuries. Improperly fitted or worn-out shoes can increase risk of injury by not contributing effective mechanical support, energy transfer, or force dispersion. By understanding the biomechanics of cycling and ballet, clinicians can improve recovery and decrease injury incidence by better assisting patients in selecting proper footwear, making personalized footwear adjustments, and providing effective rehabilitation counseling.

Introduction

The design and form of athletic footwear caters to the respective demands of each activity. Some athletic shoes have more internal or external modification than others, yet all athletic footwear share the same function of maximizing performance and minimizing risk of injury. There is always potential for structural or mechanical improvement. In appreciating the biomechanical nuances of niche athletic footwear, quality diagnoses and recommendations can be provided to improve patients' performance and reduce incidence of injury. This review will evaluate the biomechanics and limitations of cycling and ballet shoes based on current literature.

Cycling

Cycling is an endurance sport generally regarded as a low-impact and non-weight bearing exercise.[1] However, seated cyclists can apply forces equivalent to half their body weight while pedaling and up to three times their body weight when cycling while standing.[2] The cyclist propels a bicycle by exerting a push force on the pedals, causing their circular rotation and thus forward motion.[3] A complete pedal cycle is divided into two phases: the power phase followed by the recovery phase.[3] The greatest magnitude of force is applied in the power phase by the downstroke motion from top dead center (TDC) to bottom dead center (BDC), while the recovery phase is the upstroke motion from BDC to TDC and provides a rest period before the next power phase (Fig. 1).[3] The lower extremities are responsible for the principle energy output to the pedals, which can unfortunately lead to overuse injuries from repetitive high loads on the joints.[4]

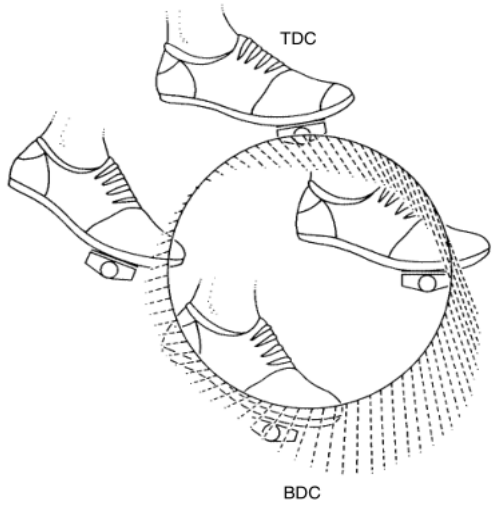

Figure 1: The pedal cycle's power phase goes from top dead center (TDC) to bottom dead center (BDC), followed by the recovery phase from BDC to TDC. The dashed lines represent the direction and magnitude of the force in the shoe/pedal interface. Adapted from Journal of the American Podiatric Medical Association.[18]

Cycling Footwear Biomechanics

Cycling shoes are designed with the purpose of providing smooth transfer of energy in the shoe/pedal interface to maximize power output and minimize

trauma to the legs.[4] Compared to recreational shoes, cycling shoes feature cleats, wedges, and stiffer midsoles. The midsole is the primary structural area where transmission of force from shoe to pedal occurs. A prior study by Jarboe et al. found that cycling shoes with stiffer midsoles resulted in decreased localized pressure on metatarsal heads from improved redistribution of load and enhanced transfer of energy, suggested by a lower heart rate at a given power output while pedaling.[5, 6] Another important feature of cycling shoes is cleats located on the sole. Cleats enable the shoe to securely lock to the pedal, allowing the hamstring muscles to contribute a positive propulsive movement in the early recovery phase by forceful knee flexion.[3] When more muscles contribute to propulsion, the workload of the quadriceps muscles are decreased in late recovery and early power phases.[3] Cycling is a closed-kinetic chain exercise and muscle fatigue can encourage improper pedaling technique, inducing the development of muscle imbalances and extraneous stresses within the kinetic chain.[1, 7] In addition, some cycling shoes have cleat wedges that realign the lower extremity into a neutral position to accommodate for the flat surface of the pedals. Approximately 86.67% of the population has forefoot varus; thus, varus wedges applied to the sole can improve energy transmission efficiency and decrease strain by properly adjusting for forefoot discrepancy.[3, 8]

Figure 2: Cycling shoe anatomy. Adapted from Complete Tri.[19]

Potential Footwear-Related Injuries

Although midsole stiffness offers load dispersion, the degree of stiffness in cycling shoes is still a controversial subject. According to a 2003 study conducted by Jarboe et al., soles built with stiff carbon fiber induced significantly greater peak plantar pressures in the forefoot region while pedaling than soles constructed with plastic.[6] Increased localized forefoot pressure and limited natural foot movement are both contributing factors for metatarsalgia.[4, 6] In addition, many cycling shoes are designed by European companies which utilize lasts, shoe molds used during assembly, that better accommodate for the narrower European feet.[3] Incorrectly fitted shoes can induce symptoms of excessive neurovascular compression such as numbness and ischemia.

Ballet

Ballet is a stage performance art form that demands considerable athleticism, technique, and flexibility of the lower extremity.[9] One of the most widely recognized elements of ballet is "en pointe" dancing, which is an advanced ballet form that means to dance "on the tips of the toes."[9] To eventually become capable of dancing en pointe, dancers train for years in "demi-pointe," dancing on their metatarsal heads, to develop proper technical skills and strength.[9] When performing en pointe, complete plantarflexion of the foot and ankle to at least 90° is required to lock the subtalar joint for the stabilization of the ankle.[9]

Ballet Footwear Biomechanics

The exterior design of modern pointe shoes has remained fairly consistent over the centuries, but has mechanically evolved to be sturdier.[13] Pointe shoes feature two structural characteristics of interest: the solid toe box and rigid shank (Fig. 3).[9] The toe box is conically constructed with layers of paper, fabric, and glue, which provides enough rigidity to support en pointe movements while still malleable enough to allow for articulations of the joints of the lower extremity.[10] The rigid shank is attached to the back of the insole and provides structural support for the arch of the foot.[11] In addition, the outer material covering the shoe is usually composed of satin material, which contributes low friction to allow for spins while still providing enough traction for jumps.[13] According to a 2005 cadaveric study conducted by Kadel et al., pointe shoes can provide significant stabilization to the ligaments of the Lisfranc midfoot region by reducing vertical shear force and displacement stresses.[11] The resulting midfoot stability is evident by toe pressures accounting for 20-30% of the total pressure in the toe box while the remaining 70-80% of the load is distributed to the vamp and sole of the shoes.[11]

Potential Footwear-Related Injuries

Pointe shoes are compulsory to execute en pointe positions, yet the protection they provide is still insufficient. Unfortunately, the integrity of pointe shoes deteriorates rapidly and requires

constant replacement; some professional ballerinas need to change their shoes after each performance.[10] Over-worn pointe shoes tend to express compliant shanks and increased frictional forces, leading to significantly greater plantarflexion and midfoot flexion.[10] When the ligaments of the midfoot and ankle undergo such excessive strain lengths and tensile forces, the dancer becomes at risk for sprains, cuboid subluxation, flexor hallucis tendonitis, and Lisfranc injury.[10,14] In addition, the symmetrical shape of pointe shoes imposes valgus forces that causes the hallux to conform to the conical shape of the toe box.[12] The ensuing chronic strain to the medial collateral ligaments of the hallux may lead to joint deformity and degeneration.

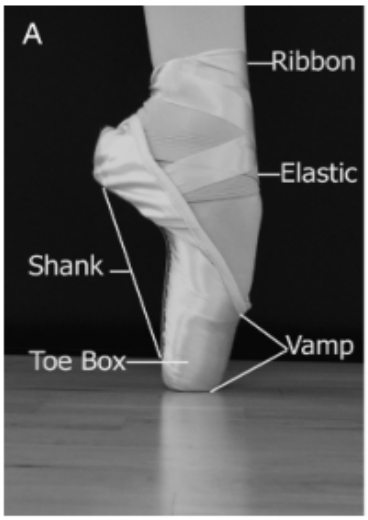

Figure 3: Pointe shoe anatomy. Adapted from Current Sports Medicine Reports. [20]

Conclusion

By providing compensation and stability, athletic shoes are efficient in enhancing performance and sparing the lower extremities from injury. However, the biomechanics of these shoes still lack perfection and can pose unintended risks of injury to the wearer. Both ballet and cycling involve performing repetitive, rotational movements: cyclists can average up to 5,000 pedal revolutions per hour, while ballet dancers practice pointe work, jumps, and spins for up to 45 hours per week.[7,16] Consequently, the most prevalent injuries to the lower extremity for both sports are due to overuse— 41.7% of cycling injuries and 53.6% to 85% of ballet injuries.[1,16] Overuse injuries can be attributed to flawed technique induced by fatigue and the athletes' conscious disregard for pain, which can also be further exacerbated by improper footwear.

In considering cycling or ballet shoes, a stiff midsole or shank is a vital element for mechanical support, energy transfer, and force dispersion. However, extensively stiff midsoles can lead to concentrated forefoot pressure and nerve compression, whereas elastic shanks may cause excessive flexion and stress to the foot and ankle.[6,10] Yet, a questionnaire conducted by Cunningham et al. reports that ballet dancers prioritized fit and comfort above durability for pointe shoes.[13] By understanding the biomechanics of cycling and ballet, clinicians can assist patients in selecting proper footwear and making personalized adjustments with the placement of orthotics, toe spacers, or padding.[12]

In addition, many ballet dancers have difficulty distinguishing between pain from injury and pain associated with dance practice due to their heightened threshold and tolerance for pain.[15] Any suggestions for rest or discontinuance of dance usually clash with their persistent mentality to dance through pain, which prompts negative responses and loss to follow-up.[15] Specialized health care catered towards ballet dancers, such as prescribing rehabilitative regimens, may result in decreased injury incidence and recuperation.[15]

Similarly, cyclists may also be wary of bed rest for concern of performance loss from long term training cessation.[17] Since overuse injuries typically present with acute-on-chronic pain from the accumulation of microtrauma, patients may decide to continue cycling activities— inducing chronic tissue degeneration.[7] Clinicians can counsel patients on a rehabilitative exercise schedule that involves lower resistance and increased cadence.[7] Through being knowledgeable and aware of the current literatures on modern athletic footwear, clinical diagnoses can be improved and injuries minimized.

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The Clinical Appearances of the Flexor Digitorum Accessorius Longus & the Soleus Accessorius: A Review

Eduardo Glass, B.S., Garrett Wireman, B.S., Charles Zillweger, B.S.

ABSTRACT

Objective: Review the literature on clinical appearances and relationships of the accessory muscles of the medial ankle.

Conclusion: The flexor digitorum accessorius longus (FDAL) and the soleus accessorius (AS) are present in pathologies such as clubfoot and tarsal tunnel syndrome. Mass effect is one explanation for how these muscles contribute to the pathologies. There is potential in improving the quality of data available, and investigating the prevalence of the muscles and their presentations within the athlete population.

Introduction

Musculoskeletal injuries are common among the lower extremity, primarily the foot and ankle, and can be exacerbated by the existence of accessory structures.[1] The goal of this paper is to examine the current literature on the flexor digitorum accessorius longus (FDAL) and the accessory soleus (AS) and their contribution to clinical appearances and applications.

The FDAL is the most common medial accessory muscle of the ankle.[4-6] Potential origin points for the FDAL include the tibia, fibula, flexor hallucis longus (FHL), soleus, and the flexor retinaculum.[2,4] The FDAL inserts into the quadratus plantae muscle or the flexor digitorum longus after traveling in the tarsal tunnel (Figure 1).[2, 4-5]

The FDAL assists in the flexion of the phalanges due to its insertions into the quadratus plantae or flexor digitorum longus.[5] The FDAL remains as a muscular tissue for most of the tarsal tunnel, where it is adjacent and part of the neurovascular bundle that courses within the tarsal tunnel.[2,6,7] Current literature rates the FDAL to exist in 2-14% of cadaveric studies.[2,5,6]

Unlike the FDAL, the AS is surrounded by its respective fascia, separate from that of the soleus structure, aiding in its identification.[2] Origin sites for the AS can be the tibia, fibula, and the anterior side of the soleus. The AS is innervated by the tibial nerve. As the AS courses distally, it will approximate the Achilles tendon to its anterior or anteromedial side.[2] The insertional properties cannot be categorized with its five common insertions because due to its muscular or tendinous properties.

The muscular insertion resides with the Achilles tendon located at the superomedial side of the calcaneus (Figure 2). Tendinous insertions include the superior and medial calcaneus. Current literature places the AS rate at 0.7-5.5% of cadaveric findings. [2,4]

Clinical Relationships of Flexor Digitorum Accessorius Longus

The FDAL may have arisen as a separation of the FHL, where it has translated more to the plantar region away from its evolutionary origins in the upper leg. While other primates lack a quadratus plantae to flex their digits, an FDAL exists to compensate for the missing quadratus plantae.[5-6]

In 2014, Mi-Sun Hur et al. created a classification system for the FDAL to readily describe its characteristics (Figure 3).

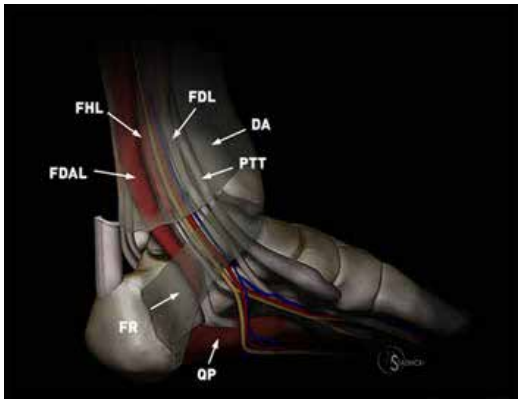

Figure 1. Represents a 3D graphic model of the FDAL coursing through the medial side of the leg and ankle where it abuts the tarsal tunnel neurovascular bundle. Adapted from Carroll 2008.[2]

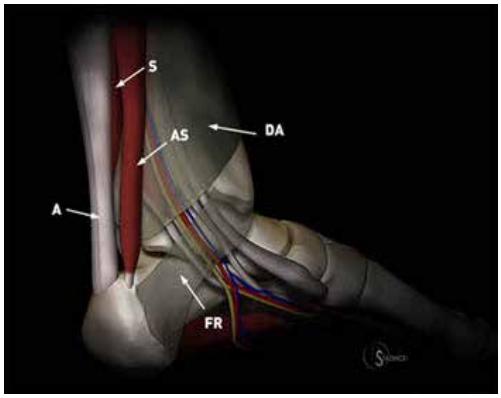

Figure 2. Represents a 3D graphic model of the AS coursing through the medial side of the leg and ankle where it abuts the triceps surae and inserts into the calcaneus. Adapted from Carroll 2008.[2]

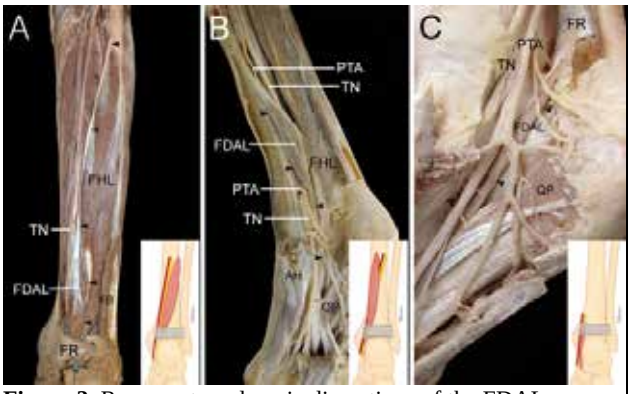

Figure 3. Represents cadaveric dissections of the FDAL coursing through the medial side of the leg and ankle where it abuts the tarsal tunnel neurovascular bundle, corresponding to Mi-Sun Hur et al classification system: Ia (A), Ib (B) and II (C) respectively. Adapted from Clinical Anatomy, 2014.[6]

Type I describes the FDAL that originates in the leg. Type Ia describes a structure that runs parallel and superficial to the posterior tunnel neurovascular bundle, Type Ib crosses the neurovascular bundle within the tarsal tunnel.[6] Type II has no subtypes and describes a FDAL that originates within the tarsal tunnel regardless of its coursing with the posterior tunnel neurovascular bundle.[6]

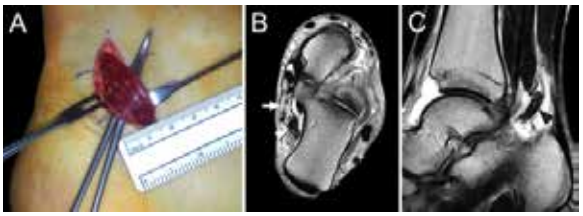

Figure 4. Represents surgical resection and MR imaging of the FDAL. The FDAL in the image set are a type II FDAL with a hypertrophic muscle belly within the tarsal tunnel, compressing the neurovascular bundle and leading to tarsal tunnel syndrome. Adapted from Clinical Anatomy, 2014.[6]

Patients are often misdiagnosed when presenting to clinic with compartment syndrome symptoms due to the rarity of both the FDAL and tarsal tunnel syndrome.[5,8] The presence of FDAL can cause a space occupying lesion in the form of tarsal tunnel syndrome. This space increases pressure and crowding in the neurovascular bundle, specifically the tibial nerve, causing nerve pain.[6,9] Type 1b, a subtype which originates in the leg and crosses the neurovascular bundle, has been associated with pain after heavy exercise. This is due to increased pressure via hypertrophy of the muscle due to frequent contractions and compression of the adjacent neurovascular bundle in a Type 1b FDAL.[6] Type II FDAL has also been observed to cause neurovascular bundle compression (Figure 4).[6]

The FDAL was the source of 12% of tarsal tunnel syndromes in a surgical report (6 feet out of 49), with surgical treatment confirming presence. Five out of seven cases that involved an accessory muscle had a preoperative MRI accessory muscle diagnosis. The other two cases were not given an MRI study but were confirmed at surgery. The additional non FDAL accessory case involved presence of the AS. Resection of the accessory structures were undertaken and full recovery was reported without incident.[10]

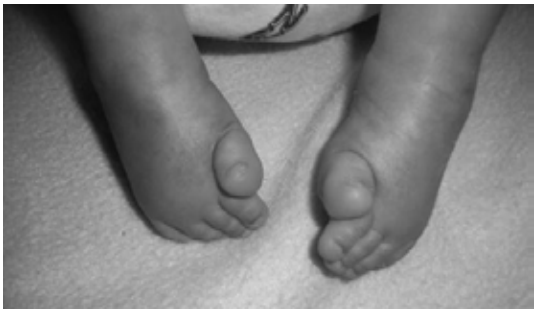

Figure 5. Photograph representing the Samir-Adams sign in a resistant clubfoot patient. The hallux appears as a "thumbs up", being relatively extended compared to the other digits. Adapted from Journal of Pediatric Orthopaedics B.[13]

Another space occupying mass was reported with no compression of the tarsal tunnel neurovascular bundle but had involvement of the FHL and FDL tendons. The narrowing of space within the tarsal tunnel limited the pull of the FHL and FDL tendons upon contraction, leading to diminished flexion and plantarflexion of the digits and ankle, respectively. These symptoms mimicked flexor hallucis syndrome, a syndrome associated with overuse and attendant tenosynovitis of the tendon. Yet again a resection of the FDAL was performed.[11] A separate tarsal tunnel case reported FDAL presence in T2 MRI and stated it as the cause of the tarsal tunnel syndrome.[12]

FDAL has also been noted in varus deformities in resistant clubfoot patients. It is prevalent in 13% of patients requiring soft tissue release in a study that also tested an examination technique to detect FDAL presence in resistant clubfeet. The presence of the FDAL can be predicted in 95% of patients (48) prior to surgical release via observation of the Samir-Adams sign (the hallux being relatively extended to the other digits), (Figure 5). All of the cases were resistant and either failed Ponsetti method treatment or were neglected with late presentations.[5, 13] Dobbs et al. found that the FDAL was associated with Familial Idiopathic Clubfoot. Children with a family history of clubfoot had an six-fold increased probability of having a FDAL accessory muscle.[14] Lack of clinical awareness of the FDAL and its relationship with the tarsal tunnel can create difficulties in identifying the structure on exams

and imaging, leading to missed diagnosis or misdiagnosis.[5]

A defining feature of the FDAL is its course within the tarsal tunnel, unlike other medial accessory structures such as the AS which insert into the calcaneus.[2,4] This defining feature is used in FDAL imaging.[4] The highest prediction of the FDAL in imaging is via magnetic resonance imaging (MRI) from an axial vantage point as it descends the leg and enters the tarsal tunnel.[4] Imaging the structure at its insertion points can be difficult as many other soft tissue structures can obscure its presence.[4,15]

Clinical Relationships of Accessory Soleus

The AS has also been termed as the supernumerary soleus, soleus secundus, and soleus accessorius.[16] Only a few cases about the AS have been reported in anatomic, orthopedic, podiatric, and radiologic journals.[16,17] The AS may present as a soft tissue mass in the posteromedial region of the ankle, congenital in origin and typically presenting in the second or third decade of life.[4,18] The AS should be regarded in a differential diagnosis of soft-tissue swelling of the ankle, despite its lower prevalence. Specific findings of imaging studies combined with awareness of the clinical presentation can assist in making a diagnosis without necessity of surgical exploration for AS.[18,19] Identification of the AS is simple within imaging and with confirmation of the mass with an incisional biopsy.[4,16] Painless posterior masses can be diagnosed without biopsy with CT and MR imaging.[4] The AS can be identified within the surface anatomy of a patient (Figure 6).[20]

Among AS cases, asymptomatic swelling and painful swelling appears to be frequent primary case findings. Club foot and crepitus are also apparent within past cases.[16,21-23] AS has been noted to be a rare finding within clubfoot deformities. A larger series contained 20 observations in 16 patients with idiopathic clubfoot treated by the Ponseti method where full ankle dorsiflexion was prevented by the AS after Achilles tendon tenotomy.[23]

A study reported high association in a small patient population with AS presence and Achilles tendinopathy. A study reported high association in a small patient population with AS presence and Achilles tendinopathy. The study reviewed 15 consecutive cases with a diagnosis of accessory soleus muscle from a database of MRI examinations. Two cases were eliminated from review due to incorrect initial diagnosis. There were 13 cases of AS in 11 patients, five male and six female, with nine cases (69.2%) in which Achilles tendinopathy was associated with the AS. Two patients had bilateral AS and Achilles tendinopathy of each Achilles tendon. Further investigation of this correlation in higher population numbers is needed to strengthen significance.[24]

A combined literature review and case report of AS in a soccer player also discussed a similar relationship of the muscle in athletes. The report stated that high incidence of tendon pathologies in soccer players should be considered, as tendinopathies were ranked fifth in incidence in a top Italian soccer team and Achilles tendon injuries were ranked seventh in the Australian Football league. The report also cited a case series where 17 athletic patients out of 21 total patients reported symptomatic AS and obtained treatment. An 18-year-old semi-professional soccer player presented with a three month history of exertional pain and swelling on the medial aspect of his left ankle, that worsened during sustained training and promptly improved at the end of training. This patient complained of symptoms that did not let him complete practices or games. Examination and MRI revealed an AS with no signs of Achilles tendinopathy. Surgical excision of the AS was done, and the patient returned to play three months after surgery. The patient reported no discomfort to the left ankle upon the six month follow up.[17]

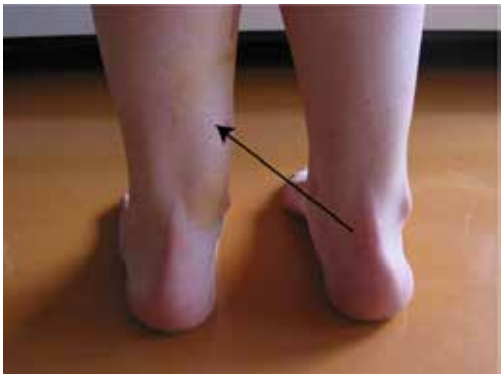

Figure 6. Surface Anatomy: Accessory soleus muscle identified in clinical examination. Muscle mass (black arrow) localized in the medial retromalleolar region of the left leg. Adapted from *Scandinavian Journal of Medicine & Science in Sports*, 2015.[20]

More recently, a case reported a 17-year-old male with exertional compartment syndrome and associated tarsal tunnel syndrome secondary to a very large accessory soleus muscle. This patient presented with complaints of pain and swelling to the distal Achilles tendon area, with a history of swelling in the posterior medial aspect of the ankle and tenderness in the entire posterior compartment. This cross country running patient noticed that his pain and swelling was aggravated during the running season but improved when he stopped running. Examination appreciated a soft mass with palpation and a MRI study revealed a large AS separate from the Achilles tendon. A mild mass effect on the flexor hallucis longus and a slight

flattening of the neurovascular bundle posteromedially was noted. The accessory muscle was removed surgically (Figure 7).

This patient was interviewed at 12 months postoperatively and reported being asymptomatic. This patient participated in all previous activities without limitations or pain after treatment.[25] There is potential in investigating correlations between athletic history and symptomatic presentation of the AS for greater population numbers.

The frequent asymptomatic nature of AS may falsely depress the overall incidence of symptomatic AS in the general population. If there is an increased latent population with AS, trauma, or overuse resulting in compartment syndrome may be exacerbated by the AS and cause its discovery. Clinical prevalence and cadaveric prevalence of the muscle may potentially differ significantly.[16]

The AS can be detected with multiple imaging modalities, more specifically with lateral radiographs, CT, ultrasonography and MRI.[4, 18,19] MRI allows the most specific diagnosis for AS out of the imaging modalities.[4] The AS is observed as a tubular soft tissue density that partially obscures the Kager fat in lateral radiographs. It travels anterior to the achilles tendon and superficial to the deep aponeurosis, surrounded by its own fascial sheath.[4]

The AS appears isoechoic with muscle within ultrasound imaging, being located between the FHL and the Achilles tendon.[4] The AS appears similar in CT and MRI imaging as a well-defined soft tissue mass in Kager fat with the AS descending posterior to the tarsal tunnel.[4]

Treatment for a symptomatic or asymptomatic accessory soleus depends on the specific pathology and intensity of symptoms.[16] Asymptomatic AS identified in imaging rarely need to be treated.[16] An incisional biopsy and/or surgical exploration of the potential AS is recommended to confirm the diagnosis of AS and rule out a possible malignant mass.[16] A full or partial fasciotomy, or excisional biopsy is the usual treatment modality for a symptomatic AS once conservative therapy fails.[4,16,17,2,-26] One review also recommended closure of blood supply as another treatment option.[17]

The AS has been utilized as protective coverage for the posterior tibial nerve in a revisional procedure for tarsal tunnel syndrome.[26] More recently, a minimally invasive tendon release has been reported in a case of recurrent symptomatic AS in an athlete. The patient returned to game play in five weeks and full competition by three months postoperatively. There were no complications and the patient was asymptomatic upon 3 year follow up.[27] Local botulinum toxin type A injections for symptomatic AS was used in a novel way for five physically active patients. Treatment efficacy was evaluated based on resolution of exercise induced pain and resumption of normal physical/sports activity levels. Exertional pain disappeared in all five patients with resumption of normal level of physical activity and no side effects or motor deficits.[20]

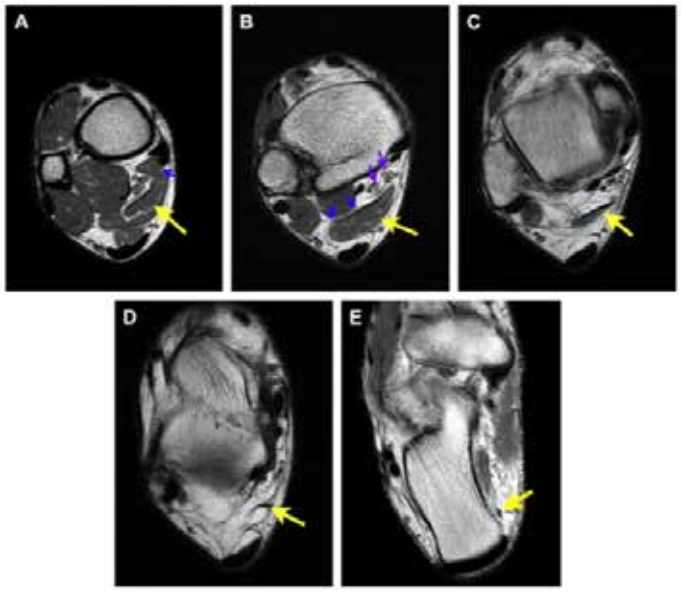

Figure 7. Proton-density weighted MR images in a 37 year old man with ankle pain. (A): Axial view of the ankle. (B): Proximal to plafond. (C): Tip of Medial Malleolus. (D): Tip of Lateral Malleolus. (E): Body of calcaneus. The accessory soleus muscle belly (yellow arrows) lies superficial to the deep aponeurosis (blue arrows in A and B), posterior tibial neurovascular bundle (purple arrows in A and B). Adapted from Magnetic Resonance Imaging Clinics of North America, 2017.[4]

Similar Pathologies and Future Directions

Most pathologies associated with the FDAL, such as tarsal tunnel syndrome or flexor hallucis syndrome, are due to the mass effect, possibly via hypertrophy from exercise.[4,9-10] Similar to FDAL, the symptoms stemming from AS usually occur due to mass effect of the accessory muscle, with painful masses occurring upon exertion. One theory suggested to explain symptomatic AS is that exercise-induced hypertrophy of the AS leads to increased intrafascial pressure and compartment syndrome development causing pain. Another theory suggests increased activity with the additional muscle leads to inadequate blood supply and claudication. The potential in the AS compressing the adjacent posterior tibial nerve is also a possible explanation.[4,9-10]

Future research may observe the accessory muscles within athletic patients. Fasciotomy or excision of the AS has produced resolution of pain and a shorter return to play in athletes once conservative treatment is attempted.[17,25]

The exercise-induced hypertrophy theory may help explain a potentially higher incidence of symptomatic AS within athletes, and a resultant higher prevalence of AS in athletes.[4,17] This could be the same for the FDAL when athletic cases involve the muscle as similar theories were discussed for causes of symptomatic FDAL.[4,9-10] Continued case reporting involving these muscles in athletes would be extremely valuable to further elucidate information and relationships in this patient population.

A FDAL and an AS were found as incidental findings upon surgical correction of a clubfoot deformity, another unidentified aberrant muscle also appeared upon correction of a separate clubfoot case.[28] The FDAL and AS appear in similar pathologies such as tarsal tunnel and clubfoot.[10,12,25] Their shared occurrences explains that they are both accessories in the same region with nearby routes of origin and insertion.[4] Despite the similar location, muscles have a developmental relationship with an appearance of both in a clubfoot deformity.[28]

There is still work to be done in improving the depth and quality of the data involving these accessory structures. The majority of available literature being case reports or small case series limits the strength of the relationships and correlations gained from the literature.[17] Meta-analysis combining all cases into a higher total population would strengthen significance. A retrospective or prospective MRI study can analyze exact efficacy of diagnosing the accessory structures in related cases and obtain sensitivity and specificity data involving this imaging modality.[4]

The continued case reporting of these muscles and further research into the incidence of these structures and their relationship with surrounding structures can help improve clinical awareness and further clarify presence of these muscles.[4,16] The development of novel procedures to help treat these pathologies minimally would be a product of this labor in developing robust clinical awareness and data of the FDAL and AS.[20,26-27]

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Gait and Attention Deficit/Hyperactivity Disorder: A Review

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Abstract

Objective: To summarize the current research on the association between attention-deficit/hyperactivity disorder (ADHD) and gait disturbances in children.

Methods: A PubMed search on relevant research pertaining to childhood ADHD and gait deficits was conducted. Five studies from the years of 2007-2018 were identified and included in this review.

Results: In our literature review, we observed repeated associations between ADHD and stride time variability when compared to controls. This relationship was specifically pronounced in situations where heightened attention was required such as in dual tasking paradigms. Additionally, stimulant medication and an age-dependent improvement in attention was found to reduce the stride time variability.

Conclusion: Recent studies indicate that ADHD has the potential to impact gait variability in children. This finding supports the current understanding that executive function and attention are required in the production of smooth and coordinated gait. We believe this topic is of the utmost importance for the practicing podiatric physician due to the potential therapeutic measures and patient education for children with ADHD.

Introduction

Walking requires an effective integration of visual information, balance, and muscle movements. This forms an important and highly complex mode of human locomotion involving neural control systems that produce coordinated action (Figure 1).[1] Recent research has shown that walking is not just an automated process; it requires higher cognitive processes to maintain postural control.[2] It is now acknowledged that executive and attentional functions are involved in the control of gait. One area of research which has specifically investigated the developmental link between cognition and gait focuses on ADHD, a childhood onset neuro-behavioral condition involving inattention and hyperactivity. Problems with executive functions and attention are among the core ADHD symptoms. However, research involving gait and ADHD is scarce.[2]

ADHD is particularly prevalent in youth, affecting approximately 6-11% of school-aged children. Children with ADHD suffer from three main core symptoms: impulsivity, hyperactivity, and inattention. They have more difficulties in keeping their balance, producing rapidly alternating or correctly timed movements, and hurt themselves more often when falling.[2] Several studies indicate that children with ADHD show higher inconsistency when walking than typical developing children, with major differences found in their gait timing. These results suggest a decrease in sustained attention that alters the rhythmic nature of the gait cycle, specifically the measure of stride time variability. Therefore, the study of children with ADHD offers a unique opportunity to further probe the contribution of attention to gait as well as the pharmacological impact.

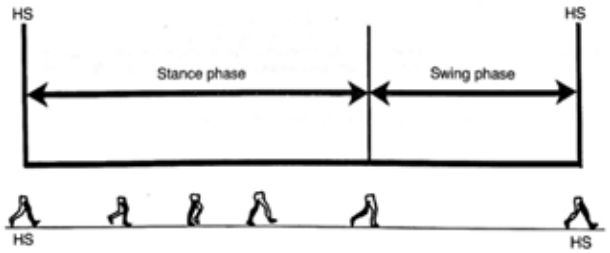

Figure 1: The gait cycle is defined as heel strike of one foot to heel strike by the same foot at the next step. Adapted from Foot Function: A Programmed Text.[1]

Methods

A PubMed search was conducted on relevant research pertaining to childhood ADHD and gait deficits. Five studies from the years of 2007-2018 were identified and included in this review. The research pertaining to these two topics, specifically how they relate to each other is slim. The five articles addressed the relationship we wished to research and thus were included in our review.

Discussion

Gait variables

A multitude of gait variables including gait speed, stride length, stride cadence, stride time, and stride time variability have been researched in concordance with normal gait patterns. Researchers found that the average stride time and length were similar when compared between controls and those diagnosed with ADHD at baseline and during passive dual tasking.[3,4] However, there is some inconclusive evidence that suggested a difference in cadence. Those with ADHD showed a slight increase in cadence that was nearly statistically significant ($p=0.052$), yet it should be noted that the sample size was small at 14 participants.[4]

Researchers did conclude that there was a statistically significant difference among ADHD populations and non-ADHD populations, in regard to stride time variability. Multiple studies revealed an increase in stride time variability, which further reinforced the notion that those diagnosed with ADHD showed an irregular gait pattern compared to controls and that variability is a better data point to compare in relation to the average stride length.[3,5]

Effects of dual tasking on gait

A common way of assessing the influence of higher order processes on a person's gait is to utilize dual-tasking paradigms. This evaluation combines walking with another concurrent function such as listening to a story.[3] This causes healthy adults, irrespective of age, to walk with a reduced gait speed.[3] However, less is known about the effects of dual tasking on children with ADHD especially when comparing medicated versus non-medicated patients. There is a conflict of opinions when comparing ADHD and controlled gait profiles when undergoing dual tasking in the literature. Both Lietner et al. and Manicolo et al. found that there was a statistically significant reduction in gait speed and stride time variability in both ADHD and control groups.[3,5] Both concluded that there was no difference between groups when undergoing dual tasking.[3,5] Another study found that passive dual tasking significantly decreased stride time variability in ADHD. However, their sample size was only 16 and did not account for ADHD subtypes.[3]

Möhring et al. found that both children diagnosed with ADHD and controls showed an increased irregularity of gait when tested by a dual tasking procedure.[2] They also found that those diagnosed with ADHD were more susceptible to gait abnormalities when compared to developmentally appropriate controls, which is in direct contrast to previous studies.[2] The authors suggest that gait is not an automatic procedure in which no cerebral attention is required. This data was controlled for ADHD subtypes and had a larger sample size. One possible explanation for this discrepancy is the use of different parallel tasks, specifically the difference between receptive and active cognitive tasks.[2] For instance, Möhring et al. used active/production tasks in which the child was asked to count backwards or name examples in a designated category while walking.[2] This type of dual tasking resulted in an increase in gait variability consistent with previous studies involving adult subjects with impaired executive function.[3] These results however differed from Lietner et al., which found decreased gait variability during the dual task of processing auditory stimuli while walking.[3] The difference may be due to the use of receptive processing tasks versus active production tasks.[2]

Impacts of medication

To treat the symptoms of ADHD, it is necessary to increase the signal strength of certain neurotransmitters in the frontal cortex of the brain. This can be done by stimulants such as Methylphenidate (MPH).[6] Multiple investigators have sought to examine the effects of MPH on children with ADHD while studying gait. Researchers found that stride time variability tends to be increased in ADHD while off of medication.[2] Although Leitner et al. found that when off MPH, children undergoing dual tasking revealed a decreased stride time variability and gait efficiency.[3] While, Konicarova et al. found that balance deficits seen in ADHD that were not seen in controls.[7]

Studies revealed that children taking MPH had significantly increased stride time and consistency of gait.[2,3] Interestingly, while children taking MPH showed similar effects on stride variability when compared to passive dual tasking, there was evidence that it increases gait speed while dual tasking decreased gait speed.[3] This all lends to the notion that MPH, although known to aid in aspects of attention, also enhances executive functions of gait in ADHD.[2,3]

The effect of age on ADHD gait symptoms

There is ongoing debate on whether reported deficits in children with ADHD result from a maturational delay or instead, a persistent deviance from typical development. Previous research has suggested that the brain of children with ADHD matures about three years later compared to typically developing controls. Therefore, it was hypothesized that the gait of children with ADHD will eventually reach that of controls with increased age. Manicolo et al. addressed the maturational delay hypothesis. This speculates that children who have ADHD are delayed developmentally but catch up to normal development as age increases (Figure 2).[5] Faraone et al. stated that this would be supported by the finding that 80% of those with ADHD tend to outgrow their associated symptoms, unrelated to gait, in adulthood.[8] Möhring et al. also found that children with ADHD displayed an age-dependent decrease of their stride time variability compared to controls.[2]

Further explanations can be found by looking at the brain dimensions of those with ADHD compared to controls. Previous research revealed underdeveloped prefrontal regions which are consistent with a lack of executive function seen in those with ADHD. It also revealed an early maturation of the primary motor cortex.[9] This may be

a combination that leads to the poor gait in those with ADHD as corroborated by the evidence found by Manicolo et al.

Conclusion

Gait is a highly complex process involving the association of multiple brain regions. In this review, we focused specifically on the impact of executive function and attention on gait in children with ADHD. There has been evidence that certain aspects of gait, namely gait variability, can be altered in children with ADHD especially in dual tasking paradigms which requires a higher level of attention.[2] Conversely, stimulant medication which increases cognitive function was found to improve gait in ADHD subjects.[2] As previous studies have linked gait variability with impaired executive function in adult participants, it can be hypothesized that the observed changes in gait seen in children with ADHD are also due to deficits in executive function and attention.[5] Additionally, as a child matures and the behavioral symptoms of ADHD subside, gait was found to trend towards that of control participants which not only supports the maturational delay hypothesis but also the close association between the behavioral and motor symptoms of ADHD.[5]

The variation in results for gait studies involving dual tasking is still debatable. Discrepancies between data could be due to differences in dual task protocols given to participants, specifically the difference between receptive/processing and active/production cognitive tasks.[2] Future studies that investigate gait variability in children with ADHD for each of these two separate task conditions are needed.

An additional consideration for future studies would be to investigate gait difficulties within the different subtypes of ADHD: predominantly inattentive, predominantly hyperactive-impulsive, and combined type.[4] While previous studies on motor deficits and ADHD have revealed that differences do exist within the three subtypes, most studies on gait and ADHD thus far have not taken the subtypes into account. A study which specifically investigated gait within the context of different ADHD subtypes would help to guide our understanding of the link between motor-cognitive processes and the behavioral symptoms typical of ADHD.

Researchers are still unsure of the specific mechanism by which MPH is affecting the cognitive function of gait, although there are existing hypotheses. Further research is needed to specifically attempt to answer these questions.

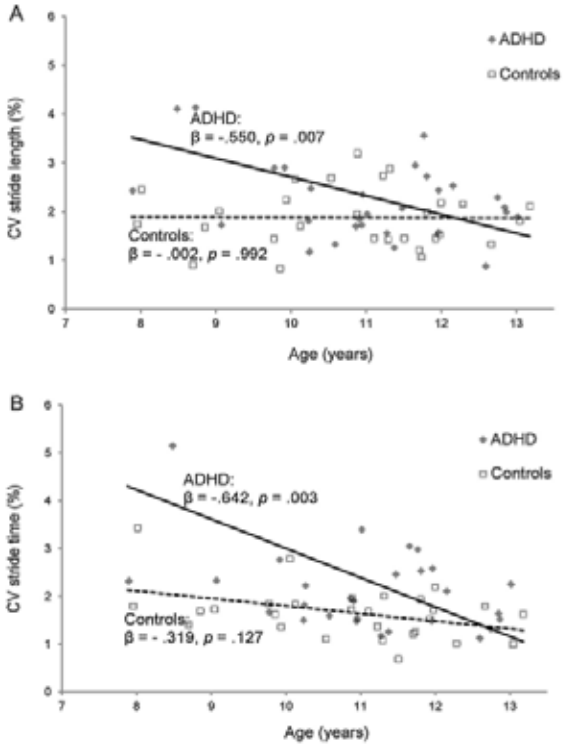

Figure 2: Age-dependent associations of gait variability for children with ADHD compared to controls (A: stride length; B: stride time). Adapted from Age-related decline of gait variability in children with attention-deficit/hyperactivity disorder: Support for the maturational delay hypothesis in gait.[5]

One final consideration would be to increase the sample size in future studies. Of the articles reviewed, the largest sample size consisted of 30 participants with diagnosed ADHD.[5] Future studies with larger sample sizes would help to strengthen the power of the study.[2]

A further understanding of the connection between gait and ADHD is important in the screening and treatment of children with ADHD as well as those with gait disturbances. This association between higher order cognitive processes and gait can also be incredibly useful in further distinguishing the multiple neurological influences on gait during mature locomotion.

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Cerebral Palsy and Spasticity

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ABSTRACT

Objective: To discuss the various stages of spastic hemiplegia and paraplegia in CP patients alongside treatments and diagnostic testing methods.

Methods: Individualized treatment methods based on stage progression and evaluation methods are analyzed with respect to the level of conservativeness of treatment. Various research studies and articles were cross referenced in order to obtain a consensus on staging and subsequent treatments.

Results: Patients with cerebral palsy commonly present with pathologic deviations of gait. These deviations can present in two various forms, Spastic hemiplegia and Spastic Diplegia. Clinical gait analysis can be used to identify the classifications to concretely diagnose and treat patients with cerebral palsy. Spastic Hemiplegia can present as drop foot, recurvatum knee, jump knee, and a combination of the three in addition to anterior pelvic rotation. Spastic Diplegia may present as true equinus, jump knee, apparent equinus, and crouch gait. Orthoses are the main treatment option for stages one and two in spastic hemiplegia, however, stages three and four warranted surgical intervention followed by the use of various types of ankle foot orthoses as post-op stabilization. Similarly, true equinus and jump gait allow for more conservative treatments using solid and hinged ankle foot orthoses for the former, and the addition of stretching for the latter. Crouch gait and pseudo-equinus both require surgery.

Conclusion: CGA may prove to be a suitable tool for gait pathology diagnosis. Ultimately, the later stages of both spastic hemiplegia and paraplegia required more surgical intervention in addition to conservative treatments.

Introduction

Cerebral palsy (CP) is a developmental disorder manifesting in children during their first year of development and is the most common cause of motor disability in early development. CP is caused by an upper motor neuron lesion to the developing motor cortex of the brain.[1] Motor disabilities are usually in the form of decreases in movement and posture needed for daily activities such as walking. The disorder is not progressive; however, secondary conditions can get worse over time - particularly muscle spasticity which is seen in 60% of children with cerebral palsy.[2,3] Within spastic motor impairment exists two forms: hemiplegic which is defined as having one affected lower limb, and paraplegic with both lower extremities affected. Each form is further subdivided into categories with treatment depending on age and progression.[3] Spasticity can interfere with the passive stretching of muscles during relaxed states and prevents children with CP from reaching maximum potential velocity needed for mobility during gait.[1] Thus, a child with spasticity has a lower threshold of stretch response and shows restriction in muscle length, strength, and control.[1] After diagnosis, treatment is individualized using evaluation methods such as gait analysis and options ranging from orthotics to corrective surgery. The purpose of this paper is to discuss the various stages of spastic hemiplegia and paraplegia found in CP patients in relation to treatment options as seen in current research.

Methods

Multiple articles and studies on Cerebral Palsy classification and treatment were analyzed in order to reach a consensus for the currently accepted methods used by podiatrists and practicing physicians. Clinical gait analysis was also reported on regarding usefulness for cerebral palsy related gait pathology.

Clinical Gait Analysis

Normal gait consists of a stance and a swing phase, the former taking precedence as 60% of gait.[4] The stance phase allows for stabilization of the body while the swing phase allows lower extremity kinesis.[3] In patients with CP, the gait cycle becomes altered due to damage to sections of the brain controlling voluntary muscle control. Tools such as clinical gait analysis (CGA) can be used to identify and understand deviations of gait seen in CP patients.[2] This mode of assessment recruits quantitative methods including kinematic sensor systems, kinetics, video footage analysis, electromyography, and pressure sensing systems of the plantar foot.[2]

Using CGA, researchers and physicians have adopted a three-stage method for diagnosis and treatment. They include identification of deviance, linkage to clinical impairment, and choosing the best course of action for the patient - likely considering lifestyle and quality of life as major decision-making components.[2]

The gait cycle is used to quantify characteristics such as cadence, stride, and phase duration. Kinematics allow for the angular measurements of the joints around the trunk to the ankle.[2] In order to convert to a three-dimensional analysis, planes are used to describe gait: sagittal plane for flexion and extension, transverse plane for adduction and abduction, and frontal plane for internal and external rotations. Force plates are also used to measure ground reactive forces (GRF).[2]

Orthotics

Ankle foot orthotics (AFO) are used as stability inducing mechanisms for gait, standing, and energy efficiency.[4] Several types can be used depending on the progression and type of spasticity along with the age of the patient.[5] Rigid AFO will suppress ankle movement in all planes in order to provide stance support and prevent neuropathological malformity.[6] Flexible AFO's allow movement in a chosen plane and restriction in another, along with aiding in preventing drop foot.[7] Hinged AFO will cease any range of motion needed, commonly used for varus or valgus feet. This fixture will stop movement in the frontal plane while allowing sagittal movement to allow dorsiflexion and plantarflexion without inverting or everting the foot.[7] Figure 1 outlines a study following the effects of ankle foot orthoses on dorsiflexion in a cross sectional population based study on children with cerebral palsy.

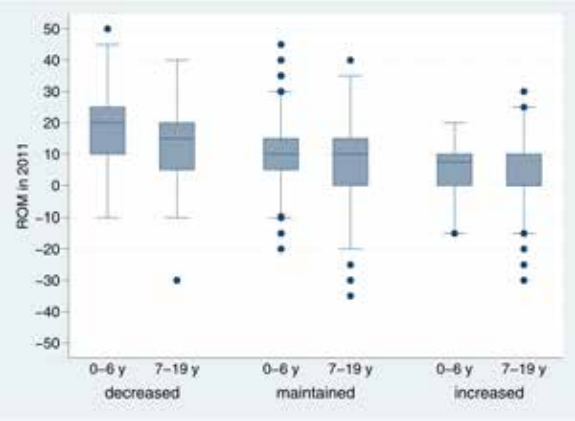

Figure 1: Range of ankle dorsiflexion at baseline in 617 children using AFO in 2011 to 2012 in order to maintain or improve range of motion. Decreased means >5 degrees decrease in dorsiflexion while increased means > 5 degrees increase. N = 338 ages 0-6 and n = 279 for ages 7-19. [8] Adapted from Wingstrind et al. "Ankle-Foot Orthoses in Children with Cerebral Palsy: a cross sectional population based study of 2200 children.". [8]

Spastic Hemiplegia

The main gait related symptoms of spastic hemiplegia are muscle spasticity, muscle weakness, and bony deformity. Confounding factors revolve around motor disorders with posture and movement. However, it is important to mention that 75% of children afflicted with CP are ambulatory to some extent.[7] In patients with bilateral spastic CP, the parameters of gait speed, step length, step width, cycle length, single support, and double support are significantly deviated from normal.[2]

There are four types of gait patterns commonly found within spastic hemiplegia. Type 1, drop foot, is categorized by the inability to dorsiflex the ankle. This is caused by hypotonia of the muscles within the anterior compartment of the leg: tibialis anterior, extensor digitorum longus and extensor hallucis longus.[3,9] In the contact phase of gait, foot drop introduced during swing phase causes a lack of heel rocker upon contact with the ground. Treatments for type 1 include the use of hinged or leaf spring ankle foot orthosis and physical therapy.[3]

Type 2A (equinus foot) involves foot plantar flexion due to gastrocnemius and soleus muscle spasticity also leading to neutral knee position and hip extension. As in type 1, issues during gait involve drop foot during swing phase in addition to permanent plantar flexion during stance phase. Treatments remain the same as in type 1.[3] Type 2B consists of equinus foot, hip extension and genu recurvatum.[3] This type is generally synonymous with contracture of the triceps surae muscle.[9] Treatment options usually involve a combination of ankle foot orthosis, physical therapy, and injections of botulinum toxin type A.

Type 3 has the same biomechanical issues as in type 2 with the addition of rectus femoris and hamstring muscle spasticity. This causes limited flexion of the knee during swing phase, hyperextension of the hip, and lumbar lordosis. Treatments are similar to type 2B with the addition of Achilles and medial hamstring lengthening surgeries.[3]

Type 4 patients are seen with all the biomechanical deviations as types 1-3 with restricted motion of the hip and knee. This leads to an increased pelvic lordosis during stance phase of gait as a result of spastic hip adductors and flexors.[9] Treatment involves lengthening of the Achilles tendon, medial hamstring and rectus femoris as well as ankle foot orthosis, physical therapy, and botulinum toxin injections.[3]

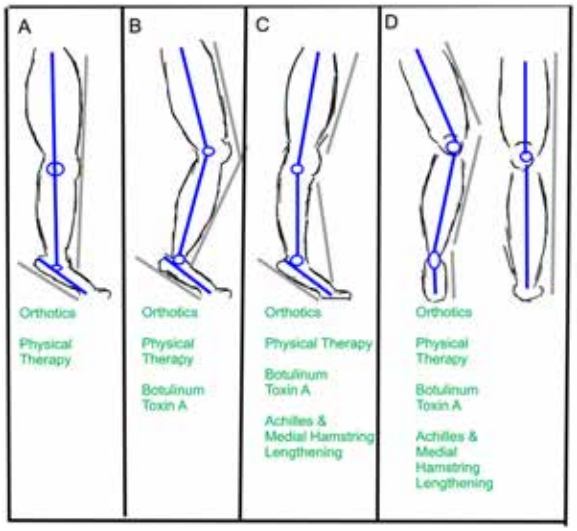

Figure 2A-D. ***Spastic Hemiplegia*** –Types of Spastic hemiplegia as related to Cerebral Palsy are depicted alongside associated treatments. [A] Type 1, known as drop foot. [B] Type 3, known as Jump Knee. [C] Type 2B, known as Recurvatum Knee. [D] Type 4 shown with rotation from pelvis from an anterior view. Genu Valgum is present in the effected leg. Adapted from *Gait Patterns in Spastic Hemiplegia in Children and Young Adults* by Winters et. al. [9]a

Spastic Paraplegia and Bilateral Spastic Cerebral Palsy

As in spastic hemiplegia, there are four common types of gait patterns found within spastic paraplegia: true equinus, jump knee, apparent equinus, and crouch gait. True equinus, Type 1, is categorized by toe walking due to bilateral spasticity of the gastrocnemius and soleus muscles. The feet are permanently plantar flexed during stance at the ankle with the hips and knees extended throughout stance phase. This condition can be managed with solid or hinged AFO. Further treatment options involve gastrocnemius and Achilles tenotomy as means to potential benefits.[10]

Jump gait, more commonly seen in diplegic children, is defined by ankle equinus and flexion of the hip and knee due to hamstring and psoas spasticity. This leads to anterior tilt and increased lumbar lordosis. A stiff knee is not uncommon when considering the activity of the rectus femoris during swing.[10] Conservative treatments options include stretching of affected muscles, orthoses, and electrotherapy. However, botulinum toxin type A injection in the hamstring has been shown to alleviate the pattern of stiff knee in swing phase in young children.[7] In older children, lengthening the gastrocnemius, hamstrings, and iliopsoas could also be a consideration alongside a rectus femoris – semitendinosus transfer.[10]

Pseudoequinus presents with normal ankle dorsiflexion, but excessive flexion of hip and knees resulting in toe walking.[6] This gives the appearance of an equinus, however, this is a commonly seen stage in spastic diplegic developing children. Treatment recommendations are musculotendinous lengthening or physical therapy on the hamstrings and iliopsoas muscles.[7] Orthotic treatment includes solid AFO, hinged AFO, or ground reaction AFO.[6]

Lastly, crouch gait consists of extensive dorsiflexion in tandem with knee and hip and flexion. This stage is seen in children with the worst prognosis, predicted by heel cord lengthening during the early years of development will translate into increased hip and knee flexion in the teenage years.[10,12] Should the spasticity go undiagnosed, the patients can experience genu pathology in tandem with an awkward and energy intensive gait.[12] Treatment includes the use of ground reaction orthosis to reinforce the Achilles tendon.[7] Surgical intervention is also a strong possibility with correction of femoral and tibial torsion.[7] At this stage, botulinum toxin will likely be ineffective.[7]

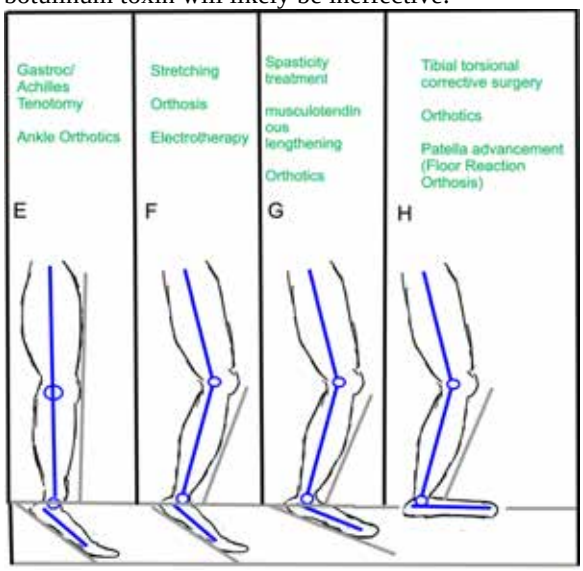

Figure 3 E-H. ***Spastic Diplegia*** –Types of Spastic Diplegia as related to Cerebral Palsy are depicted alongside associated treatments.This figure is also continuous from figure 1. [E] True Equinus: extension of the hip and knee, recurvatum may or may not be present. [F] Jump Knee: Hip/knee flexion, equinus, Ant. Pelvic tilt + lumbar torsion [G] Apparent Equinus: Further flexion of hip/knee, less equinus. [H] Crouch Gait: Extensive flexion of the hip/knee + Dorsiflexion of the foot. Adapted from *Gait Patterns in Spastic Hemiplegia in Children and Young Adults* by Winters et. al. [9]

Discussion

The etiology of cerebral palsy is quite complex. Many pre, peri, or postnatal factors can lead to a host of lesions affecting the motor cortex. This leads to a wide range of pathologies seen as deviations in gait. Nevertheless, knowing the exact

cause might not be an important part in the consideration of a treatment plan. However, gait analysis has shown specific gait deviations leading to more accurate motor diagnoses. Here, we looked at two types of gait deviations further classified into four categories (spastic hemiplegia and paraplegia).[11] Accurate motor diagnoses can be used for a more personalized approach to treatment.

Conclusion

Practitioners should consider using CGA more often as a tool in the development of an individualized treatment plan for their CP patients. Using CGA, conservative treatments, such as orthoses, have been found to be the best treatment options for stages one and two of spastic hemiplegia as well as true equinus and jump gait. Regarding crouch gait, pseudo-equinus and stages three and four of spastic hemiplegia, surgical intervention may be required. Despite initial studies, more research should be done to verify the accuracy and efficacy of CGA and on additional classifications of gait deviations in order to further personalize treatment for gait deviations seen in CP patients.

Supplemental

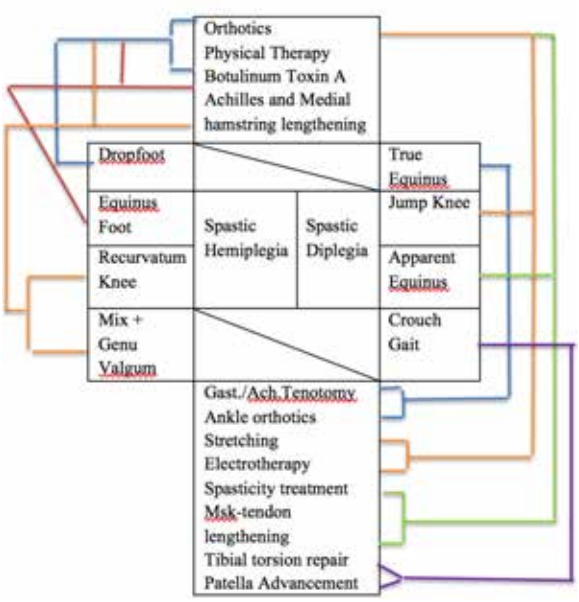

Figure 4. ***Summary of Spastic Hemi and Diplegia.*** – Here, both discussed spasticity types are shown with subsequent stage breakdowns as well as commonly used treatments for each.

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Plantar Hyperhidrosis: An overview

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Abstract

Objective: The aim of this article is to provide information for health care providers on the current principles of addressing plantar hyperhidrosis (PHH).

Methods: A literature review was performed from 1994-2018, querying PubMed, Google Scholar, ScienceDirect, Springer Link, and Wiley Online Library.

Results: Hyperhidrosis (HH) affects at least 4.8% of the population in the United States. Treatment options such as topical antiperspirants, iontophoresis, botulinum toxin injections, oral anticholinergic medications, and sympathectomy have been shown to improve quality of life. PHH has also been identified as a risk factor for developing fungal and bacterial skin infections of the foot, as well as mental health conditions such as anxiety and depression.

Conclusion: PHH can have a profoundly negative effect on a patient's quality of life due to the negative social stigmas as well as hindrance of daily activities caused by excessive sweating. Health care providers who encounter patients with PHH can use these principles to provide care that will improve their patient's quality of life.

Introduction

Hyperhidrosis (HH) is defined as excessive sweating beyond the body's need for temperature regulation. The pathophysiology of HH is poorly understood, and research on the topic is limited. The purpose of this article is to provide a brief summary of current knowledge on the topic of HH affecting the feet, including background information, treatment options, and relevant clinical considerations for patients with HH.

Methods

A literature review was performed, querying PubMed, Google Scholar, ScienceDirect, Springer Link, and Wiley Online Library. Search terms included the following: hyperhidrosis, plantar hyperhidrosis, and excessive sweating of the foot. 38 articles were selected to collect information and images. Each article was analyzed to collect clinically relevant information regarding etiology, clinical presentation, epidemiology, diagnosis, current treatment options, and common comorbidities. Articles that did not contain clinically relevant information pertaining to plantar hyperhidrosis were excluded.

Etiology

HH can affect the whole body, or it can primarily occur in focal areas such as the hands, feet, and axillae. HH affecting the feet is known as plantar hyperhidrosis (PHH) and is commonly seen in association with focal HH of other areas of the body such as the palms (palmoplantar hyperhidrosis). HH can be categorized as primary or secondary, the former being excessive sweating that is not caused by an underlying medical condition or medication. Secondary HH may be caused by various endocrine, cardiovascular, neoplastic, or infectious conditions and can also be seen as a side effect of many medications.[1,2]

PHH is most commonly categorized as primary or idiopathic in origin. Primary HH has been linked to overactivity of the sympathetic nervous system and is known to be exacerbated by stress and anxiety; however, patients with primary HH may experience sweating throughout the day without known triggers, at times without stress or anxiety.[2,3] The sweat glands primarily involved are known as eccrine sweat glands and are innervated by sympathetic cholinergic neurons.[3] Hereditary patterns have been identified with a family history of excessive sweating present approximately 65% of the time.[4] Speculation on an autosomal dominant type inheritance pattern with incomplete penetrance is under further study.[4]

Clinical presentation

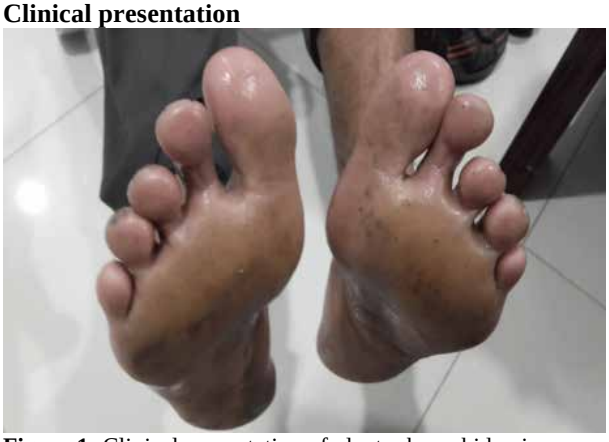

Figure 1: Clinical presentation of plantar hyperhidrosis. Adapted from Journal of Nursing and Health Sciences.[37]

Patients with PHH present with excessive sweating on the plantar surface, sides of the foot, interdigital areas, and dorsum of the toes in a pattern similar to a moccasin distribution, or the area of the foot

that would be covered while wearing low-cut socks (Figure 1). Patients complain of sweating to the extent that it can leave sweat marks on smooth flat surfaces while walking barefoot.[5]

This can cause significant distress for patients who often feel the need to hide their condition and avoid wearing open-toed footwear.[5] In a recent survey of patients with HH conducted by Glaser and colleagues, it was discovered that 85% of respondents delayed reaching out to a physician for help with their condition.[6] While the survey did not collect specific reasons for the delays, the researchers believe that embarrassment is a key factor.[6]

Epidemiology

HH has varying prevalence dependent on geographic location; the United States is at least 4.8%.[7,8] In a study by Lear et al., 45% of patients with HH had sweating occurring on the plantar surface of the feet.[10] Patients with PHH commonly experience concomitant excessive sweating in other areas of the body, but isolated PHH may also be seen.[11] In a study by Walling, it was found that 93.3% of patients presenting to an outpatient dermatology clinic with excessive sweating had primary HH while the other 6.7% had HH of a secondary origin.[12] The onset of primary HH is most commonly seen during childhood. The mean age of onset of primary HH is 14 years of age.[10] This study also found that, on average, PHH tends to have an onset at a younger age than axillary HH.[10]

Diagnosis

Diagnosing primary HH can be a challenge. Using criteria from Hornberger et al., primary HH can be diagnosed when at least two of the five criteria are met (Table 1).[13,14]

Treatment options

Topical Antiperspirants

First-line treatment for primary PHH includes topical solutions containing aluminum chloride hexahydrate.[15,16] Aluminum chloride is used in prescription axillary antiperspirants but at much lower doses (usually 10-20%). For PHH, physicians can prescribe aluminum chloride solutions with differing concentrations depending on the severity of the patient's sweating.[16] Skin irritation commonly occurs with the use of aluminum-based antiperspirants, which can be severe enough to cause discontinuation of use.[15,16]

Patients must meet *at least two* of the following criteria to diagnose primary hyperhidrosis	
Criteria for diagnosis	**Y/N**
Sweating lasts at least 6 months	
Sweating occurs in a bilateral or symmetric pattern	
Focal sweating stops while the patient is sleeping	
Sweating impairs daily activities	
There is a positive family history for excessive sweating.	

Table 1: Making a diagnosis of primary hyperhidrosis. Adapted from Journal of the American Academy of Dermatology.[13]

Iontophoresis

Iontophoresis involves applying an electric current to the affected skin by submerging the feet in shallow pools of water containing electrodes. The mechanism of action by which iontophoresis works is currently unknown, however it has been shown to be an excellent option for patients with moderate to severe HH when topical antiperspirants fail to provide sufficient relief.[15,17,18] Iontophoresis devices are available commercially and can be used at home, requiring about seven 20-minute sessions to achieve the desired results of sweat reduction. Patients must continue to perform maintenance therapy with regular iontophoresis sessions or their excessive sweating will return.[17,18] Adverse effects can include paresthesia while using the iontophoresis device as well as post-treatment development of pruritus, erythema, and vesicle formation.[17]

Botulinum Toxin Injections

If topical antiperspirants are not effective, patients may consider botulinum type-A toxin (BTX-A) injections in the affected aspects of the foot (Figure 2). BTX-A inhibits the release of acetylcholine from the presynaptic neuron that innervates eccrine sweat glands. This treatment modality has been shown to improve quality of life for PHH patients.[19,20,21] Injections are not a permanent means to decrease sweating and typically need to be repeated every 3-6 months to maintain the desired effect.[20,22] BTX-A injections can be cost

prohibitive as they are not covered by most insurance providers. Adverse effects may include transient muscle weakness and pain at the injection site, which may be reduced with lidocaine or ice.[20]

Anticholinergics

Oral anticholinergics have also been found to be useful in the treatment of mild and severe HH when previous therapy has failed. Anticholinergic medications such as oxybutynin and glycopyrrolate can treat HH by antagonizing the muscarinic receptors of eccrine sweat glands, resulting in a decreased amount of sweat secretion. When taken orally, anticholinergics come with significant systemic side effects such as dry mouth, blurry vision, confusion, and in some cases, urinary retention.[23,24,25] This treatment modality may be used alone or in conjunction with other treatment options such as topical antiperspirants or iontophoresis.[1] The antimuscarinic side effects can make them difficult for some patients to tolerate. Topical anticholinergic therapies are currently being developed and have been shown to carry less systemic side effects with use.[25]

Sympathectomy

Lumbar sympathectomy is considered the last resort in treating PHH, only to be considered after all other treatment options have failed. This option involves surgically resecting a portion of the sympathetic chain, usually involving the portion between the L2/L3 and L4/L5 intervertebral spaces.[26] While commonly seen in the treatment recommendations for palmar HH, this treatment modality is not included in some treatment recommendation algorithms for PHH.[1,26] Despite a 96% success rate in decreasing plantar sweating, there is controversy surrounding lumbar sympathectomy as a treatment due to commonly associated side effects such as a 65% incidence of compensatory sweating that affects the lower extremity and trunk, as well as irreversible sexual dysfunction.[26,27,28] Reports exist of patients expressing regret after undergoing this procedure due to the adverse effects experienced.[29]

Treatments Summary

Treating PHH can be a challenge. Each treatment option has adverse effects which can impose limitations on long-term effectiveness. Physicians should consider these effects when prescribing treatment and while assessing a patient's compliance with a given treatment. Treatments and indications are summarized in Table 2 below.

Figure 2: BTX-A injections, a treatment option for plantar hyperhidrosis. Adapted from Podiatric Medicine and Surgery.[38]

Treatment Option	*Mild / Moderate*	*Severe*
Topical antiperspirants	1st line	1st line
Iontophoresis Therapy	2nd line	1st line
Botulinum Toxin Injections	2nd line	1st or 2nd line
Oral anticholinergics*	2nd or 3rd line	2nd or 3rd line
Sympathectomy**	Last resort	Last resort

*= used alone or in combination with 1st line options
**= not included in some treatment recommendation algorithms

Table 2: Summary of treatment indications for Plantar Hyperhidrosis.[1,15,16,17,18,19,20,21]

Common comorbidities

HH can have a devastating effect on a patient's quality of life due to the social stigmas associated with excessive sweat. Focal HH has been identified as a leader among dermatological conditions that negatively impact the quality of life in patients. Among 38 other dermatological conditions included in a 2003 study, focal HH commonly falls in the "severe impact" score ranges on the Dermatology Life Quality Index (DLQI) which measures the effect that a dermatological condition has on the different aspects of a patient's quality of life.[30,31] The DLQI was created by Finlay and Khan in 1994 and continues to prove useful in research today.[30,31] In recent literature, HH has been linked to anxiety and depression. A study by Bahar and colleagues measured odds ratios of 3.7:1 and 3:1 for depression and anxiety, respectively. The prevalence of anxiety and depression was 21.3% and 27.2% in patients with HH ($P < .001$), respectively. In contrast, the prevalence of anxiety and depression in patients without HH was 7.5% and 9.7%, respectively.[32]

In a study by Davidson and colleagues, 25-33% of patients with Social Anxiety Disorder (SAD) were found to have HH.[33] While the associated mechanism between HH and anxiety and depression requires further investigation, it can be postulated that fear and/or avoidance of social interactions due to embarrassment, as well as difficulty with performing daily tasks may play a role. It is also common for HH patients to feel the need to change their clothes multiple times a day to maintain hygiene.[33] This study highlights an association between HH and SAD and supports the claim that HH is not only socially, but physically debilitating for some patients. Excessively sweaty feet cause many functional and social handicaps in patients' lives. Patients report reluctance to remove shoes or socks due to the potential embarrassment of their condition being noticed. The amount of sweat produced by the feet also leads to faster breakdown of footwear, leading to the need to replace shoes and socks more frequently which can also place an increased financial burden on patients. Some patients report needing to change socks 3-4 times daily to maintain hygiene.[11]

Risk of cutaneous infection has been shown to be increased in patients with HH. Incidence of dermatophyte infection is increased with an odds ratio of 9.8 (95% CI 3.4-27.8; P< .0001).[34] Dermatophytes such as epidermophyton and trichophyton spp. are responsible for tinea pedis, a fungal infection commonly known as athlete's foot. Patients experience a pruritic rash on the foot commonly accompanied by erythema and interdigital maceration.[34] Another condition that HH patients are shown to be at risk for developing is pitted keratolysis, which is caused by a corynebacteria infection of the stratum corneum of the skin (Figure 3). This association was demonstrated in a study by Walling et al. which recorded an odds ratio of 15.4 (95% CI 2.0-117 and P = .0003).[35,36]

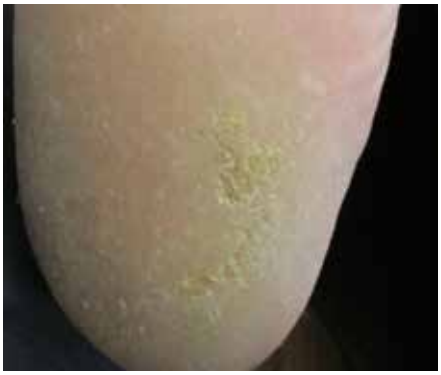

Figure 3: Pitted keratolysis of the plantar aspect of the foot. Adapted from The Journal of Pediatrics.[39]

Conclusion

PHH is a common condition that has a negative effect on patient's quality of life. The etiology of primary HH is currently not well understood, and further research is needed. Increased understanding of the mechanism behind idiopathic excessive sweating could lead to the development of more effective treatment options for patients with this disorder. Therapies such as topical antiperspirants, botulinum toxin injections, iontophoresis therapy, oral anticholinergics, and sympathectomy have been shown to be effective in alleviating the problem of excessive sweating for sufferers of PHH. Patients with PHH are at increased risk for conditions such as dermatophyte infection and pitted keratolysis as well as mental health disorders such as anxiety and depression. Health care professionals should be familiar with the principles discussed in this article in order to better serve their patients with PHH.

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Identification of Melanoma and Non-Melanoma Skin Cancers on the Lower Limb: An Overview

Heather Kopecky B.S., Cameron Hadley B.S., Jacob Nelson B.S., William Galbraith B.S.

ABSTRACT

Objective: The purpose of this article is to identify the common and uncommon presentations of melanoma and non-melanoma skin cancer on the lower limb to raise familiarity with their diagnosis and treatment.

Methods: We performed a review of current literature regarding the identification and treatment of lower limb skin cancers using keyword searches. We queried PubMed, Google Scholar, ScienceDirect, Wiley Online Library, and Springer Link. Search terms included: lower limb melanoma, plantar melanoma, lower limb non-melanoma skin cancer, and skin cancer identification.

Results: There are several identified growth patterns of skin cancers on the lower limb which should not be overlooked. Common areas requiring extra vigilance include the plantar surface, under toenails, and in existing ulcers or wounds.

Conclusion: There is still much to be learned about the appearance of skin cancers on the lower limb. Because skin cancer is treatable with early diagnosis, routine health screenings must include careful examination of the lower limbs, plantar surface, between the digits, and under the nails with special attention given to areas of broken skin or discoloration.

Introduction

Skin cancer can be divided into two categories: melanoma skin cancer and non-melanoma skin cancer (NMSC) which is subcategorized into squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). Skin cancer in general poses an enormous public health burden. Non-melanoma skin cancers represent 40% of all malignancies worldwide.[1] In the U.S., incidence has increased 200% in the last three decades.[2] Malignant melanoma accounts for only about 1% of skin cancers but is responsible for the majority of skin cancer deaths.[3]

SCC and BCC are frequently distributed in areas of sun exposed, UV damaged skin, such as on the head, face, forearms, and hands. Less common yet clinically important is the small percentage of NMSC that can occur in areas that are less exposed to UV light, such as the skin of the foot. SCC and BCC carry a relatively low metastatic potential but can be locally invasive. NMSC poses an interesting diagnostic challenge when suspected in the lower limb given its low incidence and insidious presentation as compared to other more common conditions such as skin ulcers. Melanoma of the lower limb and foot is increasingly common in Caucasian females, Asian, and African American populations and carries a poor prognosis.[3] Melanoma, especially of the sole of the foot, is unique in that it appears to have strong genetic predisposition given its lower proportion of damaging UV exposures. The purpose of this article is to identify the common and uncommon presentations of melanoma and NMSC on the lower limb to raise familiarity with their diagnosis and treatment.

Melanoma

Epidemiology

In the past decade, melanoma cases diagnosed annually have increased by 53%.[4] It is estimated that there were 9,320 deaths from melanoma in 2018, 83% of which were caused by UV radiation.[3] The site distribution for melanoma appears to be greatly affected by race. In the U.S., about 4.5% of cases of melanoma occur on the sole of the foot compared to 28.9% in Japan.[5] Similarly high incidence on the plantar surface was found in a South African study.[6] For melanoma skin cancer, the highest frequency for males is on the trunk and the highest frequency for females is on the lower limbs.[7] Before age 50, melanoma tends to present in higher rates in women than in men, but by age 65, rates are twice as high in men.[4]

Identification

Melanoma is characterized by uncontrolled proliferation of melanocytes in the basal layer of the skin.[8] There are four major sub-types including superficial (which accounts for 70% of all melanomas), nodular, lentigo maligna, and acral lentiginous.[9] These deadly malignancies are often identified by a sudden change in an existing melanocytic lesion or by sudden appearance and rapid growth. Most melanomas remain for several years in a horizontal or radial growth phase in which they are typically curable by excision alone. Melanomas that infiltrate into the dermis are considered to be in a vertical growth phase and have metastatic potential. Nodular subtypes have no

identifiable radial growth phase and enter the vertical growth phase almost immediately.[8]

In 1985, dermatologists from New York University devised the acronym ABCD to educate primary care clinicians on the identification of early melanoma.[3] There has since been the addition of the letter "E" for further help in recognition (Table 1).

Asymmetry	one half is not identical to the other
Border Irregularities	lesion is not a perfect round circle
Color Variegation	presence of multiple shades or red, blue, black, gray, or white
Diameter	> 6mm
Evolution	a lesion that is changing in size, shape, or color, or a new lesion

Table 1: ABCDE criteria for melanoma screening.[3]

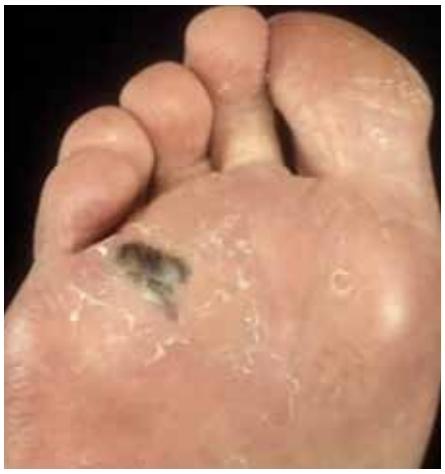

Figure 1: Plantar melanoma (adapted from Journal of Foot and Ankle Research, Figure 1, Bristow et al., 2010)[9]

The clinical appearance of melanoma of the foot is varied and often misdiagnosed as a fungal infection, blood blister, or verruca (Figure 1). Due to the high rate of metastases of melanoma, a biopsy should be performed as early as possible in any lesion that has any degree of suspicion for melanoma as early diagnosis offers the best prognosis.[8] Some clinicians choose to follow nevi clinically with serial measurements or photographs for observation of change from baseline, but it should be noted that 43% of melanomas on the plantar foot arise from a preexisting lesion and so a high degree of suspicion for any change is necessary.[10] Subungual melanoma (Figure 2) has the potential to be misdiagnosed as subungual hematoma, or bleeding under the nail.[9] It may also stay hidden underneath onychomycosis which is exceedingly common in the older population. Clinical examination revealing proximal growth of the nail suggests a subungual hematoma, as growth of normal nail would typically not be seen in the presence of nail unit melanoma.[9] Differential diagnosis should also include longitudinal melanonychia. Cases involving any degree of suspicion for melanoma should always be further investigated due to the clinical characteristics that longitudinal melanonychia shares with subungual melanoma in its early stages.[9]

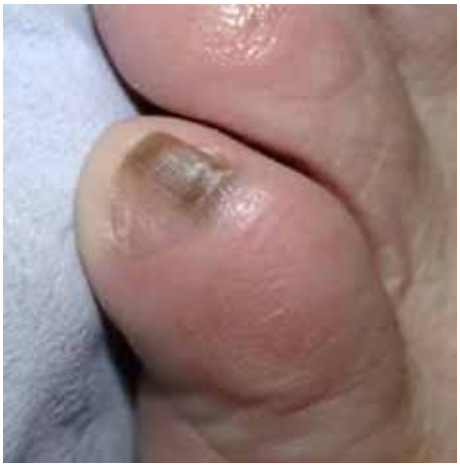

Figure 2: Subungual melanoma, also known as nail unit melanoma (NUM) (adapted from Journal of Ankle and Foot Research, Figure 3, Bristow et al., 2010)[9]

Treatment

Skin cancer staging follows the TNM format where T designates the primary tumor, N designates the nodal involvement, and M designates metastasis. Two additional staging tools are especially important in the diagnosis of melanoma and development of a treatment plan. Breslow's depth identifies the depth of invasion and Clark's level describes the anatomic level of invasion (Table 2). Breslow's depth and Clark's level are accurate predictors for lymph node involvement in metastatic melanoma (Table 3). In contrast to NMSC, the high metastatic potential of melanoma may warrant a systemic workup. Popliteal and inguinal lymph node involvement may indicate the presence of distant metastases and should always be palpated to assess for signs of the cancer spreading.

Treatment for melanoma of the foot poses unique challenges due to the consequences of excising large areas of skin. Melanoma of the plantar surface is more difficult to evaluate for depth of invasion based simply on the nature of the thickened skin and is therefore usually excised with a minimum of 3 cm margins and subsequent skin grafting.[8] Melanoma of the dorsum is excised with 1 to 3 cm margins per the tumor stage, consistent with

melanoma guidelines for the rest of the body. Subungual melanoma and melanoma of the toes are often treated with local amputation at DIP or PIP joints.[12] Melanomas rated pT1 and beyond warrant sentinel lymph node biopsy for further staging.[11] Overall, melanoma of the foot must be treated aggressively.

T		Breslow	Clark
Primary Tumor			
pTx	Primary tumor cannot be assessed		
pT0	No evidence of primary tumor		
pTis	In situ	Level I	Level I
pT1	Invasion of the papillary dermis ≤ 0.75 mm	Level I	Level II
pT2	Invasion of the papillary-reticular junction from 0.76 mm to 1.5 mm	Level II	Level III
pT3	Invasion of the reticular dermis from	Level III	Level IV
a	1.51 mm to 4 mm		
b	>1.5 mm and ≤ 3 mm >3 mm and < 4 mm		
pT4	Invasion of the subcutaneous tissue	Level IV	Level V
a	>4-mm		
b	Satellite lesion within 1-cm of primary tumor		

Table 2: Breslow and Clark levels (adapted from Journal of Foot and Ankle Surgery, Table 2, Schade et al., 2010)[11]

Breslow	Clark	N		M	
		Lymph Node Involvement		Metastasis	
		X	Regional nodes cannot be assessed	X	Presence of distant metastases cannot be assessed
Level I	Level I	0	No involvement of regional nodes	0	No distant metastases
Level I	Level II	1	Metastases ≥ 3- m in any regional lymph node	1	Distant metastases
Level II	Level III	2	Metastases	a	Skin or subcutaneous tissue or lymph nodes beyond regional lymph nodes
		a	>3 mm in any regional node	b	Visceral metastasis
Level III	Level IV				
		b	in transit metastasis		
		c	Both a and b		
Level IV	Level V				

Table 3: Metastatic potential based on Breslow and Clark levels (adapted from Journal of Foot and Ankle Surgery, Table 2, Schade et al., 2010)[11]

Non-Melanoma Skin Cancer

Epidemiology

More than 5.4 million cases of NMSC were treated in the U.S. in 2012, thus making it the most common cancer.[4] About 90% of these cases are associated with exposure to ultraviolet radiation from the sun.[4] The annual cost of treating NMSC is estimated at $4.8 billion.[4] BCC is rare on the lower limb and feet. Extra-facial locations account for roughly 17% of cases of BCC with only 3% of these occurring on the foot.[1] Cases tend to be found in fair-skinned individuals with outdoor careers and inadequate sun protection. Exposure to other pathogenic factors such as arsenic, ionizing radiation, and repeated trauma may increase the incidence.[1] The rates for SCC in the lower limb are similar to BCC with slightly higher incidence in females compared to males.[4]

Basal Cell Carcinoma Identification

BCC is characterized by a slow-growing pink or skin-colored, pearly nodule of the basaloid epithelium often with apparent blood vessels overlying its surface (Figure 3).[13] It may demonstrate crusting or a thin rolled border consisting of fine translucent small papules.[1] Bleeding with minor trauma is frequently noted. The main clinical subtypes include nodular, superficial, and morpheaform with nodular being the most common. Superficial subtypes favor the trunk and extremities. Melanin pigmented BCC is sometimes seen. Due to the varying presentation, BCC on the foot can go unnoticed or untreated for long periods of time, especially in older individuals who may have comorbid skin lesions.[14, 15]

BCC can be diagnosed by experienced physicians based on a clinical exam, however a skin biopsy should be performed in order to provide a definitive diagnosis. Experienced physicians sometimes elect to perform an excisional biopsy with concurrent histological examination of the margins as definitive treatment.[2] Despite the low probability of metastasis, BCC can be highly invasive to local structures and cause destruction of surrounding tissues if not identified and treated in early stages.[2]

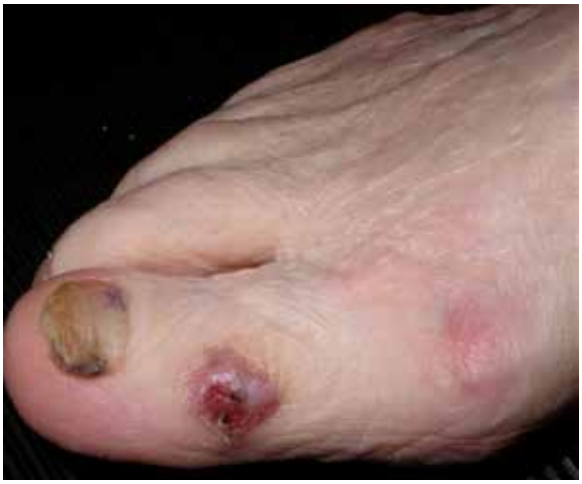

Figure 3: Basal cell carcinoma of the great toe (adapted from Basal Cell Carcinoma of the Toe, Figure 1, Suzuki et al., 2010)[16]

Squamous Cell Carcinoma Identification

SCC is generally characterized by a small red or pink scaly, often crusted skin lesion (Figure 4). Patients may describe the area as “non-healing” despite treatment efforts. SCC is pathologically composed of nests of squamous epithelial cells originating from the epidermis extending into the dermis.[17] It can also

present as a focus of induration, ulcerated lesion plaque, or an exophytic, cauliflower like growth.[18] There are many SCC variants which can be identified histologically and have widely variable clinical presentations. One such variant is known as verrucous carcinoma (VC). Palmoplantar VCs can be identified on all surfaces of the feet most commonly in elderly Caucasian males and are often initially mistaken for plantar warts. These lesions, however, usually evolve into bulky exophytic masses with ulceration and foul-smelling discharge.[19]

While rare, SCC of the foot can also develop secondary to lichen planus, deep mycosis, lichen simplex chronicus, and plantar verruca.[18] Furthermore, the probability of SCC increases eightfold in areas of chronic injury or irritation such as a skin ulcer.[20] Ulcers which undergo cancerous proliferation are termed Marjolin's ulcers. These ulcers are said to have a worse prognosis than de novo SCC due to their high rate of metastasis and delayed diagnosis, leading to the need for more extensive surgery.[20] Additionally, there is potential for patients with diabetes mellitus to present with SCC disguised as or hidden within an ulcer. If a suspected diabetic ulcer is nonresponsive to traditional treatment, suspicion for SCC may be raised and a biopsy can be performed in order to check for cancerous growth.[21]

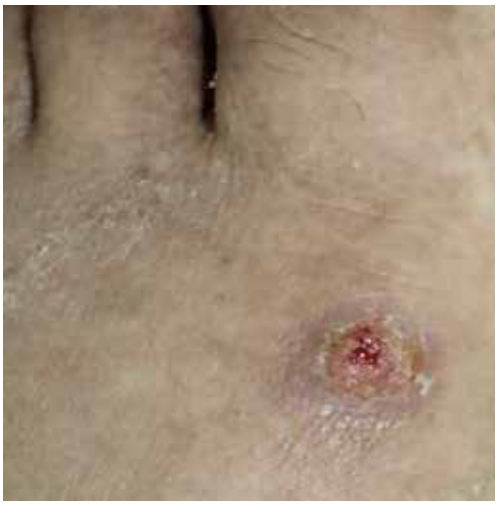

Figure 4: Squamous cell carcinoma on dorsum of foot (adapted from Case Reports in Dermatology, Figure 1c, Seok et al., 2015)[22]

Treatment for NMSC

Therapies for NMSC are generally driven by the initial office biopsy results. Skin cancer staging follows the TNM format. BCC and SCC are typically slow growing, non-invasive, and often treated by surgical excision.

A wide range of treatments have been described for BCC based mostly on desired cosmetic outcome. Surgical excision through subcutaneous fat is an effective option as it allows for post-surgical histological evaluation of clear margins and carries only a 2% chance of recurrence over five years.[23] Very small or superficial BCC has been effectively treated with less invasive measures including topical application of 5% imiquimod cream applied five to seven times per week for up to six weeks or until a reaction occurs, curettage, and cryotherapy.[13,23] These methods carry a higher chance of recurrence due to absent post-treatment histological evaluation. In areas of challenging excision such as on the taut skin of the foot or anterior leg, Mohs surgery may become the treatment of choice. Mohs surgery involves repeated careful excision of small areas of skin which are then evaluated by a pathologist until clear margins are achieved.[13] This surgery aims to remove as little skin as possible in one procedure.

Similar to BCC, SCC is treated with surgical excision. There is a higher metastatic potential for tumors arising in non-sun-exposed areas such as on the sole of the foot or in the location of a chronic ulcer or skin infection and more aggressive treatment is warranted.[24] Furthermore, patients on chronic immunosuppressive therapy have a higher incidence of SCC and a poorer prognosis.[25] Excision with 4 mm margins is standard for low risk SCC and 6 mm margins should be considered for higher risk SCC such as those on the foot.[24] Mohs surgery is often employed on the foot and leg. As with BCC, biopsy-confirmed superficial SCC may be treated with curettage or cryotherapy, however these lesions should be carefully followed for recurrence.

Discussion

New cases of NMSC and melanoma diagnosed each year are continuing to rise and early detection and treatment provide the best prognosis. There are numerous education campaigns in the U.S. aimed at early detection and prevention for future generations but there is still more to be learned about cancers which arise in areas of non-sun-damaged skin such as on the plantar surface of the foot. Lesions in this location tend to go unnoticed for some time and they tend to be disguised as other conditions which further complicates the prompt diagnosis. As access to technology is at an all time high, it may be beneficial for physicians to photograph and document the size and quality of all dermatopathologic lesions of the lower limb and foot. Not only can lesions be efficiently followed among providers, but patients will also be able to more easily notice any changes to their lesions from online access to their chart. In an aging population with many comorbidities,

something as simple as uploading a photograph of a lesion into the chart may help put both the physician and patient at ease. Early detection may save significant cost and reduce extreme complications such as loss of digits or large excisional surgeries.

Conclusion

In conclusion, it is imperative that routine screenings include careful examination of the sole of the foot, between the digits, and nails with special attention given to any areas of broken skin or discoloration. Skin cancer is very treatable with early diagnosis; therefore, a high index of suspicion and low threshold for biopsy of concerning pathology on the foot and ankle is warranted. As the majority of skin cancers present in older adults, it is of increasing importance that physicians of all specialties who treat this population have a basic understanding of the screening measures for skin cancer in the lower limb and foot.

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Exploring Diagnostic Modalities for Onychomycosis: An Overview

Allyson Brahs, B.S.

ABSTRACT

Objective: Onychomycosis is a common nail condition that presents with classic discoloration and thickening of the nail plate; therefore, 46.6% of general providers bypass a diagnostic workup altogether relying on a clinical diagnosis to begin treatment. This paper seeks to examine common diagnostic modalities including direct microscopy with potassium hydroxide (KOH), histopathology, and fungal culture and then explore the rationale for and against the empiric treatment of presumed onychomycosis.

Methods: The NCBI PubMed database was utilized with search criteria involving diagnostic modalities and workup recommendations for onychomycosis. Papers that required a fee were excluded.

Results: Many confirmatory tests are available for onychomycosis. KOH preparation is the quickest and cheapest to perform, while histopathology provides the most sensitive results. A fungal culture provides speciation, yet it is time-intensive. Empirically treating suspected onychomycosis with oral terbinafine could place patients at unnecessary risk for adverse drug events and could delay the proper diagnosis.

Conclusion: For the reasons above, combined with the support from many professional societies, confirmatory testing should be conducted before initiating treatment. The choice of confirmatory test depends on the available equipment and provider expertise with KOH preparation or histopathology being the preferred initial test, followed by fungal culture.

Introduction

The term onychomycosis is derived from the Greek roots "onycho-," meaning nail, "myco-," meaning fungus, and the suffix "-osis," meaning a state of disease. It refers to a fungal infection of the nail and presents with nail thickening, discoloration, and subungual debris. An estimated 5.5% of the global population is affected by onychomycosis.[1] Causal organisms include dermatophytes, nondermatophyte molds, and yeasts like *Candida albicans*. Dermatophytes are the most common organism responsible for toenail onychomycosis, most notably *Trichophyton rubrum*.[2] When a dermatophyte causes onychomycosis, it is referred to as tinea unguium. The three most common patterns include Distal Lateral Subungual (DLSO, Figure 1), White Superficial (WSO, Figure 2), or Proximal Subungual (PSO, Figure 3).

Of the patients who present with nail dystrophy, onychomycosis comprises around 50% of causes.[3] A lengthy list of differentials constitutes the remaining 50% of nail dystrophy, including psoriasis and lichen planus.[4] Due to the extensive differential and the varied presentation of onychomycosis, many laboratory tests exist to help confirm the diagnosis.

Methods

The NCBI PubMed database was used to identify relevant literature concerning onychomycosis diagnostic modalities and workup recommendations. Papers that required a fee were excluded; otherwise, no limits were placed on publication type or date. Search terms included "onychomycosis diagnostic modalities," "onychomycosis diagnosis," and "onychomycosis guidelines." From there, specific diagnostic modalities were searched, and additional resources were discovered from the references of the primary papers. Documents of interest, such as the Lamisil Package Insert and Choosing Wisely Campaign, were acquired using the Google search engine.

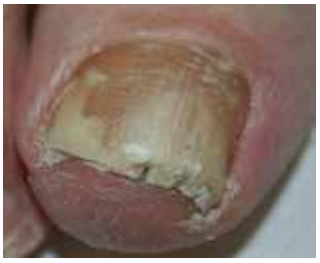

Figure 1
Distal Lateral Subungual Onychomycosis showing typical features of onycholysis and subungual hyperkeratosis. Adapted from Journal of Fungi.[5]

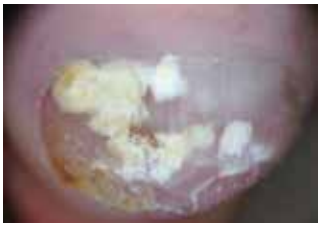

Figure 2
White Superficial Onychomycosis showing several opaque patches. Adapted from Skin Appendage Disorders.[6]

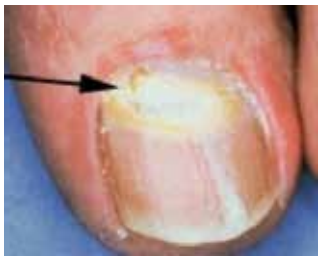

Figure 3
Proximal Subungual Onychomycosis. It is usually associated with an immunocompromised state. Adapted from Derm Report.[7]

Diagnostic Modalities

When considering a diagnostic modality for onychomycosis, important attributes to consider include cost, specificity, sensitivity, and time to perform the test (Figure 4). The most frequently used tests in clinical practice include direct microscopic evaluation (DME) with KOH preparation, histopathologic examination with Periodic acid-Schiff (PAS) stain, and fungal culture.[2]

Modality	Sensitivity	Specificity	Cost	Time
KOH	61%	95%	Least Expensive	30 min
PAS stain	84%	89%	Most Expensive	3-4 days
Culture	56%	99%	-	3-4 wks

Figure 4 Comparison of sensitivity, specificity, cost, and time for three onychomycosis diagnostic modalities. Adapted from BMC Infectious Diseases[8] and Clinical Dermatology.[2]

DME with KOH Preparation

Direct microscopic evaluation involves clipping the nail, scraping the subungual or superficial debris (a punch biopsy may be necessary in the case of PSO), applying KOH to dissolve the keratin, and then visualizing with a light microscope.[9] A positive test shows hyphae (Figure 5A), pseudohyphae, or yeast cells. This diagnostic modality can be performed in the office in under 30 minutes and only requires KOH solution and a microscope. To enhance visualization, additional stains such as Calcofluor white fluorescent stain can be applied (Figure 5B). This stain selectively binds the cellulose and chitin present in fungal cell walls and enhances the sensitivity. Overall, DME with KOH is quick, inexpensive, and specific; however, it does not provide speciation and has variable sensitivity as it depends on the skill of the clinician.[10]

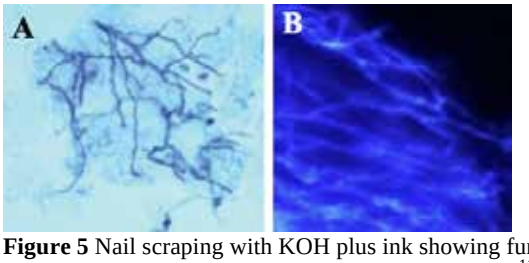

Figure 5 Nail scraping with KOH plus ink showing fungal hyphae (A). Adapted from Frontiers in Microbiology.[11] Calcofluor white stain under fluorescent microscope (B). Adapted from International Journal of Dermatology.[12]

Histopathology with PAS Stain

Like a biopsy specimen, nail clippings are placed in a formalin solution and sent to the lab. PAS stain induces a redox reaction that dyes the fungal cell wall magenta (Figure 6A). Grocott's Methanamine Silver (GMS) may also be used as an alternative stain as it dyes fungi brown rather than magenta (Figure 6B).[13] For both tests, results are available within a few days.[12] Many studies have shown PAS stain to be more sensitive than both KOH and culture (Figure 4).[8,14] Similar to KOH, PAS stain does not provide speciation. Unlike KOH, PAS stain is more expensive at $148 versus KOH at $8.[15]

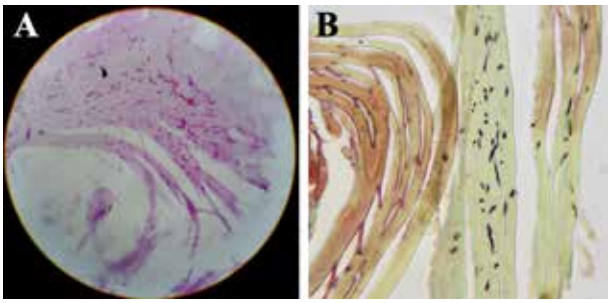

Figure 6 PAS stain (A) and GMS stain (B) with many organisms present. Adapted from Mycoses[16] and International Journal of Dermatology.[17]

Culture

A fungal culture is done on Sabouraud's medium with and without cycloheximide to support dermatophyte and nondermatophyte growth, respectively. Chloramphenicol and gentamicin are frequently added to discourage bacterial growth.[18] Fungal culture is often used in conjunction with a quicker test such as KOH or PAS stain. The culture is incubated for at least 3-4 weeks.[19] Its utilization comes from its ability to provide speciation, which allows treatment to be tailored directly at the causal organism. It has the highest specificity when compared to KOH and PAS.[12] An additional medium that is commonly used is Dermatophyte Test Medium (DTM). This agar contains phenol red, which changes the agar from yellow to red when exposed to alkaline metabolites from dermatophytes (Figure 7). It is less expensive than a traditional fungal culture because it does not need to be sent to a central laboratory, and results are available sooner, usually within 1 to 2 weeks.

Due to the different benefits and drawbacks, no method has been labeled as the gold standard for the diagnosis of onychomycosis.[17] Instead, a workup involving a combination of these tests can lead to the diagnosis.

As seen in Figure 8, the American Academy of Family Physician's diagnostic algorithm for suspected onychomycosis initially proposes KOH direct microscopic evaluation. If the KOH preparation is positive, treatment is provided to cover dermatophytes while awaiting results from culture or

PAS stain or both. Following the culture findings, treatment can be adjusted to more specifically target the causal organism. Depending on the clinical setting, PAS stain could be a valid initial option. Since PAS staining simply entails sending a nail clipping to the laboratory for analysis, it may be preferred in a setting with a practitioner inexperienced in KOH examination or a facility that lacks the equipment necessary for KOH preparation.[21] It is important to note that this algorithm recommends initiating treatment after confirming the diagnosis rather than on clinical suspicion.

Figure 7 Dermatophyte Test Medium (DTM) with *T. rubrum* growth (left) and *C. albicans* growth (right). All dermatophytes change the indicator red. Non-dermatophytes and *C. albicans* generally do not. Adapted from Arch Derm.[20]

Discussion

When a patient comes into the office with nail dystrophy suspected to be onychomycosis, many providers do not utilize the diagnostic methods described above. In France, a study found that 53% of private dermatologists did not perform any mycological sampling before treating.[22] Another international study found that only 3.4% of general physicians and 39.6% of dermatologists performed a confirmatory test.[23] A cross-sectional survey in the United States showed that 46.6% of family practitioners "almost never/never" obtained a confirmatory diagnostic test.[24] Based on these studies, it is evident that a large percentage of providers bypass confirmatory testing.

The main benefit favoring empiric treatment is the proposed cost-effectiveness. In 2016, Mikailov et al. analyzed the cost associated with KOH and PAS confirmation before treatment compared to empiric treatment with terbinafine in the United States.[15] Their results showed that empiric treatment is more cost-effective than confirmatory testing. In 2017, Gupta et al. conducted a similar study in Canada, and their data favored the opposite of Mikailov et al. Gupta et al. found less cost associated with confirmatory testing prior to treatment compared to the overall cost of an incorrect diagnosis.[25] Price differences in diagnostic methods and treatment in the United States compared to Canada could have accounted for their disparate outcomes.

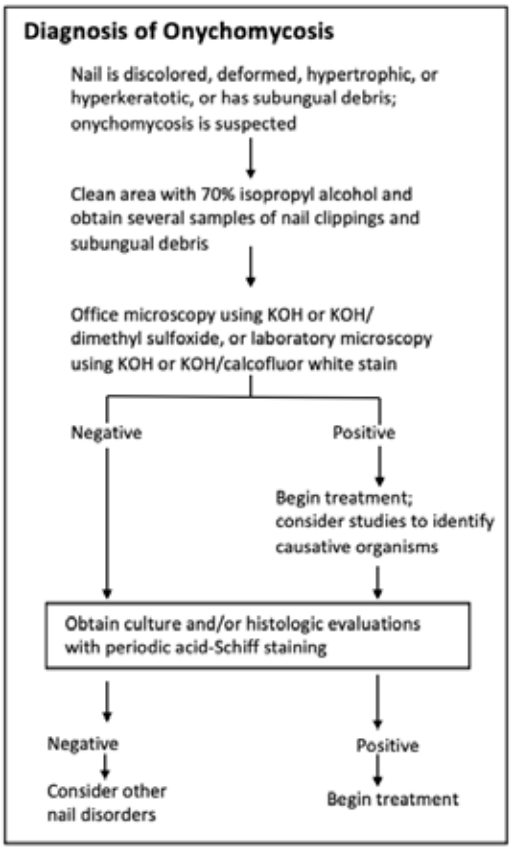

Figure 8 Onychomycosis diagnostic algorithm. Adapted from American Family Physician.[9]

Rationale against empiric treatment is that patients would be inappropriately exposed to a medication with many side effects. Twelve weeks of oral terbinafine is the preferred treatment for onychomycosis.[26] A Cochrane Library review noted that 16-54% of study participants experienced an adverse event when treated with terbinafine, with the most common being gastrointestinal symptoms, headache, fatigue, taste disorders, and rash.[27] Terbinafine has been associated with serious complications such as optic neuropathy and hepatic injury.[26,28] One in every 45,000-54,000 patients experiences a hepatic injury that may either require liver transplantation or cause death.[29] Though rare, acute liver failure from empirically-prescribed terbinafine without confirmatory testing places the clinician in legal jeopardy. Exposing a patient to the

risks of terbinafine for twelve weeks when a diagnosis could have been determined in a fraction of the time is not ideal. Due to the hepatotoxicity risk, liver function tests are recommended prior to treatment and at 4-6 weeks of terbinafine therapy, which adds excessive inconvenience and cost to those misdiagnosed.[30] A meta-analysis showed that terbinafine produced a mycologic cure rate of 76%.[31] Therefore, if patients do not respond to empiric treatment, it could be due to treatment failure or an improper diagnosis, and a diagnostic workup should then be performed. Also, terbinafine inhibits CYP2D6 and consequently, interacts with common drugs such as beta-blockers, SSRI's, dextromethorphan, and caffeine; initiating terbinafine could cause stress and alterations to medication routines.[26,32] Exposing patients to the potential adverse drug effects, recommended liver function tests, possible drug interactions, and delay in appropriate diagnosis can be minimized if the diagnosis is confirmed prior to treatment.

Relying on clinical diagnostic skills leads to many false positive results as seen in a retrospective study in Boston, MA.[33] In 541 cases of suspected onychomycosis, clinicians had a mean diagnostic accuracy of 75.4%. If those cases were empirically treated, around 1 in 4 patients would have been misdiagnosed and treated inappropriately. Two severe conditions that would be devastating to misdiagnose include subungual squamous cell carcinoma and amelanotic melanoma.[34] Subungual hyperkeratosis is a common nail feature in psoriasis and can be difficult to differentiate from onychomycosis clinically.[35] Lichen planus, another cause of nail thickening, benefits from an early diagnosis because it frequently results in permanent dystrophy if left untreated.[36,37] There are many imitators of onychomycosis including aggressive tumors and conditions that can benefit from a prompt diagnosis.

An additional reason favoring confirmatory testing is that some insurance companies may require confirmation before approving reimbursement for treatment.[24,38] Lastly, as per the previously referenced algorithm from the American Academy of Family Physicians, many professional societies strongly urge that all physicians confirm the diagnosis before prescribing oral antifungal medication for suspected onychomycosis. The British Association of Dermatologists recommends obtaining a positive culture prior to commencing treatment.[39] The American Academy of Dermatology even deemed this topic important enough to include as their first recommendation of their "Choosing Wisely" campaign.[40]

Conclusion

Onychomycosis affects around 5.5% of the population, thus it is important to be well-versed in the diagnostic options. When a patient presents with suspected onychomycosis, practitioners should utilize confirmatory diagnostic tests. The PAS stain has the highest sensitivity, yet many proposed algorithms, such as the one listed above, favor KOH preparation for its speed and cost-effectiveness. Practitioners should make the choice of KOH preparation versus PAS stain based on their own experience and available materials. Treatment should be initiated following a positive KOH or PAS stain. If the practitioner is inexperienced in KOH preparation and PAS stain is too expensive, then DTM offers an alternative that is quicker than a fungal culture. Following initial screening with a quicker modality, a culture should be performed to identify the specific organism, and treatment should be adjusted accordingly.

A discrepancy certainly exists amid the recommended and practiced management of onychomycosis. Around 46.6% of general clinicians do not perform confirmatory testing, yet guidelines and moral obligation conflict with providing empiric treatment. Onychomycosis only constitutes 50% of onychodystrophy, and clinicians have a diagnostic accuracy of 75.4%. To enhance diagnostic accuracy and minimize unnecessary treatment, all clinicians should follow recommended guidelines by confirming the diagnosis of onychomycosis before initiating treatment.

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Comparing the Efficacy of Oral Terbinafine and Itraconazole for the Treatment of Onychomycosis

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ABSTRACT

Objective: This study compares the efficacy of oral terbinafine and itraconazole which are second line of treatment choices for patients affected with onychomycosis and to compare strengths and weaknesses of both agents. Both drugs are evaluated by comparing their efficacy in producing clinical and mycological cures. Due to the significant side-effects of both terbinafine and itraconazole, evaluating both drugs for their efficacy and long-term cure is necessary to avoid exposing patients to more of the drug than necessary.

Methods: Firstly, after conducting a literature search, both agents were compared on the criteria of producing a mycological and clinical cure. Secondly, both agents were compared after researching their respective physiological effects and penetrance. Lastly, both agents were compared on the criteria of continuous and intermittent dosing regimens and the respective cure rates achieved.

Results: The results of this study demonstrate that terbinafine proves to be a superior agent when compared to itraconazole in the treatment of onychomycosis. While both drugs have optimal pharmacokinetics for treating onychomycosis, terbinafine shows greater efficacy and a lower rate of relapse. Over the course of a 48-week treatment period, terbinafine had a mycological cure rate of 73% as opposed to a mycological cure rate of 45.8% for itraconazole. After 24 weeks of treatment, continuous and intermittent dosing for both itraconazole and terbinafine show no major difference in their efficacy. However, intermittent dosing resulted in a higher concentration of both drugs in keratinized tissue with the circulating amounts of the drug reduced.

Conclusion: Terbinafine and itraconazole are routinely prescribed in practice for the treatment of onychomycosis. However, in the long-term treatment of onychomycosis terbinafine has proven itself to be a better agent. With a minimum fungicidal concentration lower than that of itraconazole, terbinafine garners better results with less of the drug.

Introduction

Onychomycosis is a mycological infection of the nails with the population-based prevalence of the infection being 4.3% in North America and Europe. Most patients with onychomycosis present with nails that are dystrophic, discolored, and sometimes painful.[1] Half of all nail pathologies are fungal in origin.[2] Most infections are caused by dermatophyte fungi with 80-98% of individuals affected by *Trichophyton rubrum* or *Trichophyton mentagrophytes.*[3] The first line of treatment in the podiatric setting for onychomycosis is often a topical antifungal, but these drugs are seldom effective in curing the infection due to inefficient penetrability of the nail bed.

Oral terbinafine and itraconazole are routinely used for the treatment of onychomycosis; however, they have the potential for inciting more serious side effects than topical treatments. Liver function tests need to be closely monitored for patients receiving oral treatment of itraconazole due to the risk of hepatotoxicity.[4]

Prior to initiating Terbinafine treatment for onychomycosis, baseline liver function tests are needed to assess for underlying chronic and acute liver conditions. Treatment should not be initiated in the presence of liver disease. However, after treatment has been initiated routine monitoring is not necessary if signs and symptoms of liver disease are not present.[5]

The efficacy of treatment of onychomycosis can be evaluated by two approaches: clinical and mycological. A clinical cure is said to be achieved when the treated nail is void of discolored streaks within the nail plate and onycholysis is absent. In comparison, a mycological cure is a negative presence of an infectious organism under a microscope and a biopsy that results in negative cultures. Additionally, a mycological cure may present with no clinical signs of a cure or with minor clinical symptoms such as distal hyperkeratosis under the nail and slightly thickened nails.[6]

Although onychomycosis is not a life-threatening condition, the hyperkeratotic and discolored appearance of nails affected by onychomycosis can cause patients to become self-conscious, lose self-esteem, and become depressed. These symptoms can have a significant negative impact on a patient's overall quality of life, so finding a safe and effective treatment becomes necessary. Topical treatments are seldom effective and oral agents may cause significant side effects due to their toxic metabolic byproducts. By finding the most efficacious oral agent, the possibility of side effects can be avoided by reducing overtreatment and avoiding repeat treatments. The objective of this study is to compare the efficacy, strengths and weaknesses of both agents by researching multiple studies and

decipher which agent and respective dosing regimen is better in terms of clinical and mycological cure rates.

Pharmacokinetics

Both drugs act by inhibiting the synthesis of ergosterol in fungal cell walls. Each of these pharmacological agents works along a different point in the ergosterol synthesis pathway as shown in Figure 1.[7] Terbinafine is an allylamine that acts earlier in the pathway to inhibit squalene epoxidase which converts squalene to 2,3-Oxidosqualine.[8] Itraconazole is an azole that acts by inhibiting lanosterol 14α-demethylase, therefore arresting ergosterol synthesis.[7]

Inhibition of squalene epoxidase by allylamines results in an accumulation of the toxic substance squalene within the fungal cells. This gives terbinafine secondary fungicidal properties in addition to its primary fungistatic action.[7] Itraconazole, on the other hand, has more of a fungistatic action than a fungicidal action. It causes membrane leakage which prevents the organism from reproducing and eventually leads to its death.[7]

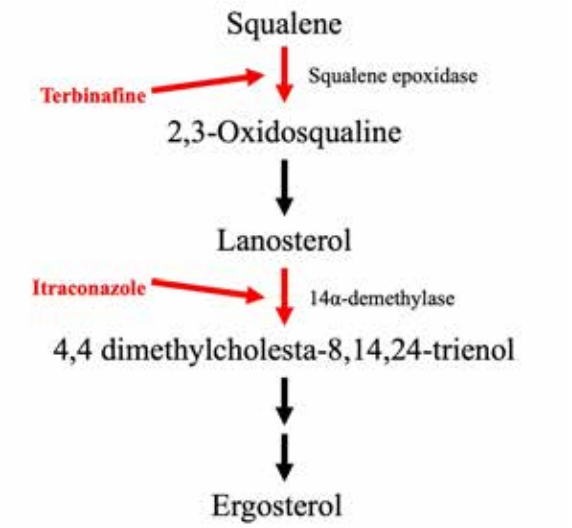

Figure 1. Targeted actions of Terbinafine and Itraconazole.

Both itraconazole and terbinafine are lipophilic with a high affinity for keratinized tissue, making both agents great candidates for targeting the toe nail tissue.[7] Terbinafine is available as a tablet and topical solution while itraconazole is available as a capsule and an oral solution. Continuous or intermittent dosing regimens are available for both medications as shown in Table 1. [9-10]

Itraconazole is metabolized by cytochrome P-450 3A4 enzyme in the liver giving rise to the possibility of adverse drug to drug interactions. Terbinafine is metabolized by multiple cytochrome P-450 enzymes.[11] Terbinafine has a half-life up to 156 days while itraconazole has a half-life of 28 hours in a single dose and 42 hours with repeat dosing.[6-11]

The minimum inhibitory concentration (MIC) is the concentration of a drug necessary to inhibit growth of an organism, whereas the minimum fungicidal concentration (MFC) is the concentration of a drug necessary to eradicate an organism. Terbinafine and itraconazole have a MIC of 0.004 µg/ml and 0.078 µg/ml, respectively. While itraconazole's MFC increases to 0.595 µg/ml from its MIC, terbinafine's MFC is the same as its MIC at 0.004 µg/ml.[7]

Dosing for Terbinafine and Itraconazole

Terbinafine		
	Continuous:	250 mg tablet daily for 12 weeks
	Intermittent:	200 mg tablet twice daily for one week with three drug-free weeks repeated for 12 weeks
Itraconazole		
	Continuous:	200 mg capsule daily for 12 weeks
	Intermittent:	200 mg capsule twice daily for one week with three drug-free weeks repeated for 12 weeks

Table 1: Continuous and intermittent dosing schedules for terbinafine and itraconazole in tablet and capsule forms.

Results

Terbinafine can be administered in a continuous or intermittent regimen. In one study conducted by Yadav et al. that comprised of 76 individuals, the efficacy of continuous dosing was compared with the efficacy of intermittent dosing. After 12 weeks of treatment, patients receiving the continuous dosing saw a mycological cure rate of 28.9%; whereas, patients receiving the intermittent dosing saw a mycological cure rate of 18.4%. However, the difference in the mycological cure rate for patients on an extended 24-week regimen had no significant difference between continuous or intermittent dosing.[10]

Like terbinafine, itraconazole may also be given in a continuous or an intermittent regimen. A study consisting of 129 patients found comparable mycological cure rates at 12 months between continuous and intermittent dosing.[14]

Continuous therapy of both terbinafine and itraconazole have comparable negative mycology rates at the 12-week mark for continuous dosing. However, between the 12th and 48th week, terbinafine begins to show a higher mycological cure rate. At the 48-week mark, continuous dosing of terbinafine has a mycological cure rate of 73% as opposed to a mycological cure rate of 45.8% with continuous dosing of itraconazole.[15] This could be the direct result of terbinafine requiring a lower concentration of the agent to be fungicidal in addition to having a much longer half-life.

Sigurgeirsson et al. conducted a long-term follow-up study to evaluate the effectiveness of terbinafine and itraconazole. They evaluated efficacy of continuous terbinafine dosing with intermittent itraconazole dosing. A total of 151 patients were followed. At the 12-month mark, 57 of the 74 terbinafine treated patients and 32 of the 77 itraconazole treated patients had achieved a mycological cure.[16]

Limitations

The evaluation of clinical cures vastly depends on the practitioner's experience, and clinical judgment. It is difficult for researchers to precisely evaluate the mentioned clinical cures due to many factors. To illustrate, once treatment begins in an affected patient infected nail(s) may take several months to show signs of improvement and between 12 to 18 months for a healthy nail to fully regrow. Additionally, many research endeavors do not allocate enough time to analyze this healing process.[17-18] Due to these limitations, accessing the mycological cure rate to evaluate the effectiveness of treatment is more appropriate.

Discussion

Both terbinafine and itraconazole are more effective with continuous dosing during a short 12-week treatment period. However, the mycological cure rate during this short treatment window proves to be ineffective for an overwhelming number of patients. During a longer 48-week treatment period the overall mycological cure rates are significantly increased for both terbinafine and itraconazole.

In addition, mycological cure rates for itraconazole did not show a significant difference between the continuous and intermittent dosing regimen during a 52-week treatment period. Therapeutic levels of itraconazole are reached in the nail faster with intermittent therapy than continuous therapy, while reducing the overall plasma concentration of the drug.[14] With a lower plasma concentration of itraconazole, the risk for drug-drug interactions and other adverse effects is reduced. This aspect in addition to no significant difference in efficacy between continuous and intermittent dosing of itraconazole allows for the feasibility of a direct comparison between intermittent dosing of itraconazole and continuous dosing of terbinafine.

Conclusion

Both itraconazole and terbinafine are routinely prescribed to treat onychomycosis due to their pharmacokinetic properties. However, when compared to itraconazole on the criteria of adverse reactions, drug interactions, half-life and mycological cure rates, terbinafine prevails as the superior agent of treatment. Terbinafine showed higher mycological cure rates. The highly lipophilic keratinized makeup of nail tissue allows terbinafine to reach the MFC quicker with intermittent treatment quicker than continuous treatment, making the intermittent regimen a stronger choice in treating onychomycosis.

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Assessing the Potential Benefits and Limitations of Oral Terbinafine Dosing Strategies

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ABSTRACT

Objective: This study assesses the benefits and limitations of oral terbinafine dosing strategies. The tablet formulation of terbinafine is a medication commonly used to combat onychomycosis caused by dermatophytes. Studies have suggested that intermittent high doses of the drug can rival the efficacy of continuous dosing, creating an opportunity to deliver a lower cost therapy to patients.

Methods: Five studies addressing the topic were selected for review following a literature search. The studies reviewed in this article demonstrate the fungicidal capability of pulse dosing, examine the effect changing the interval between pulses has on mycological cure rates, and compare the efficacy of intermittent and continuous dosing. Studies were selected based on their objectives, definition of cure utilized, and in the comparative studies, application to the lower extremity.

Results: In comparing three trials with 628 patients completing the studies, 69.6% of patients receiving a continuous dose and 72.2% of patients receiving a pulse dose were found to achieve mycological cure.

Conclusion: The findings demonstrated that patients could successfully reach a comparable rate of mycological cure with intermittent dosing. This dosing regimen was also found to achieve mycological cure with a cost up to fifty percent lower than that of continuous dosing.

Introduction

Onychomycosis in the podiatric setting is a fungal infection of the toenails commonly caused by yeasts, dermatophytes, and non-dermatophyte molds.[1] The systemic form of terbinafine is an oral antifungal agent indicated in cases of onychomycosis caused by dermatophytes in the lower extremity.[2] Several topical forms of the medication also exist and both forms exhibit fungicidal activity by inhibiting squalene epoxidation of sterols in the fungal membrane.[3,4] In cases of toenail onychomycosis, the oral tablets can be taken as continuous doses or intermittently as pulse doses. This discussion reviews several studies comparing the efficacy of the two dosing strategies of the oral systemic formulation.

Pharmacokinetics

The systemic formulation of the drug is a highly bioavailable lipophilic allylamine that is well absorbed gastrointestinally and accumulates in the skin, nail, and fatty tissues.[5] The drug reaches effective concentration against dermatophytes in 1-2 weeks and remains in the tissue for several months due to a lengthy half-life that can be up to 156 days.[6]

While the drug exists in multiple forms, the oral tablet formulation in particular is indicated for toenail onychomycosis. The recommended continuous dosing regimen for adults weighing over 40 kg is 250 mg once daily for twelve weeks, but studies evaluating pulse dosing regimens utilized significantly higher doses in comparison.[7,8] In most cases, patients are administered a daily dose of 500 mg for one week every four weeks for three months.[8]

Methods

A total of five published studies on the efficacy of pulse-dose terbinafine were reviewed. Studies were selected based on their objectives, definition of cure utilized, and in the comparative studies, application to the lower extremity. One study of 7 patients investigated if pulse dosing could reliably elicit a mycological cure of dermatophyte onychomycosis.[9] Another study of 59 patients investigated optimal pulse intervals.[10] Three studies consisting of 628 patients completed studies comparing the efficacies of pulse dosing and continuous dosing.[8,11,12] A “mycological cure” was defined as a normal-appearing nail with a negative KOH test and negative culture.[10]

Results

In a study of seven patients, Valkova demonstrated that terbinafine in pulse doses could effectively produce mycological cure of dermatophyte nail infections in the upper and lower extremity.[9] In the study, a dose of 500 mg was administered daily for one week every month for a total duration of three to four months. Three months of treatment were administered for patients with fingernail onychomycosis while four months of treatment was administered for toenail onychomycosis. In a non-randomized prospective study evaluating 59 patients, Zaias delved further into the topic by experimenting with the interval between each pulse week.[10] When evaluating the efficacy of varying the number of months between one week pulses of 250 mg daily, the study found no significant drop in cure rate with a pulse frequency of once every one to three months. When the frequency was

decreased to once every four months, there were significantly more failures ($p < .01$).[10] (Figure 1).

Both studies demonstrated that pulse doses of terbinafine could effectively cure dermatophyte onychomycosis. The Zaias study demonstrated that a pulse dosing strategy of 250 - 500 mg dose given daily administered for one week with a frequency within the range of every one to three months would be efficient in a clinical setting.

With the fungicidal capability of intermittent dose terbinafine established, we looked at several trials comparing the mycological cure rate of intermittent dosing and continuous dosing. Three separate trials by Yadav et al., Warshaw et al., and Pavlotsky et al. studied 628 patients in total.[8,11,12]

All of the patients were examined in an outpatient setting, and the pulse doses for all three trials were 500 mg daily for one week for every four weeks. Out of the 286 patients given continuous dosing, 199 patients (69.6%) achieved mycological cure within 48 weeks. Out of the 342 patients given intermittent dosing, 247 (72.22%) achieved mycological cure by 48 weeks.

Overall, 69.6% of patients receiving a continuous dose were cured and 72.22% of patients receiving a pulse dose were cured. With the three studies considered, there was no decrease in total efficacy when pulse dosing was utilized, confirming the idea that pulse dosing regimens could potentially be prescribed in place of continuous dosing while maintaining efficacy.

Discussion

Several limitations were noted in these studies. The follow-up period was not standardized across all of the comparative studies, and not every study specified whether a mycological cure was found on a single target toenail or across all toenails. The clinical setting in which the study took place created potential limitations in the ability to generalize the findings. The comparative study by Warshaw et. al had the most apparent limitation of population; it was limited to a population of older males as it was conducted in a Veterans Affairs facility.[8] This could prove to be problematic when attempting to generalize the findings for the general public.

Variations in the study type also creates potential limitations; two of the three comparison studies were randomized control trials while one was a retrospective study. As all of the studies were conducted in the outpatient setting, potential limitations include patients who failed to adhere to the prescribed regimen and the possibility of unaccounted drug interactions affecting the active concentration of the drug in the target tissue.

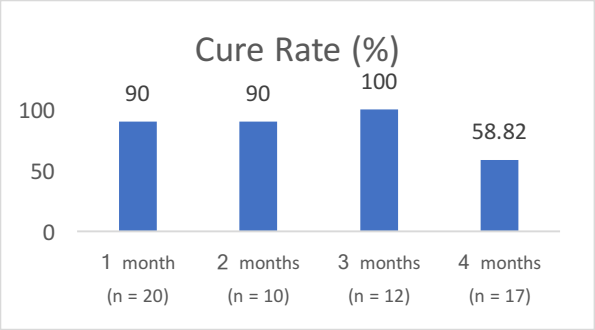

Figure 1: The study completed by Zaias et al. demonstrated that there was no significant drop in efficacy of pulse dosing until the frequency was decreased to one week every four months.[10]

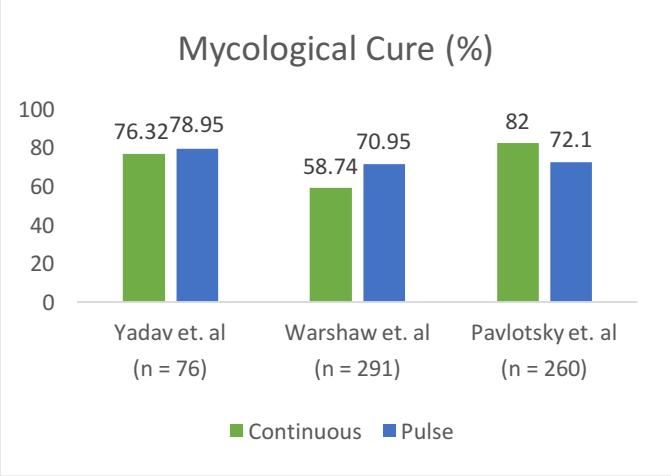

Figure 2: The efficacy of each drug regimen in the three studies compared shown as a percentage.[8,11,12]

Conclusion

Overall, the rate of mycological cure achieved by pulse dosing in these three studies had a slightly higher rate of mycological cure than that of continuous dosing, making it a viable alternative to prescribing a continuous dose. Having multiple dosing strategies available opens the door to individualizing care for patients and further research into potential benefits. Other positive findings could lie in cost efficiency, adverse reaction modulation, and patient medication adherence.

While Pavlotsky et al. did not note any differences in the prevalence of adverse side effects, they noted that patients could potentially be spared 50% of the medication cost with pulse dosing.[12] Medication cost is a barrier to patient adherence.[13] As such, lowering the cost of the drug could potentially improve mycological cure rates by improving medication adherence. With the efficacy demonstrated by these studies, patients harness the benefits of pulse dosing while safely maintaining the

mycological cure rate of the traditional continuous dosing strategy.

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Biochemical Perspective of Diabetic Hyperglycemia's Contribution to Diabetic Neuropathy: A Review

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Abstract

Objective: The purpose of this review is to analyze how the molecular processes in diabetes-induced hyperglycemia contributes to the development of diabetic neuropathy.

Methods: A search of literature published in MEDLINE-PubMed database was performed using keywords such as diabetes, diabetic neuropathy, and oxidative stress in combination with other phrases relating to the topic of diabetic hyperglycemia.

Results: Hyperglycemia increases production of reactive oxygen species (ROS) through the AGE-RAGE pathway leading to the inhibition of glyceraldehyde-3-phosphate dehydrogenase activity (GAPDH). The inhibition of GAPDH activity contributes to the increased activity of the polyol pathway resulting in oxidative stress which has a critical role in the pathogenesis of diabetic neuropathy.

Conclusion: Diabetes-induced hyperglycemia contributes to the development of diabetic neuropathy by increasing the activity of the polyol pathway resulting in oxidative stress which damages the peripheral nervous system.

Introduction

Diabetes mellitus (DM) is the seventh leading cause of death in North America.[1] DM is a complex disease characterized by hyperglycemia due to the body's inability to produce or utilize insulin for the uptake of glucose. Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which the immune system destroys beta cells in the pancreas resulting in the decreased production of endogenous insulin. Type 2 diabetes mellitus (T2DM) is a condition characterized by insulin-resistance in which the body is unable to efficiently utilize endogenous insulin to regulate glucose homeostasis. DM is a global concern with over 366 million people diagnosed with diabetes in 2011.[2] The debilitating effects of DM are due to its severe complications such as diabetic neuropathy (DN).

Diabetic neuropathy is the damage of nerves due to high blood-glucose levels causing neuronal dysfunction. It is one of the most common complications of DM with more than 50% of diabetic patients developing DN.[3] DN is a major risk factor for lower limb amputations in diabetic patients with diabetic patients accounting for approximately 60% of non-traumatic lower-limb amputations.[1]

Hyperglycemia induces the overproduction of reactive oxygen species (ROS) which leads to increased activity of the polyol pathway, an underlying mechanism in the pathogenesis of DN.[3,4] Finally, DN contributes to the development of foot ulcers and limb amputations.[5] The objective of this review is to analyze how the molecular processes in diabetes-induced hyperglycemia contribute to the development of diabetic neuropathy.

Hyperglycemia leads to inhibition of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity

Hyperglycemia leads to peripheral neuron damage, which ultimately causes DN. High glucose concentrations result in an increased rate of glycation reactions involving non-enzymatic bondage of glucose molecules to nearby proteins, forming molecules called Amadori products.[3] After a series of reactions, the Amadori products convert to advanced glycation end products (AGEs).[6] The primary AGEs in vivo include pyrraline, N-carboxymethyl lysine (CML), methylglyoxal/glyoxal lysine amide, and pentosidine. Excessively high amounts of AGEs are pathological since they bind to their cell-surface receptors, resulting in the increased intracellular production of ROS.[7] A study conducted by Folmer et al. found that mice on a high-glucose diet (hyperglycemic mice) had significantly higher superoxide (a type of ROS) production in comparison to mice on a high-starch diet (non-hyperglycemic mice), hence supporting the conclusion that hyperglycemia induces ROS overproduction.[8]

AGEs mediate increased ROS production by interacting with the receptors of advanced glycation end products (RAGE) (Figure 1). RAGE is a multi-ligand receptor belonging to the immunoglobulin superfamily.[9] The binding of AGE to RAGE results in the activation of mitogen-activated protein kinase (MAPK), which induces the expression of nuclear factor kappa B (NFkB). NFkB induces the transcription of proinflammatory cytokines.[10] Moreover, the AGE-RAGE interaction activates nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidases, which increases the ROS levels.[11] AGE and RAGE are significantly elevated in diabetic patients with neuropathy in comparison to healthy individuals, further

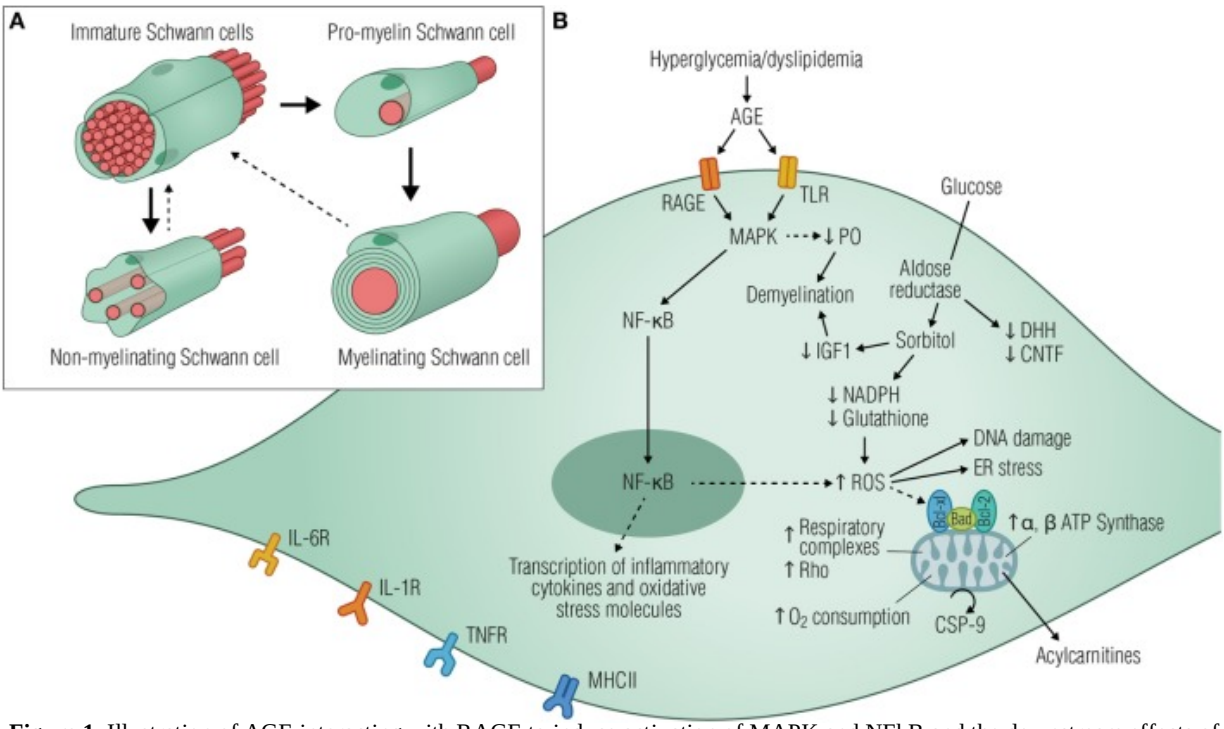

Figure 1: Illustration of AGE interacting with RAGE to induce activation of MAPK and NFkB and the downstream effects of increased proinflammatory cytokine transcription and ROS production. Adapted from Frontiers in Neurology.[14]

underscoring the significance of AGE-RAGE interaction in the pathogenesis of diabetic neuropathy.[10]

Increased levels of ROS activate pathological pathways that lead to DN by inhibiting GAPDH, a glycolytic enzyme.[12] GAPDH is inhibited due to chemical modifications by polyadenosine diphosphate

ribose polymerase (PARP), a DNA repair enzyme, which becomes activated when ROS overproduction breaks the DNA strand.[12] A study conducted by Du et al. found that using an electron transport chain inhibitor to reduce the overproduction of mitochondrial superoxides prevented the inhibition of GAPDH activity.[13] This supports the notion that overproduction of superoxides inhibit GAPDH activity. Finally, the inhibition of GAPDH increases the activity of pathological mechanisms that contribute to the development of DN, such as the polyol pathway.[4] Thus, ROS overproduction due to diabetes-induced hyperglycemia is the initial change that enhances the activity of various pathological mechanisms that contribute to the development of DN.

GAPDH and the polyol pathway

Since oxidative stress inhibits the activity of GAPDH, upstream glycolysis molecules like glucose increase intracellularly.[4] In the polyol pathway, the aldose reductase enzyme responds to the high glucose concentration by reducing glucose to sorbitol while consuming the cofactor nicotinamide adenine dinucleotide phosphate (NADPH).[15] The resultant low intracellular NADPH contributes to the development of DN since NADPH is utilized for the formation of reduced glutathione, an essential antioxidant which inactivates toxic ROS.[4] However, due to higher production of sorbitol in diabetes, intracellular NADPH levels will be lower resulting in decreased levels of reduced glutathione production (Figure 2). Consequently, the cell becomes more susceptible to oxidative stress which has a critical role in the pathogenesis of DN.[4]

The key enzyme of the polyol pathway, aldose reductase, is regulated in part through nitric oxide (NO) availability.[16] Nitric oxide is synthesized from L-arginine by nitric oxide synthase, which also uses NADPH as a cofactor.[17] Reduced NADPH levels therefore lead to attenuated NO levels, increasing the risk of vascular complications under hyperglycemic conditions as well as flux through the polyol pathway.[18] The second reaction of the polyol pathway produces NADH from nicotinamide adenine dicnucleotide (NAD^+), a major contributor to redox imbalance.[19] Excess NADH can overwhelm mitochondrial complex I, which relays electrons from NADH to coenzyme Q. The more electrons complex I transports, the more superoxide it produces, contributing to the ROS burden.[20] NADH has other effects including inhibiting glycolysis and the Krebs

cycle, leading to increased amounts of glucose being shunted through the polyol pathway.[21] Decreased NAD^+ from the hyperglycemia induced redox imbalance inactivates sirtuins, which are involved in protein deacetylation. Overall, this would lead to less effective glucose metabolism. One way of combating some of these dysregulated redox effects may be nutritional supplementation. For example, the administration of the NAD^+ precursor, nicotinamide riboside, led to the amelioration of diabetes and diabetic neuropathy in mice.[22]

Oxidative stress contributes to the development of DN since it is associated with peripheral neuron and glial cell apoptosis, hence damaging the peripheral nervous system.[23] A study conducted by Schmeichel et al. concluded that oxidative stress causes DNA damage, resulting in dorsal ganglion neurons in streptozotocin (STZ)-induced diabetic rats to undergo apoptosis.[24] Furthermore, they found that the longer the duration of diabetes, the higher amount of neuronal apoptosis. For instance, STZ-diabetic rats with diabetes for 12 months had a significantly higher amount of neuronal apoptosis in comparison to STZ-diabetic rats with diabetes for 1 month. Therefore, this study provided information regarding the relationship between the duration of diabetes-induced hyperglycemia and DN due to neuronal apoptosis. Such findings suggest that uncontrolled hyperglycemic condition for longer periods of time result in increasingly severe DN. A study conducted by Russell et al. found STZ-diabetic rats to undergo Schwann cell apoptosis and also dorsal root neuronal cell apoptosis; Russell et al. proposed that oxidative stress disrupted the mitochondria of these cells leading to the activation apoptosis.[23] A study conducted by Kato et al. demonstrated that immortalized adult mouse Schwann (IMS32) cells exposed to hyperglycemic conditions underwent apoptosis via oxidative stress and ER stress responses.[25] All in all, hyperglycemia induced by diabetes causes oxidative stress, which damages various parts of neurons and Schwann cells resulting in apoptosis, hence leading to DN development in diabetics. This is of importance since it helps establish the involved pathological processes and the cell types that are susceptible to damage in diabetic complications. Such findings can provide a direction for the targets of therapeutic interventions and diagnostic tools.

Discussion

The mechanisms by which hyperglycemia leads to tissue damage are multifaceted and include the direct glycation of macromolecules, as well as enhancing cellular pathways like increasing production of advanced glycation end products,

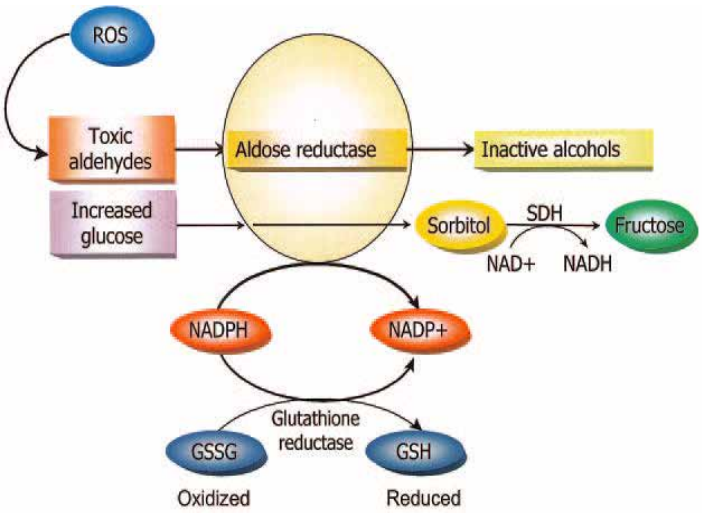

Figure 2: Illustration of excess glucose converting to sorbitol by consuming NADPH. Lower NADPH levels result in reduced levels of an essential antioxidant, GSH. Adapted from *Nature*.[26]

upregulated expression of receptor for AGEs, and an increased activation of the polyol pathway.

There are several research gaps regarding the pathogenesis of DN. One question that calls for future research is why hyperglycemia results in DN via damaged peripheral neurons and supporting cells to a greater extent than central nervous system (CNS) neurons and supporting cells. As a result, future research should investigate how CNS neurons and supporting cells are able to cope with hyperglycemic conditions. Such research may aid in developing new therapeutics for the treatment of DN by allowing peripheral neurons and supporting cells to develop similar hyperglycemic management mechanisms as CNS neurons. Future research should also investigate possible mechanisms to reduce the formation of AGEs, since previous studies showed excessive AGEs production increases the activity of the polyol pathway contributing to DN development.

The RAGE pathway results in the production of ROS, which contributes to diabetic neuropathy. Therefore, future studies should investigate ways to slow down the progression of diabetic neuropathy by attenuating the downstream effects of the RAGE pathway. A possibility is establishing methods to enhance the activity of advanced glycation end products receptor 1 (AGER1). When AGEs interact with AGER1 instead of RAGE, it results in reducing ROS production. AGE-AGER1 interaction diminishes the downstream effects of RAGE by inhibiting NADPH oxidase, resulting in the reduction of ROS production from the RAGE pathway.[27] Also, AGER1 is associated with sirtuin1, a deacetylase. The increased activity of the

AGER1 pathway results in suppression of NFkB-mediate inflammation due to NFkB inhibition via deacetylation by sirtuin1.[28] Thus, therapeutic outcomes can possibly be attained by upregulating the AGER1 pathway.

Another potential therapeutic target is the utilization of miRNA-25. A study conducted by Zhang et al. found that the transfection of miRNA-25 into diabetic-mice models has reduced the serum and peripheral nerves levels of AGE and RAGE.[29] The study found miRNA-25 downregulated the AGE-RAGE pathway and numerous other inflammatory factors that contribute to the development of diabetic neuropathy. These findings illustrate the role of miRNA-25 as a protective factor against the pathological process of diabetic neuropathy. Hence, future studies should investigate the role of miRNA-25 in humans for its possible utilization as a diagnostic and therapeutic target for the treatment of diabetic complications.

Conclusion

One of the most common DM complications is diabetic neuropathy, which contributes to the development of foot ulcers and limb amputations among diabetic patients. Hyperglycemia as a result of uncontrolled DM facilitates an abnormal increase in the production of AGEs resulting in pathologically excessive production of ROS via AGE-RAGE interaction.[3] High amounts of ROS cause DNA damage, resulting in the activation of PARP, which inhibits the activity of GAPDH.[13] Inhibition of GAPDH activity increases the activity of the polyol pathway resulting in cells becoming more susceptible to oxidative stress, which plays a critical role in the pathogenesis of DN.[4] Oxidative stress contributes to DN since it damages the peripheral nervous system by facilitating the apoptosis of peripheral neurons and Schwann cells.[23] DN leads to loss of foot sensation in diabetics resulting in the manifestation of debilitating outcomes such as foot ulcers and amputations.[30] Future therapeutic studies for DN should aim at investigating the attenuation of the RAGE pathway.

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Prevalence of Charcot Neuroarthropathy and Peripheral Arterial Disease in Diabetic patients: A Literature Review

Jeremiah Thomas, B.S. and Ashley Joy Panganiban, B.S.

ABSTRACT

Objective: Charcot neuroarthropathy (CN) and Peripheral Arterial Disease (PAD) are associated with diabetes mellitus (DM) and are increasing in prevalence. These diseases have different pathogenic mechanisms by which they progress. There has been a consensus that because of these diseases' pathogeneses, there is a protective factor against developing PAD if the patient has CN. The purpose of this literature review is to examine the research on the prevalence of PAD and CN simultaneously in DM patients.

Methods: The method of data collection used one search engine: PubMed and several keywords: "Charcot Neuroarthropathy and Peripheral Arterial Disease" and "Charcot Neuroarthropathy", and "Peripheral Arterial Disease."

Results: There are multiple studies that demonstrate the prevalence of PAD increases and decreases with CN. PAD complications such as ischemia is decreased by 82% and need for revascularization is decreased by 14% in patients with CN and PAD compared to patients with PAD and without CN.

Conclusion: Overall, the prevalence of PAD decreases in patients with CN. Patients with CN have hypervascularization which decreases the likelihood of developing PAD.

Introduction

Charcot neuroarthropathy is a complication of diabetes mellitus that leads to ulcerations, deformities, and amputations. Peripheral arterial disease (PAD) is a comorbidity with DM that leads to ischemia, infection, and amputation. CN has been known to cause hypervascularization while PAD causes devascularization, leading to the belief that patients with CN are at decreased risk for having PAD.[2] Patients with PAD are also thought to have a protective factor against developing CN. CN has a prevalence of 0.1-0.4% in DM patients while PAD has a prevalence of 15-25%.[1] CN and PAD are increasing in prevalence in DM patients since 2012 by 50%.[3] The increasing prevalence of CN and PAD demonstrate that these conditions must be understood to better combat their progression. The purpose of this paper is to examine the research on the prevalence of PAD and CN together in DM patients.

Methods

A PubMed search was done with the keywords "Charcot Neuroarthropathy and Peripheral Arterial Disease", "Charcot Neuroarthropathy", and "Peripheral Arterial Disease." There were 453 results on the subject. Literature was systematically searched for prevalence of CN and PAD in DM patients, classifications, epidemiology, pathophysiology, and presentation for CN and PAD. There were no restrictions on publication dates and language. Reasons for exclusion for articles were nonclinical articles. The most relevant articles to the target topics resulted in 30 articles.

Charcot Neuroarthropathy

CN is a chronic and progressive disease that destroys the bone structure due to significant nerve damage and increased blood flow. It mostly occurs in the ankle or midfoot joints, but it can also be seen in the wrist, knee, hip, and spine. The main cause of CN in the developed world is diabetic polyneuropathy.[4] The presentation of CN can be distinguished into two categories: acute and chronic. In acute CN, the foot is warm, erythematous, edematous, and tender to palpation (Figure 1).[5] In chronic CN, there is a deformity, usually a rocker-bottom foot, causing abnormal pressures on the plantar surface that leads to callus formation and ulceration (Figure 2).[5] A classification system by Sanders and Frykberg is used to determine which type of lower extremity joints are affected.[6] Type I affects metatarsophalangeal joints and interphalangeal joints, type II affects tarsometatarsal joints, type III affects tarsal joints, type IV affects subtalar joints, and type V affects the calcaneus. Type II or midfoot CN is the most common presentation of CN (Figure 3).[6] The Eichenholtz classification describes the radiographic appearance of CN and is divided into 4 stages.[7] Stage 0 describes the local warmth, edematous, and erythematous foot without radiographic changes. Stage 1 describes bony fragmentation and dislocation. Stage 2 describes coalescence with new bone formation, and fragmentation. Stage 3 is the final stage which describes remodeling and the rocker-bottom deformity.

The pathogenesis of CN has not been fully understood, but there are theories as to how CN develops. The neurovascular theory states that an increase in blood supply to bone from damage to nerves causes an increase in osteoclastic activity leading to fractures and deformities.[9] The neuro-traumatic theory states that denervated joints have repetitive trauma which leads to fractures and deformities.[9] The most accepted explanation for the pathogenesis of CN is that it progresses from the combination of mechanisms in the neuro-vascular and neuro-traumatic theories.[10]

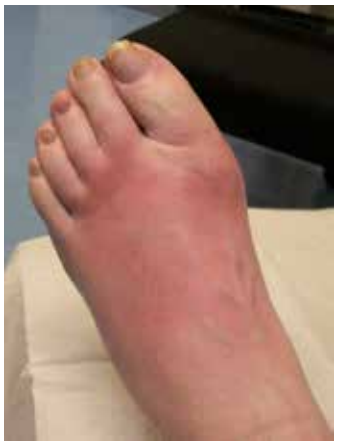

Figure 1: Acute charcot foot shows erythematous, increased warmth, and an edematous foot. Adapted from *The BMJ*.[8]

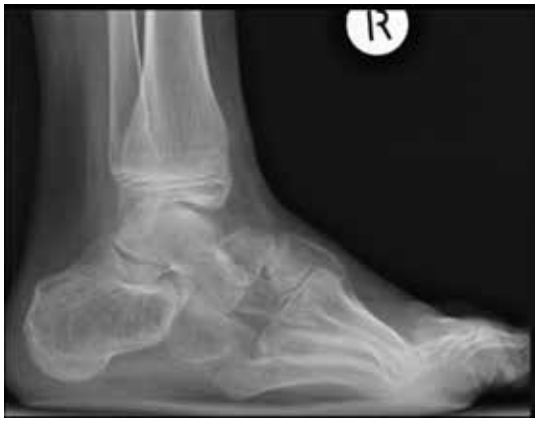

Figure 2: Chronic Charcot Foot (Stage 3, Type II) shows the rocker bottom deformity, loss of longitudinal arch, and midfoot plantar ulcer.[11] Adapted from "Rocker bottom foot." *Radiopaedia*.

Type	Localization
I	Metatarsophalangeal and interphalangeal joints
II	Tarsometatarsal articulations (Lisfranc)
III	Midtarsal joint line (Chopart)
IV	Ankle joint and subtalar joint
V	Calcaneus

Figure 3: Sanders and Frykberg classification. Adapted from Journal of Diabetes Research.[12]

Peripheral Arterial Disease

PAD is the disruption of blood flow in major systemic arteries other than the cerebral and coronary circulations. PAD can be diagnosed with ankle brachial index (ABI).[13] A normal ABI score ranges from 1.00-1.30. A reading above 1.30 signifies calcification of the arteries and an ABI less than 0.90 is 70% sensitive and 95% specific for PAD. Doppler, ultrasound (Duplex) imaging, angiography, computed tomography (CT), and magnetic resonance angiography (MRA) are also used in conjunction for the diagnosis of PAD.[14] PAD has a prevalence of 15-25% in DM patients in Western populations such as the USA and Australia.[15] The major risk factors for PAD are smoking, hypertension, hyperlipidemia, diabetes mellitus, obesity, and family history of vascular disease.[16] Symptoms of PAD are leg pain on exertion and rest, hair loss of feet and legs, intermittent claudication, impaired leg strength, and ulcerations.[15] According to the American Heart Association, there are four categories to classify PAD: asymptomatic, intermittent claudication, chronic limb ischemia, and acute limb ischemia.[16] Patients with asymptomatic PAD have 40% increased risk of stroke and MI, accounting for 50% of all PAD patients.[16] Patients with intermittent claudication experience achy pain, usually in lower extremities, that is relieved by rest, and make up 45% of all PAD patients.[16] Chronic limb ischemia in PAD is pain at rest or ulceration with or without tissue necrosis that takes 1-5 years to develop and these patients usually require amputations. Patients with chronic limb ischemia account for 2-3% of PAD patients.[16] Acute limb ischemia is increasing claudication and pain at rest with rapid onset (Figure 4). The six classic symptoms associated with acute limb ischemia are pain out of proportion, pulselessness, pallor, poikilothermia, paraesthesia and paralysis.[15] Patients with acute limb ischemia make up 1-2% of PAD patients.[16]

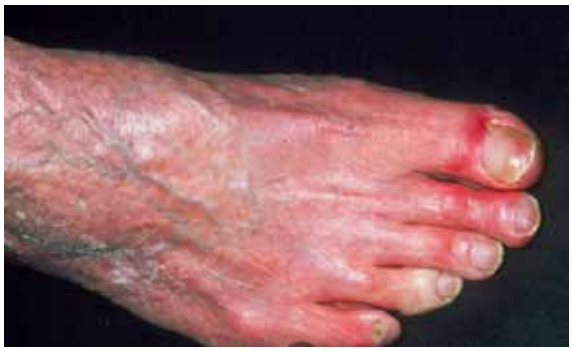

Figure 4: Foot with patient who has acute PAD shows a pale and cold 4th toe.[17] Adapted from "Occlusive Peripheral Arterial Disease." *Merck Manua*l.

The pathogenesis demonstrates that there is an overproduction of advanced glycation end-products (AGE), increased oxidative stress, enhanced inflammatory factors, and dyslipidemia.[18] This leads to sudden ischemia of arterial thrombosis and ulceration of lower extremities. DM patients with chronic inflammation and vascular damage are known to have receptors for AGE (RAGE).[18] The binding of AGE-RAGE results in production of reactive oxygen species (ROS) leading to endothelial dysfunction.[18] It also

increases proinflammatory cytokines such as ICAM-1, VCAM-1, E-selectin, IL-1a, IL-6, and TNF- α.[18] Oxidative stress occurs with activation of highly reactive molecules such as ROS and reactive nitrogen species (RNS). ROS such as O_2^- directly activates or diminishes the bioavailability of NO.[18] The expression of eNOS and NO are downregulated by proinflammatory markers such as CRP and TNF- α.[18] This leads to the development of endothelial dysfunction and atherosclerosis.[18] Poor vascular perfusion results in skeletal muscle damage which leads to ischemic leg pain, impaired calf skeletal muscle, and ischemic peripheral neuropathy.[19]

Discussion

There is substantial research that shows that PAD is less prevalent in patients with CN. The current theory regarding Charcot suggests that with the development of autonomic neuropathy, there is increased blood flow to the extremity which results in osteopenia with an increase in peripheral blood flow causing eventual osseous breakdown.[20] PAD causes significant constriction of blood vessels due to calcification of the arteries, the resulting restriction of blood vessels can have a protective factor for CN.

In measuring blood flow's response to heat, Veves and colleagues noticed Charcot patients' skin temperature was slightly higher, depicting the typical characteristic of a warm, edematous foot. They found a surprising finding with the preservation of maximal hyperemic response to heat in patients with CN with a normal transcutaneous oxygen tension ($TcPO_2$) while ischemic PAD patients had the lowest $TcPO_2$.[21] Charcot patients with normal $TcPO_2$ had a decreased incidence of PAD by 32%.[21]

The normal blood flow response and vasomotion was studied by Shapiro and colleagues. It is thought that in CN, there is sympathetic vascular denervation leading to an increase in A-V shunt flow via the arteriovenous anastomoses.[22] Shunting bypasses capillary beds and increases whole limb flow, leading to increased bone resorption as noted in Charcot joint destruction.[22] Shapiro and colleagues increased the temperature of CN patients from 35°C to 45°C and noted an increased in blood flow and vasomotion. This is significant because PAD reduces the blood flow to limbs and clinically presents as coolness in distal extremities.

A revascularization procedure such as an angioplasty is done with patients who have PAD. This restores the perfusion of blood therefore increasing temperature to lower extremities. A study done by Wukick and colleagues found that revascularization procedure have a significant effect on PAD and CN patients. They demonstrated that the prevalence of PAD is less in patients with CN and DM than patients with DM only.[1] They had 85 patients with DM and CN compared to 125 patients with only DM, 34 of the 85 CN patients had PAD compared to 73 of the 125 DM only patients.[1] They found that the need for revascularization was reduced by 82% in comparison to those with diabetes only.[1] Wukich evaluated 82 diabetic patients with foot ulcers and they found that 48% of patients with foot ulcers without CN had PAD and that 35.4% of patient had ulcerated CN.[1]

In a study by Nobrega on the incidence of acute Charcot foot in DM without PAD patients versus patients with DM and PAD, PAD was shown to be a protective factor with 5.84% of acute Charcot foot to occur in DM without PAD patients compared to 0.16% in patients with DM and PAD.[23] There is also research that shows that patients with CN are more likely to have PAD. In a study by Mancoll, there were 34 patients with CN and abnormal Doppler exams.[24] Out of the the 34 patients, 22 patients had clinically significant PAD.[24] These results show that PAD can still occur in patients with CN. A study by El Oraby, showed that patients with CN were 23% more likely to have PAD and decreased bone mineral density than patients without CN.[25]

CN and PAD are chronic debilitating diseases. Although sparing the foot is ideal, the long-term goal is functional outcome. Evaluating these studies will help clinicians to better understand which path to take to treat the patient. It will give them insight on whether to do vascular interventions and prevent ischemic events.

Conclusion

Studies show that the prevalence of PAD decreases in CN patients. There is an increase in blood flow in response to an increased temperature which is typical in CN patients. The A-V shunt flow which increases whole limb flow in CN also shows vasomotion. The normal TcPO2 is significant to this finding because their vessels are well perfused. The low TcPO2 in ischemic patients indicates poor wound healing due to decreases in blood flow. The narrowed arteries from atherosclerosis and decreased limb flow is significantly in PAD patients. Restoration is achieved with revascularization procedures which should restore limb flow and increase limb temperature. There is more data that shows PAD prevalence decreases in CN patients compared to the data that shows PAD prevalence increases in CN patients. PAD shows to have a protective effect of the development of CN because of the narrowing and obstruction of blood vessels in PAD. More studies on this topic would be ideal to obtain a better understanding of CN versus PAD. Patients with CN are at lower risk for ischemia and need for revascularization. The current consensus among medical professionals is that the hypervascularization decreases the prevalence of PAD

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Human Amniotic Membrane and Porcine Acellular Dermal Regeneration Matrix: A Review of Current Temporary Natural Skin Grafts for Diabetic Foot Ulcers

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ABSTRACT

Objective: Recently, the number of people diagnosed with diabetes mellitus has increased leading to a higher occurrence of diabetic foot ulcers. New technologies have produced a variety of skin grafts to improve the efficacy and shorten the time required for wound healing. The purpose of this paper is to analyze the performance of two types of temporary skin grafts: human amniotic membrane and porcine acellular dermal regeneration matrix.

Methods: We selected papers for our review that discussed amniotic membrane or regeneration matrix that were specific to diabetic lower extremity ulcers. All were performed in conjunction with a control such as standard wound care or topical gels. Unfortunately, there are no papers currently published that compare the two grafts directly. We analyzed the grafts with controls to understand their usage and availability in clinical practice.

Results: The amniotic membrane graft demonstrated 90% of patients had complete wound healing after standard wound care had failed in one study and a second study showed patients using the amniotic graft had statistically significant ($P<0.001$) healing compared to standard care. The acellular dermal regeneration matrix did not have statistically significant ($P=0.055$) healing compared to a becaplermin control, but another study found the regeneration matrix had significant ($P<0.05$) wound closure of lower leg ulcers compared to moist wound dressing control.

Conclusion: The studies in review show human amniotic membrane has more success in healing DFUs, but the cost and accessibility of porcine regeneration matrix is preferred. Further research is required to determine if amniotic membrane or regeneration matrix are superior and should be used in clinical settings.

Introduction

As the population of the United States has aged and become increasingly overweight over the last 20 years, the number of adult Americans diagnosed with diabetes has tripled with over 30 million Americans diagnosed with diabetes and 84 million classified as prediabetic.[1] Diabetic foot ulcers (DFUs) are a common secondary condition stemming from diabetes mellitus and are often the result of peripheral neuropathy, arterial disease, and immune system impairment. Diabetic patients have a 3-10% annual incidence of foot ulcers with a lifetime risk of 15-25% for developing a foot ulcer.[2] An uncontrolled DFU will frequently result in the development of infection, leading to hospitalization, and possible amputation of the affected area.

Skin grafts have been used to treat wounds for centuries, but their usefulness has been hampered by the unavailability of healthy skin as well as the risks associated with the harvesting procedures.[3] However, graft technology has advanced rapidly, allowing scientists to manufacture grafts and significantly increase their availability for use.[4] In some cases, skin graft therapy may be used in an attempt to increase the speed and probability of successful DFU healing. Previous testing has revealed that bi-layered human skin equivalent grafts were shown to be 2.14 times more likely to result in complete wound resolution than a saline moist gauze control.[5]

In this article, we review current literature regarding two common temporary skin grafts, human amniotic membrane and porcine acellular dermal regeneration matrix, to determine their efficacy in treating DFUs and whether more research is necessary to determine this.

Skin Substitutes

The term skin substitute refers to a diverse group of wound coverage materials intended to act as a skin replacement, either permanently or temporarily, to increase the healing prospects of what would otherwise be an open wound.[6] Temporary skin substitutes provide transient physiological wound closure, protecting the injury from physical trauma. Additionally, it creates a barrier from invasive bacteria and provides an environment conducive to granulation and epithelialization of the wound.[7]

Human amniotic membrane grafts are the first variation of temporary skin graft discussed. It is an allograft, meaning the material is derived from the tissue of another human. Human amniotic membrane has been used for wound treatment since 1910, but its usage was uncommon due to the high cost and the difficulties of obtaining, preparing, and storing the material.[7] However, recent technological advances have significantly increased its availability, storage life, and clinical efficacy. The contemporary product is formed using amniotic membrane obtained from screened donors during Cesarean section procedures. The tissue is then processed to remove blood components, dehydrated for future use, and the scaffolding is retained.[8]

The second temporary skin graft examined in this review is an acellular biomaterial created from

porcine jejunum processed to remove the cellular components, leaving only the scaffolding structure and extracellular matrix.[7] It is a xenograft, meaning the graft material has been derived from the tissues of another species. Porcine xenograft has been widely used since the 1960s and is still considered the most commonly used xenograft on the market. Its popularity is likely due to its affordability and high availability.[7]

Human Amniotic Membrane Grafts

Treatments using human amniotic membrane grafts are typically used after other conservative methods, such as wound debridement, infection control, off-loading, and hyperbaric oxygen therapy fail to heal DFUs.[9] A study by Werber and Martin examined these grafts on 20 chronic diabetic ulcer patients. The patients had ulcers on either the leg or foot for at least 12 months and were unresponsive to standard wound therapy. Standard wound therapy included conservative measures mentioned previously as well as moist dressings, antibiotics, vascular restoration, and glycemic and edema control. Over a 12-week observation period, 18 of the 20 patients (90%) had complete closure and healing of their wounds as seen in Figure 1. The other 10% did not have full wound healing. Although the results demonstrated that amniotic membrane grafts can enhance wound healing, this study did not explain if the graft alone would be more effective than traditional conservative methods.[10]

Figure 1. Progress of the DFU of one of the patients treated with a amniotic membrane graft. Wound at day 0, measuring 4.9 cm x 3.0 cm (A); wound healed at day 57 (B). Adapted from *The Journal of Foot & Ankle Surgery*.[10]

A study by Zelen et al. compared the healing attributes of human amniotic membrane grafts versus standard regiment of wound care (SOC) on DFUs. The experiment was a prospective, stratified, randomized, comparative, parallel group, non-blinded clinical trial. The 25 patients in this study had DFUs sized between 1-25 cm^2 that had persisted for greater than 4 weeks. Patients were grouped into either treatment with amniotic membrane graft (n=13) or standard wound care (n=12). SOC consisted of wound debridement, silver antimicrobial wound gel, and antimicrobial dressing. This study used a Mann–Whitney U-test with a statistical significance set at $P<0.05$ and found that patients treated with amniotic membrane grafts had higher healing rates. At the four week follow up, none of the SOC patients showed signs of healing but 10 of the 13 (77%) graft-treated patients had complete wound resolution. At six weeks, amniotic membrane graft patients again showed decreased wound size, indicating greater wound closure and healing. Of the graft patients, 12 of the 13 (92%) had healed ulcers, while only one of the 12 (8%) SOC patients had healed at six weeks.[11] These results were statistically significant ($P<0.001$). This study demonstrated that amniotic membrane grafts can be an improvement to the traditional SOC of foot ulcers.[11] Overall, amniotic membrane grafts have shown promise in healing DFUs clinically and may be a good treatment option for patients with non-healing DFUs.

Porcine Acellular Dermal Regeneration Matrix

There have been a few studies that compare regeneration matrix to control techniques. Becaplermin gel is a topical gel for DFUs that contains recombinant human platelet-derived growth factor. It was evaluated in a study with 250 DFU patients comparing the gel (n=128) to good ulcer care (n=122).[12] The occurrence of complete ulcer healing was 36% for becaplermin and 32% for good wound care, which was not statistically significant.[12] This study found that becaplermin gel was not better than standard wound care, which may support using becaplermin as a control in studies for skin substitutes.

One study by Niezgoda et al. conducted a randomized clinical trial comparing the regeneration matrix to becaplermin as a control. The study included 73 patients, all with a minimum of one DFU. The groups were divided into regeneration matrix (n=37) and becaplermin (n=36) and the patients were treated at wound care clinics for up to 12 weeks. Their wounds were cleaned, debrided, and dressed with the appropriate matrix or gel.[13] After the trial period, statistical analysis showed 18 (49%) of regeneration matrix-treated patients versus 10 (28%) of becaplermin-treated patients had complete wound closure.[13] These results were not statistically significant ($P=0.055$). Overall, the trial demonstrated that there was improved healing for the regeneration matrix at all follow-up points and the biomaterial is as effective as becaplermin in healing DFUs by 12 weeks.[13] The current standard of care for DFUs leads to 24% of ulcers healing after 12 weeks, so even though the matrix was not statistically significant, it is an improvement to conventional methods.[13]

Romanelli, Dini, and Bertone tested the porcine acellular dermal regeneration matrix on lower leg ulcers with mixed arterial and venous origins. The researchers compared the regeneration matrix with a moist wound dressing as a control.[14] The study was organized as matrix (n=25) and control (n=25). On average, regeneration matrix-treated ulcers healed in 5.4 weeks versus control in 8.3 weeks (P=0.02). An example of a wound progressing through treatment can be seen in Figure 2. Complete closure occurred in 80% of biomaterial group participants and 65% in control participants ($P<0.05$).[14] This study was not specific to DFUs, but exhibited porcine acellular dermal regeneration matrix was more effective than moist wound dressing on lower leg ulcers.

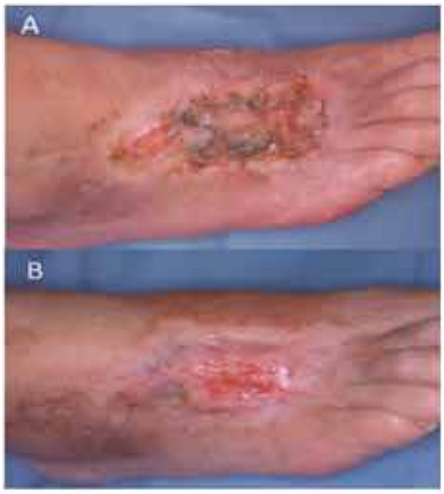

Figure 2. A mixed arterial and venous ulcer on the dorsal right foot (A) before treatment, and (B) after 4 weeks of treatment with porcine acellular dermal regeneration matrix. Adapted from *Advances in Skin & Wound Care*.[14]

Conclusion

With the research that is currently available, amniotic membrane grafts showed statistically significant improvement in DFU resolution in comparison to SOC. Porcine acellular dermal regeneration matrix trials came just short of statistically significant results when treating DFUs. Other treatments using the regeneration matrix on lower leg ulcers demonstrated statistically significant improvement over a control of a moist wound dressing.

The findings of these reviews on amniotic membrane graft and regeneration matrix suggest that future research of both grafts with larger sample sizes will be necessary to develop more concrete statistics on their efficacy in treating DFUs. There has yet to be a clinical study directly comparing the two variations of temporary skin grafts discussed in this review. Despite the recent improvements in the availability and storage life of human amniotic membrane, its price is much higher than the alternative. Until greater rates of successful DFU treatment can be demonstrated, human amniotic membrane appears nonviable in comparison to the regeneration matrix.

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Diagnostic Imaging Techniques for Plantar Fasciitis: A Review

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ABSTRACT

Objective: Heel pain is a symptom that can cause severe discomfort in young and elderly populations alike. Plantar fasciitis (PF) is a common condition associated with heel pain that affects the medial plantar aspect of the calcaneus due to stress on the plantar fascia. It is often difficult to diagnose PF because its symptoms are similar to other foot pathologies. However, a thorough history, physical examination, and the appropriate imaging modality can help to rule out confounding diagnoses. The purpose of this review is to assess the clinical utility of plain radiography, ultrasound, and magnetic resonance imaging (MRI) in order to diagnose PF. By doing so, we aim to recommend the most appropriate imaging modality to aid clinicians in diagnosing PF.

Methods: Our methods include a search of keywords such as plantar fasciitis, radiography, ultrasound, and magnetic resonance imaging (MRI) to search for peer-reviewed articles on databases such as ResearchGate, PubMed, Google Scholar, Web of Science, Academic Search Elite, and Sciencedirect. Articles published before the year of 2000 were excluded from this review. We analyzed 21 articles to determine the best imaging modality to confirm diagnosis of PF.

Results: A systematic review of various articles recommend ultrasound as the ideal method to confirm suspected cases of PF that does not respond to conventional treatment methods.

Conclusion: Ultrasound should be the gold standard to confirm diagnosis of PF because it is free of ionizing radiation, readily available, and cost-effective compared to plain radiography and MRI.

Introduction

The plantar fascia, commonly referred to as the plantar aponeurosis (PA), is a tough layer of fibrous tissue located on the plantar surface of the foot just beneath the skin (Figure 1). It extends from the medial tuberosity of the calcaneus and runs anteriorly to insert onto the deep transverse metatarsal ligament. As it extends towards the toes, it divides into five separate bands at the metatarsophalangeal joints that connect to the proximal phalanges. The PA predominantly consists of longitudinally-oriented collagen fibers that can be divided into three distinct parts: medial, central, and lateral. The central part is the thickest and largest section of the PA, running in between the relatively thinner medial and lateral parts.[2]

The PA plays an important role in both the stabilization of the longitudinal arch of the foot and during gait. Studies have demonstrated that the PA stiffens both the medial and lateral arches of the foot so that upon toe-off, the vertical loading forces acting on the foot only produce a slight amount of longitudinal arch deformation and flattening.[5] This concept is referred to as the windlass mechanism. During gait, the toes dorsiflex which causes the PA to elongate, thereby increasing tension on the medial longitudinal arch and
decreasing the distance between the calcaneus and metatarsals. This increased tension is critical during toe-off because it acts to pull the arch together, as well as raise and stabilize the foot. In turn, the subtalar joint

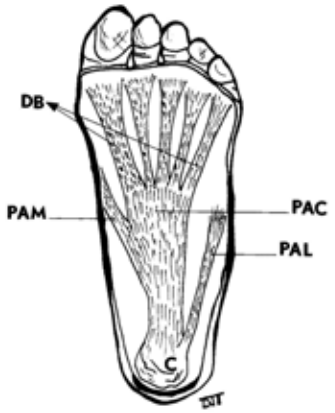

Figure 1: Schematic of the PA, where *C* = calcaneus, *DB* = digital bands of PA, *PAC* = PA central component, *PAL* = PA lateral component, *PAM* = PA medial component. Adapted from American Journal of Roentgenology.[4]

supinates the foot and transforms it into a rigid lever needed for propulsion.[6] The PA also plays a passive role in shock absorption of the foot. Therefore, damage to the PA has many biomechanical implications leading to tissue stress and heel pain.[2] One of the most common causes of heel pain is plantar fasciitis (PF) which affects approximately two million patients annually.[2] There are two types of PF - acute and chronic. Acute PF is characterized by a sharp pain that worsens with the first step after prolonged rest and is amplified with weight-bearing movement. In contrast, chronic PF typically lasts for more than six months and is characterized by a constant, aching pain.[7] Normal wear-and-tear and excessive pressure on the PA may result in inflammation and heel pain, but the causes of PF are

Characteristic of Plantar Fasciitis

	Plain radiography	Ultrasound	Magnetic resonance imaging
Plantar fasciitis	• PF thickening • Narrowed/ absent fat pad deep below the PF • Cortical changes (sclerosis/ lucency and loss of smooth contour) at the PF calcaneal attachment • Calcaneal spurs within the PF	• PF thickening • Loss of fibrillar structure • Perifascial fluid collections • Calcifications within the PF • Hyperemia in the PF/ • perifascial soft tissues • (Doppler imaging) • Reduced PF elasticity (elastosonography)	• PF thickening • Intrasubstance areas of immediate T1/ high T2 signal • Edema in the adjacent soft tissues • Bone marrow edema at the PF calcaneal attachment
Plantar fasciitis Band Thickness	> 4.0 - 5.0 mm	3.0- 7.0 mm	> 5 mm

Table 1: Pathognomonic features of PF as shown on plain radiography, ultrasound, and MRI. Adapted from Insights into Imaging.[8]

multifactorial. Structural risk factors include pes cavus, pes planus, leg-length discrepancy, excessive lateral tibial torsion, and excessive femoral anteversion. Systemic risk factors include rheumatoid conditions such as rheumatoid arthritis and gout.[9] Populations at greater risk for developing PF are females, athletes, seniors, and obese individuals.

Physical Examination

Clinicians can propose several differential diagnoses for heel pain; therefore, it is important to conduct a comprehensive history and physical exam to confirm a diagnosis of PF. In PF, palpation of the medial aspect of the calcaneal tuberosity and dorsiflexion of the foot and toes causes the patient to feel pain and discomfort. Patients also endure significant amount of pain with their first step after a prolonged resting period. If the sharp pain continues with rest and weight bearing activities, the patient most likely suffers from calcaneal stress fractures. Swelling or ecchymosis may be obvious, but the patient will most likely have a positive calcaneal squeeze test because the pain can be recreated from squeezing the medial and lateral aspects of the calcaneus. On the other hand, heel pad disorders can have a similar effect, but patients usually bear pain on the weight bearing portion of the calcaneus. Furthermore, heel pad pain cannot be reproduced when dorsiflexing the toes or foot. [1] However, if the patient presents with burning and tingling sensations, neurological conditions should be considered in the differential diagnosis.[10] Nerve entrapments usually cause unilateral pain. If the patient presents with severe burning or tingling sensations with a painful lump on the proximal midfoot, the most likely diagnosis is neuroma, a benign growth of a nerve.[1] A variety of imaging techniques can be used to aid in the diagnosis of PF or to rule out other heel pathologies.These imaging techniques include radiography, ultrasound, and MRI. Table 1 summarizes different features of PF as seen on these imaging modalities.

Plain Radiography

Plain radiography is a standard imaging technique known for its ability to visualize bone. It is produced by electromagnetic radiation that can penetrate skin due to its high energy. The radiograph produced is of varying intensity due to the densities of the structures being visualized. Bone appears to be more radiopaque whereas soft tissue is more radiolucent. Overall, plain radiography is a commonly used diagnostic imaging technique because it is widespread and cost-effective.

Conventional radiographs can detect a variety of factors suggestive of PF. For example, PA thickness can be measured with accuracy on a lateral radiograph of the ankle and foot. Studies have determined that the average PA thickness at its calcaneal origin is 4.0 mm. A measurement greater than 4-5 mm, within 5 mm of its calcaneal attachment of the PA on a lateral radiograph, is suggestive of individuals with PF.[8] Deep to the PA is a triangular-shaped fat pad that is absent in

individuals with PF due to mechanical and inflammatory mechanisms (Figure 2). Studies have shown that a combination of PA thickness greater than 4 mm and fat pad abnormalities resulted in the best group differentiation ($p < 0.0001$) with sensitivity of 85% and specificity of 95% for PF. According to Osborne et al., 106 (27 PF and 79 controls) plain non-weight bearing lateral radiographs were examined to document the key features of X-rays between individuals with and without PF. It was concluded that the key radiological features that confirm the diagnosis of PF are changes in soft tissues, as calcaneal spurs were observed in both groups.[12]

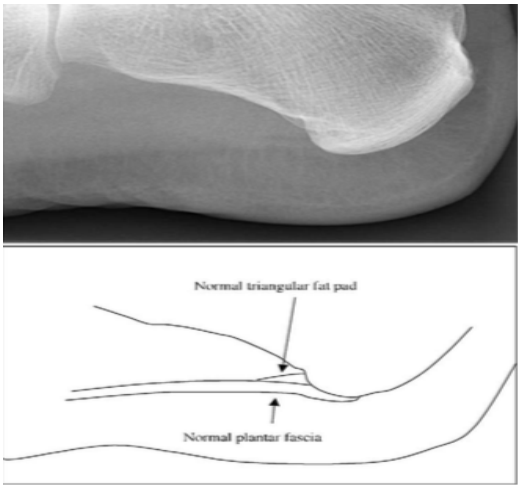

Figure 2: Lateral plain x-ray and schematic diagram of a normal PA and triangular fat pad. Adapted from Journal of Science and Medicine in Sport.[8]

Plantar Calcaneal Spurs

Radiographic films allow for visualizing bony features, making them a good option for identifying plantar calcaneal spurs known as enthesophytes.[8] Spurs occur as a result of excessive repetitive traction, leading to microtrauma of tissues and eventually periostitis and ossification. Risk factors include obesity, diabetes, acromegaly, and diffuse idiopathic skeletal hyperostosis.[10] The significance of plantar calcaneal spurs and other bony calcifications as a cause of PF have received notable attention as they become symptomatic in the setting of plantar heel pad atrophy. However, their importance in the diagnosis of PF is not supported as they can occur in asymptomatic individuals.[13] Calcaneal spurs associated with PF include those located within the PA, an uncommon occurrence. The most common site of plantar calcaneal spurs is the insertion point of the abductor hallucis and flexor digitorum brevis further dorsal to the PA.[8] Although calcaneal spurs can be visualized on radiographs, it is typically disregarded as a pathognomonic sign of PF.

Ultrasound

According to Drs. Hsu and Manekar, ultrasound uses a transducer to emit a high- or low-frequency sound wave to a medium and it collects the returning sound waves to produce a digital image. They also state that low frequencies can travel deep into tissues and produce images with low resolution; higher frequencies cannot travel far and therefore produce high resolution images.[11]

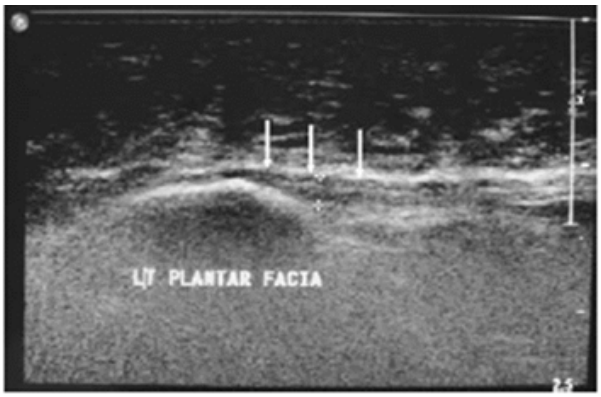

Figure 3: Sagittal ultrasound image of the PA from the study by Anwar et al. Long arrows demonstrate normal thickness of the PA (0.189 mm) and fibrillar echogenicity. Adapted from International Journal of Rheumatic Diseases.[9]

High resolution ultrasonography is an imaging modality that can be utilized to confirm a clinical diagnosis of PF. As seen on Table 1, the most common morphological characteristics of PF include PF thickening, loss of fibrillar structure, calcifications within PF, and fluid collections. According to Anwar et al., asymptomatic patients revealed normal thickness of the PA (0.189 mm) with fibrillar echogenicity (Figure 3). Ultrasound examination of those with PF revealed increased thickness (3.0 – 7.0 mm; 4.9 ± 1.3), hypoechoic sites, and few ruptures of the PA. Excess of fluid collections were evident around the PA and soft tissues of some symptomatic heels, but calcifications were not detected (Figure 4). In this study, diagnostic accuracy of assessing thickness was 73.9%, PA rupture was 69.5%, and fluid collections was 78.2%. This led to the conclusion that differentiating characteristics of PF can be clearly visualized using high resolution ultrasonography. Therefore, clinicians can rely on this imaging technique as the first method to confirm suspected cases of PF.[9]

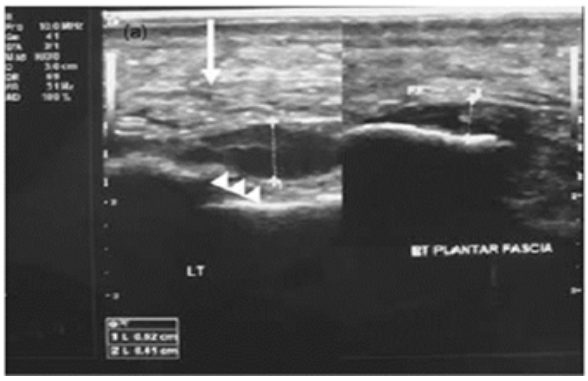

Figure 4: Sagittal ultrasound image of a patient with bilateral PF from the study by Anwar et al. Long arrow shows thickening of the left PA to be 0.57 cm, right PA to be 0.41 cm, irregular echogenicity, and subcutaneous edema. Arrowheads represent fiber ruptures due to fluid collections on the left PA. Adapted from International Journal of Rheumatic Diseases.[9]

In a study conducted by Lee et al., ultrasound elastography was compared to B mode imaging for early diagnosis of PF because most common morphological changes are not always obvious in the early stages of PF. [14] According to Dr. Kevin Martin, B mode imaging produces a cross-sectional image which represent normal and scattered ultrasound echoes reflected from tissue boundaries.[15] Similarly, Kapoor et al. and Lee et al. stated that elastography uses sound waves to examine tissue stiffness by taking advantage of elastic properties of biological tissues.[14,16] According to Table 1, one of the common features of PF include reduced PF elasticity. In this study, B mode imaging did not show a significant difference of thickness of the PA between patient and control groups (*p-value* = 0.124 where $p < 0.05$ *is considered significant*). However, ultrasound elastography showed significant softening of the PA in the patient group when compared to the control group (*p-value* = 0.027). For example, Figure 5 shows normal characteristics of the PA seen on B mode imaging and characteristics of PF on ultrasound elastography. The results from this study suggested that patients develop abnormalities seen in ultrasound elastography first before the abnormalities seen in B mode imaging.[14] Therefore, Lee et al. concluded that ultrasound elastography is a useful imaging modality to detect early development of PF based on changes in the mechanical properties of the PF.[14]

Hyperemia in the PF is another US feature of PF (Table 1). Mcmillan et al. investigated the presence and absence of hyperemia in the PA using Doppler ultrasonography. This technique was utilized to look at the frequency of ultrasound pulse given off from moving objects that is different from the original transmission. Power Doppler ultrasound was conducted by analyzing the power of frequency shifts based on the concentrations of moving objects. Results showed that 8 out of 30 participants in the study group and 2 out of 30 participants in the control group displayed hyperemia on ultrasound images. Mcmillan et al. stated that the difference between the two groups were statistically significant (*p-value* = 0.03). Therefore, mild hyperemia is possible in some patients with PF. Doppler ultrasound should not be used for diagnosis but may help to improve personalized treatment plans for individual patients.[17]

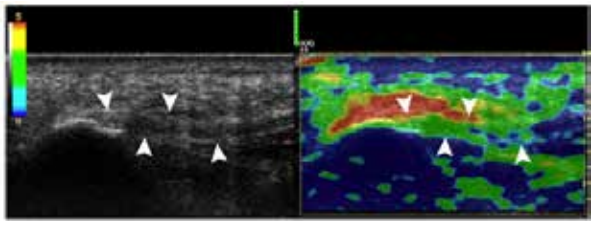

Figure 5: PA of a patient with pain on her left heel from the study by Lee et al. On the left B mode image, the arrowheads represent features of a normal PA. On the right ultrasound elastography image, the arrowheads and green areas represent softening of the PA. Adapted from Journal of Clinical Imaging.[14]

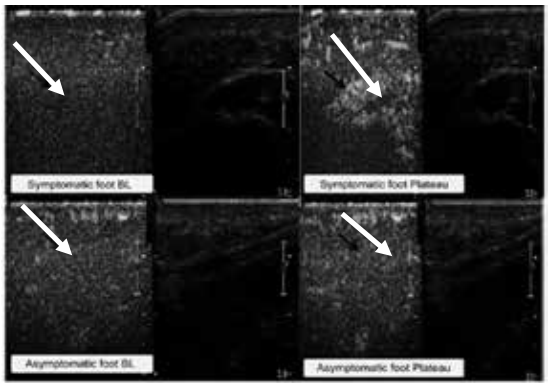

Figure 6: Contrast-enhanced ultrasound image of a symptomatic and asymptomatic PA indicated by the black arrows from Broholm et al. Left column images were taken before injecting contrast agent and right column images were taken after injecting contrast agent. Adapted from Scandinavian Journal of Medicine.[18]

In a study by Broholm et al., contrast enhanced ultrasound was performed to feature microvascular changes in painful PA because power Doppler ultrasound revealed mild hyperemia in only a small number of symptomatic heels. This technique utilized 5 mL of intravenous injection filled with contrast agent and a flush of saline solution. The results revealed significant changes in the microvasculature of the PA at its insertion in the patient group (*p-value* = 0.006) which can be seen in Figure 6. At its distal site, there were significant changes in microvasculature along with a spindle-

shaped thickening when compared to the control group (*p-value* = 0.04). There was also a significant increase in the microvasculature in the fat pad of the patient group (*p-value* = 0.007). Therefore, contrast-enhanced ultrasound is a reliable method to assess the microvasculature of the PA and fat pad. Broholm et al. concluded that this is a valuable modality to obtain an accurate diagnosis and track the progression of recovery from PF, due to its sensitivity to changes in microvasculature.[18]

Magnetic Resonance Imaging

In a study by Theodorou et al., magnetic resonance imaging (MRI) uses a strong magnetic field and radio waves to provide a clear outline of the gross anatomy of the foot (Figure 7).[19] The plane in which clinicians take MR images depends on where the pain is located. The coronal plane is best suited for portraying the trifurcation of the PA into the central, medial, and lateral components. The sagittal plane is excellent at demonstrating the extent and anatomic integrity of the PA such as the central band of the PA, the dorsoplantar PA thickness, and the perifascial soft tissues. Although both lateral and medial components of the PA can be seen on the coronal and sagittal images, the sagittal lateral oblique plane provides the best angle for the lateral component of the PA. Aside from determining the plane of the image, clinicians have to choose between T1- and T2-weighted MR images. Even though both types of MRI can show all three bands of the PA, the T1-weighted MR image provides a better visualization of bones and soft tissues than T2-weighted MR images.[19] T1-weighted images can strikingly delineate the PA as a uniform, hypointense, and bandlike structure with low signal intensity, the heel fat pad appears as high signal intensity, and the intrinsic foot muscles as intermediate signal intensity.[19]

On an MR image, the normal PA appears to be 2-4 mm thick and hypointense on both T1- and T2-weighted sequences. In contrast, frequent findings of PF included PA thickening, increased signal intensity on T1-weighted images within the PA, and increased signal intensity on T2-weighted images within the PA and adjacent subcutaneous tissue.[19] According to Grasel et al., patients with thickening of the PA greater than 5 mm were more likely to require surgical intervention (Table 1). The low signal intensity regions on T1-weighted images and high signal intensity regions on T2-weighted images and short-tau inversion recovery (STIR) images are indications of bone abnormality or marrow edema within the calcaneus at the site of PA insertion (Figure 8).[20]

MRI can be used in determining the characteristics and confirming the clinical diagnosis of PF. In a retrospective study, Fazal et al. analyzed 141 MRI scans of patients who were already diagnosed with PF and found that 20.7% of the cases were false positives and 1.3% of cases were misdiagnosed. In these misdiagnosed cases, they found that the clinical diagnoses were made solely on the results of the physical examination with no indication of using any type of imaging modality. Their results suggest clinical assessment itself is not sufficient in diagnosing heel pain and instead, they recommend clinicians to obtain an ultrasound or MRI to confirm diagnosis of PF.[22]

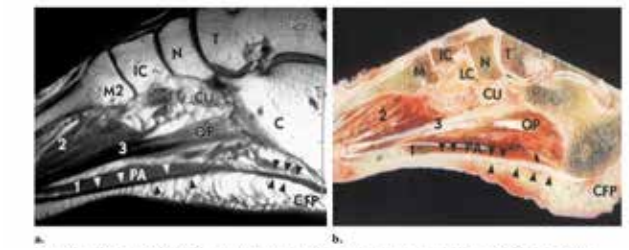

Figure 7: Correlation of MR imaging with gross anatomic findings in the cadaveric PA and perifascial tissues. Arrowheads = PA, C = calcaneus, CFP = calcaneal fat pad. Adapted from RadioGraphics.[19]

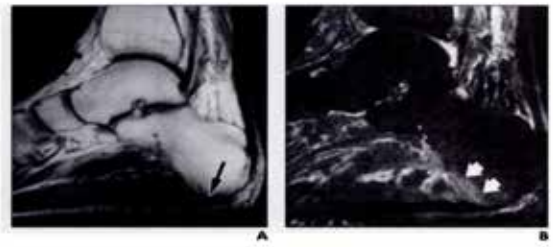

Figure 8: (A) Sagittal T1-weighted image (arrows) PA thickening. (B) Sagittal fast STIR image (arrowheads) reveals marrow signal abnormality at calcaneal insertion of PA. Adapted from American Journal of Roentgenology.[21]

Discussion

Although it is common practice to order a lateral radiograph of the foot to aid in the diagnosis of a patient's heel pain due to osseous abnormalities, it is of limited use in the initial evaluation of those presenting with non-traumatic heel pain as the presence of a spur does not necessarily indicate PF. Plain radiographs should be reserved for those who either present with an unusual history and physical examination or do not respond to routine treatment.[8,12] Furthermore, on plain radiography, the PA's overall structure is not well-defined as stated by Jeswani et al.[10] According to Drahgi et al.,measurement of the PA must be significantly greater than 4-5 mm on a plain radiograph to confirm diagnosis of PF thereby making it unreliable.[8] MRI is

not the best method to confirm diagnosis of PF because it is expensive and less accessible compared to other diagnostic imaging modalities. Therefore, it is more clinically sensible to use ultrasound over MRI because MRI creates a greater economic burden to patients and the healthcare system.

According to Anwar et al. and Nakhaee et al., ultrasound is a widely used imaging tool because of its numerous advantages. Ultrasound is easily accessible, portable, inexpensive, painless, and free of ionizing radiation.[3,9] It provides comprehensive, real-time visualization of the microanatomical features of tendons, ligaments, and muscles which assists in pinpointing the source of PF-causing symptoms.[9] Ultrasound images can also be utilized to obtain biopsies, perform treatment plans, and assess the effectiveness of different types of therapeutic interventions for different pathological conditions including PF.[3,9] Therefore ultrasound is a valuable imaging modality that can sharpen therapeutic interventions and prevent misdiagnosis of heel pain.[3,9] Although ultrasound provides the most optimal visualization of the PA, further studies are needed to compare the sensitivity and specificity of ultrasound, MRI, and plan radiography to aid clinicians in choosing the most appropriate modality of diagnosing PF.

Conclusion

While a complete medical history and physical examination can be indicative of PF, diagnostic imaging modalities are essential to eliminate confounding differentials of heel pain including heel pad disorders, calcaneal stress fractures, and neurological conditions. Radiographic examination of the foot lacks the clinical utility needed for the diagnosis of PF as it only provides a basic visualization of the PA. Per Chimutengwende-Gordon et al., MRI provides a better depiction of the PA than plain radiography but MRI is only necessary in cases of persistent heel pain following treatment of PF.[23] On the other hand, Anwar et al. and Lee et al. recommend high resolution ultrasound and ultrasound elastography, respectively, because of numerous benefits such as being inexpensive, non-invasive, and highly accessible. Additionally, Nakhaee et al. states other significant benefits of ultrasound such as its use in treatment plans and its ability to assist clinicians in tracking the progress of those treatment plans.[3,9] Although each diagnostic imaging modality has their unique advantages, ultrasound should be considered as the first option due to its overall efficiency and accuracy.

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The Accuracy of Point-Of-Care Ultrasound in Diagnosing Long Bone Fractures as Compared to Plain Film Radiographs: A Systematic Review and Meta-Analysis

Melissa Mueller, B.A., Brianna Beaver, B.S., Kyleigh Gaylord, B.S.

ABSTRACT

Objective: Trauma, particularly with suspected fracture of lower extremity long bones, is a common presentation of patients in the Emergency Department (ED). Radiographs are frequently performed in the ED for evaluation and diagnosis of these injuries. However, the World Health Organization estimates that up to 75% of the world population does not have access to radiographs or other imaging modalities such as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) to make a diagnosis. Point-of-care ultrasound (PoCUS) is an excellent solution to this problem because of its affordability, portability, and accessibility, even in rural settings. Furthermore, PoCUS is rapid, non-invasive, cost-effective, and does not cause exposure to ionizing radiation like plain film radiographs do. This paper attempts to fully assess the capability of using PoCUS in diagnosis of long bone fractures when compared to plain film radiographs.

Methods: A systematic literature review of recent random controlled trials and meta-analysis regarding the use of PoCUS v plain film radiographs in diagnosing long bone fractures was performed.

Results: Thorough analysis of nine studies revealed PoCUS is as accurate in diagnosing long bone fractures as compared to plain film radiographs.

Conclusion: It can be concluded that PoCUS is a capable diagnostic method for long bone fractures.

Introduction

Long bone fractures are one of the most frequently obtained injuries after a trauma and account for almost 4% of ED visits in the United States every year.[1] In 2013, the Centers for Disease Control and Prevention found that fractures made up more than 3.8 million ED visits in the United States and are expected to cost an estimated $35 billion by the year 2025.[2] With the prevalence of this issue, the importance of an accurate diagnostic measure is necessary. This importance is highlighted due to the nature of these injuries which can include risk of bleeding, neurovascular compromise, loss of limb, and even death.[1] Although the current standard of care involves diagnostics with plain film radiography, this has its limitations. Radiographs cause exposure to ionizing radiation, which can lead to cancer when prolonged.[1] PoCUS has many advantages including portability, safety, repeatability, and affordability. Its advantages have caused ultrasound to be used in emergent diagnostic protocols including FASTER protocol (Focused Assessment Sonography in Trauma with Extremity and Respiratory Evaluation) for trauma and CAVEAT protocol (Chest, Abdomen, Vena Cava, and Extremities for Acute Triage) for mass casualty incidents, both of which involve screening for extremity fractures.[3,4]

Prior to the decision to use PoCUS for the evaluation of long bone fracture, physical exam findings indicating long bone fracture, or a suspicious history, should be observed and/or reported. Hematoma and soft tissue swelling are often seen as indirect evidence around fracture sites,[3] in addition to tenderness or pain on palpation or percussion of the bone. Ecchymosis, crepitus, obvious deformity, or neurovascular injury may also occur.[5] A patient may additionally present with inability to bear weight or abnormal range of motion of the affected limb.

Diagnosis of fracture on ultrasound is made due to certain characteristic findings. The step-off sign, a displacement of two normally aligned parts of bone, is seen on ultrasound on the hyperechoic cortical surface of bone (Image C, Figure 1). The presence of cortical disruption is a defining sign for fracture diagnosis.[3,5] Distance of the step off, angulation of the fracture, extent of fracture into the joint space, and reverberating echo are other findings that can determine the severity of the deformity.[2,5] Extension of a fracture into a joint space can show an elevated fat pad, surrounding subperiosteal hematoma, and hemarthrosis on PoCUS.[2,3] The diagnostic findings of fracture on PoCUS can furthermore be used to determine the treatment plan and process of fracture healing.

Methods

A systematic literature review of studies published from December 2008 to January 2018 comparing the use of PoCUS and plain film radiographs in diagnosing long bone fractures was performed. The following search terms were used: PoCUS in long bone fracture, PoCUS versus radiographs in fracture, and PoCUS versus radiographs in fracture. Only studies involving a direct comparison of ultrasound and radiographs were used. Additionally, only studies involving a

majority of measures of long bones were used. Nine studies were selected for inclusion in this review.

Results

Nine studies assessing the use of PoCUS compared to plain film radiographs in diagnosing long bone fracture met selection criteria. The sensitivity and specificity of PoCUS was determined by using plain radiography as the gold standard of fracture diagnosis. It was revealed that PoCUS is a useful and efficacious method of diagnosing long bone fractures when compared to radiography by eight of the nine studies.[1, 5, 6, 8, 9, 10, 11, 12] The ninth study found that although ultrasound is useful for minor fractures, it has a low diagnostic value of widespread fractures when compared to radiography.[7]

In 2010, Weinberg et al. performed a cohort study of patients under 25 years old who needed radiographs for suspected fracture in the ED. Pediatric emergency physicians who received one hour of PoCUS training to detect fracture performed PoCUS on the 212 patients with 348 suspected fractures. Radiographs or CT scans were also performed to have a comparison for the PoCUS diagnostics. Of the 348 suspected fractures, 58% of these were of long bones. There was a prevalence rate of fracture of 24%. It was found that the use of PoCUS in diagnosing long bone fracture was 73% sensitive and 92% specific. Overall, it was determined that the accuracy of PoCUS was highest at the diaphyses of long bones, while most of the errors in diagnosing fracture was and the end of bone or near a joint. Weinberg et al. concluded that PoCUS can be used as an alternative diagnostic measure to radiographs to diagnose midshaft fractures.[6]

In 2013, Waterbrook et al. performed a single-blinded, prospective observational study of patients who presented to the ED with long bone trauma. PoCUS was used to evaluate the injury to long bones and radiographs were taken after the PoCUS. While the PoCUS was interpreted by the emergency physician, the radiographs were interpreted by a radiologist. Of the 106 patients, 147 long bone PoCUS studies were completed. It was found that there was a 29% prevalence rate of fracture with 42 fractures being found on plain film radiograph. PoCUS had a sensitivity rate of 90.2% and a specificity rate of 96.1% compared to plain film radiographs. It was found that false positives occur most often when there was underlying reactive arthritis or when the ends of bones were examined. Waterbrook et al. concluded that long bone fractures can accurately be measured in the ED with PoCUS and can be excluded with a high degree of confidence.[8]

A study by Kozaci et al. in 2017 performed a prospective study that examined the use of PoCUS versus radiography in the diagnosis of tibia and fibula fractures. Patients in the ED who had a suspected lower leg fracture were evaluated with both PoCUS and plain film radiography. This study enrolled 62 patients. It was found that radiography discovered tibia fractures in 21 patients and PoCUS found tibia fractures in 24 patients. Fibula fractures were found by radiography in 24 patients and by PoCUS in 25 patients. Overall this study found PoCUS had 100% sensitivity and 93% specificity in diagnosing tibia fractures and 100% sensitivity and 97% specificity in fibula fractures. It was therefore concluded that PoCUS is just as efficient in diagnosing both tibia and fibula fractures as radiography. In addition, Kozaci et al. found that fissure-type fractures, fractures near the end of the bone extending to the joint space, and those containing the epiphyseal line were easily identified.[5]

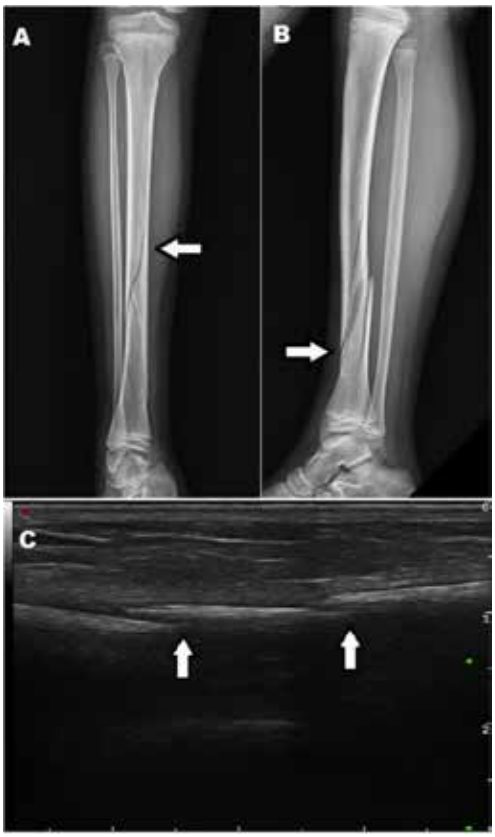

Figure 1. Circular tibial fracture as seen in Xray (A,B) and PoCUS (C). (Adapted from Injury)[5]

Ekinci et al. performed a study in 2013 that evaluated the use of PoCUS in diagnosing foot and ankle fractures in the ED. They evaluated patients over 16 years old with positive Ottawa Ankle Rules with

PoCUS first, followed by radiographic imaging. The study involved 131 patients, 20 of which were found to have fractures on plain film radiograph. All of these fractures were found on PoCUS, and one patient was found to have a silent fracture on PoCUS that was not discovered on radiograph. Ekinci et al. found that PoCUS was 100% sensitive and 99.1% specific in evaluating ankle and foot fractures. They concluded that PoCUS can be successfully used to diagnose foot and ankle fractures with high confidence.[10]

In 2011, a prospective study by Sinha et al. examined trauma patients in the ED who received both PoCUS and radiographs for their upper and lower limb injuries. The physicians who performed the ultrasound examinations received a brief training to detect fractures. Of the 133 patients in the study, 42 were found to have fractures. 36 fractures were found by PoCUS, making the sensitivity 85.7% and the specificity 100%. Plain film radiograph detected 6 additional fractures that were not detected on ultrasound. Sinha et al. concluded that PoCUS can be used by emergency physicians who have received training to identify long bone fractures. The 6 missed fractures were around the elbow and knee joints, indicating that PoCUS may be more limited with near-joint or end-of-bone fractures; however, the small sample size limits the ability to fully make this distinction.[11]

Patel et al. in 2009 examined the use of PoCUS versus radiography in identifying long bone fractures in pediatric patient populations. The study included 33 patients aged under 18 years old who presented to the ED with long bone trauma. Ultrasonography was performed prior to radiographs. Of the 66 bones examined, fractures were found in 59.1% of bones. Patel et al. stated that bedside ultrasound and radiography agreed with fracture diagnoses at a rate of 95.5%, making the sensitivity and specificity 97% and 100% respectively. They concluded that PoCUS can be effectively comparable to radiography in the diagnosis of fractures of long bones, as well as determining the need and adequacy of reduction. This study was restricted due to the small sample size, which did not include a wide variety of different locations of fractures. Therefore, the study states that further investigation of lower extremity, growth plate, and joint injuries are necessary.[12]

An additional pediatric study was performed by Barata et al. in 2012. It was a prospective study that evaluated the use of PoCUS versus radiography in diagnosing long bone fractures of pediatric patients. In this study, 53 patients under the age of 18, who presented to the ED with at least 1 suspected long bone fracture. PoCUS was performed by an investigator who received ultrasound training for fracture diagnostics, in which 43 fractures were discovered. It was found that PoCUS sensitivity and specificity was 95.3% and 85.5% respectively. Barata et al. determined that ultrasound successfully detected 100% of diaphyseal fractures and 93.1% of end-of-bone or near-joint fractures, which made PoCUS more accurate in diaphyseal diagnoses than metaphyseal/epiphyseal.[1]

In 2013, Bolandparvaz et al. compared the accuracy of PoCUS versus radiography in screening for long bone fractures in the ED. In this study, 80 trauma patients received both bedside ultrasound and radiography. The findings of both diagnostic tests were assessed blindly by two radiologists. It was found that PoCUS sensitivity in diagnosing lower limb long bone fracture was 75%, depending on the fracture site, and the specificity was 72%. However, for upper limb long bone fractures the sensitivity and specificity was 75% and 55%, respectively. Bolandparvaz et al. therefore concluded that ultrasound cannot be considered as an alternative for radiography due to its low diagnostic value. They do state that although radiography is better for diagnosing widespread fractures, ultrasound is more efficient at diagnosing minor fractures and fractures that would have been otherwise undiagnosed by plain film radiographs. This study was restricted due to the subjects being in critical care and follow-up for false positive ultrasound results was not possible.[7]

Discussion

Eight of the nine studies reviewed concluded that PoCUS can be effective in diagnosing long bone fractures as compared to radiography.[1, 5, 6 8, 9, 10, 11, 12] The long bones examined in each study varied from upper extremity to lower extremity, including tibia, fibula, and metatarsals. Due to the emergent nature of the patients who were enrolled in these studies, they were not matched for gender, race, level of activity, or mechanism of injury. Two of the studies featured in this review focused solely on pediatric patients, while others included patients of all ages. In all of the studies, PoCUS was compared to radiography. Most of the studies involved an emergency physician who performed and interpreted the PoCUS, while the radiographs were interpreted by radiologists or orthopedic specialists. Different physicians reading PoCUS versus radiographs is realistic to a real-world ED setting; however, some may find that this would cause varying subjectivity in the reading of each diagnostic test. One of the examined studies stated that radiologists interpreted both the PoCUS and radiography findings.[7] This study was also incidentally the only study that did not recommend

PoCUS as a comparable diagnostic measure for long bone fracture than radiography. While the ninth study found that ultrasound can be used to diagnose minor fractures and fractures that would have been otherwise undiagnosed by plain film radiographs, it was found to have a low diagnostic value in the diagnosis of widespread fractures as compared to radiography.[7]

Some of the reviewed studies indicated that when an error was made in using PoCUS to diagnose a fracture, it was usually when a fracture was near the end of the bone. [1, 6,]. Barata et al. found that PoCUS successfully diagnosed 100% of diaphyseal fractures, but only 93.1% of end-of-bone or near-joint fractures. This discrepancy indicates that PoCUS is less accurate in diagnosing end-of-bone fractures.[1] Weinberg et al. also found that most of the errors in diagnosing fractures with PoCUS were at the end of bones.[6] Kozaci et al. found that PoCUS made diagnosing fissure-type fractures and fractures near the ends of bones extending into the joint spaces easier; however, they do note that this finding could have been influenced by the small sample size.[7]

It is notable that in three of the studies, the mention of a brief training for emergency physicians on long bone fracture diagnosis using PoCUS was done prior to the study.[1, 6, 11] Barata et al. describes the training as a brief didactic lesson with a video review.[1] Weinberg et al. describe the training session as being one hour long.[6] Sinha et al. stated that the examiners received a one day didactic session along with a hands-on training session specifically to diagnose fractures.[11] However, due to the other five studies reviewed that determined PoCUS can be successful in comparison to radiography when diagnosing long bone fractures, without mention of a brief training, it is difficult to say whether this training leads to a better ability to make long bone fracture diagnoses on PoCUS. Haas et al. determined that medical students who receive PoCUS training in diagnosing fractured chicken bones have statistically significant improvement in identification of fractures after receiving training.[13] They additionally report higher confidence. Eight weeks after training, the results of significant improvement in identification of fractures and diagnostic confidence are still present, indicating learning retention.[13] These results and training method could be repeated in real world populations, particularly when studying long bone fracture diagnosis using PoCUS versus radiography, to standardize the previously discussed brief training session.

Conclusion

Overall, this review found eight of nine studies determined that PoCUS can be as effective in diagnosing long bone fractures as compared to traditional radiography. The data provided in each study in this review is not fully matched regarding each patient's gender, age, race, level of activity, mechanism of action of injury, or specific site of injury. These factors should be considered when further studies of the efficacy of PoCUS are performed. Regardless of the lack of patient matching in the studies reviewed, the potential for this technique to be utilized extensively in the emergency department setting is present. In addition to the findings of this literature review, PoCUS is already known to be cost-effective, non-irradiating, and easily available,[2,3] making it an efficient method of diagnosing that could be used in parts of the world with limited access to imaging modalities. Further studies could be done on the standardization of PoCUS physician training in making a long bone fracture diagnosis to determine how much training is sufficient. Although using PoCUS has not become standard practice, there is more research being done on its use and efficiency, hopefully leading to emergency physicians using it more consistently in the future.

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Systematic Review on Ultrasound Guidance for Plantar Fascia Injections

Sahar Gholam, B.S., Brandon Maijala, B.S.

ABSTRACT

Objective: The objective of this article is to present a review of the current literature on ultrasound-guided corticosteroid injection reliability and effectiveness for patients suffering from plantar fasciitis compared to non-ultrasound guided injections.

Methods: EBSCOhost search engine utilized with terms including "sonography", "plantar fascia", and "corticosteroid injections".

Results: The increased visibility of ultrasound has the potential to be more effective at treating plantar fasciitis, with all studies showing equal or better results after treatment with ultrasound guided injections.

Conclusion: In conclusion, the literature shows that ultrasound guided injections are just as reliable and effective as non-ultrasound guided injections and possibly even more effective at treating plantar fasciitis.

Introduction

Approximately 10% of the United States population experiences bouts of heel pain, which results in 1 million visits per year to medical professionals for treatment of plantar fasciitis.[1] It is roughly estimated that 1 in 10 people will develop plantar fasciitis during their lifetime. Plantar fasciitis is more common in middle-aged females and young male athletes and has a higher incidence in the athletic population.[2] There are a few theories on the etiology of plantar fasciitis, with the mainstay theory being that the inflammation is caused by repetitive microtrauma. Possible risk factors for plantar fasciitis include obesity, occupations requiring prolonged standing or weight-bearing, and heel spurs. The clinical presentation of plantar fasciitis consists of heel pain that usually presents worse in the mornings, after a workout, or pain that is relieved with the patient plantar flexing the forefoot.

Accurate diagnosis of plantar fasciitis is achieved through adequate examination of the calves, heel, and the plantar aspect of the foot. Imaging and thorough questioning are also used by healthcare providers to properly rule out differential diagnoses such as fractures or possible conditions mimicking plantar fasciitis.[1] Figure 1 shows an MRI image of a foot with the plantar fascia labeled as PF. [3]

Once a plantar fasciitis diagnosis is established, the patient should be directed towards a standardized treatment plan. Currently, plantar fasciitis is not managed in a consistent and uniform way. There is significant variation in how these patients are managed including therapeutic pain relief, medicinal pain relief, and self-evaluative care. Conservative treatment alone has a high success rate but is highly dependent on the patient's compliance with a long-term course of treatment and their ability to withstand the plantar fasciitis symptoms.

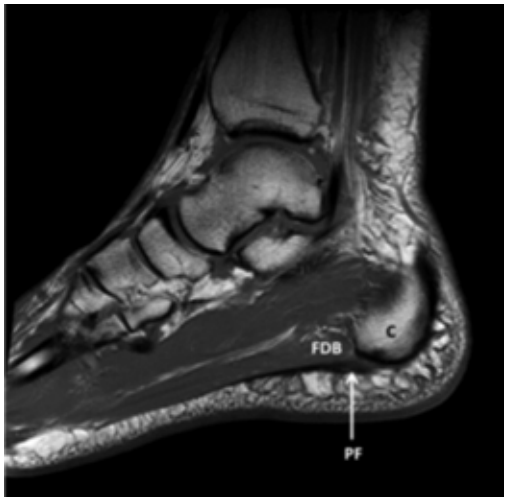

Figure 1. MRI of the foot showing the location of plantar fascia. Adapted from The Journal of Ultrasound Medicine.[3]

When the patient has exhausted other conservative treatment options, corticosteroid injections are an alternative option.[4] Steroid injections can be palpation guided, scintigraphy guided, or ultrasound guided. A common approach is to put the ultrasound along the long axis of the foot anterior to the heel to guide the injection.[4] Ultrasound guided injections can be both in the plane of the image as well as out of the plane of the image.[5] When the injection is performed in the plane of the image, the injection is administered in parallel with the plane of the ultrasound transducer. When the technique is described as an out of the plane approach, then the injection is made perpendicular to the plane of the transducer.

Steroid injections have shown to significantly reduce pain and provide relief for patients. However this relief is short lived, requiring patients to come back for multiple injections. Consistent use of injections can cause major

complications and plantar fascia rupture due to plantar fascia thinning.[4] With regards to the use of the ultrasound guided technique of steroid injections, no limitations and side effects have been reported as a direct result of the ultrasound device.

The goal of this review is to investigate and compare literature on patients who have received steroid injections with and without the use of ultrasound and contrast its effectiveness in decreasing complications of plantar fasciitis.

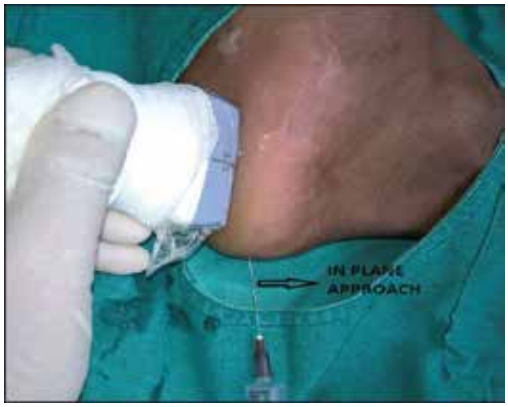

Figure 2. Ultrasound guided injection therapy for plantar fasciitis showing an in-plane approach technique. Adapted from Saudi Journal of Anesthesia. [5]

Methods

A systematic review was chosen with the use of EBSCOHost as the journal and literature search engine. The literature search was conducted December 27 through December 30 of 2018. The search includes the terms plantar fasciitis, ultrasound guidance, and related terms such as sonography, plantar fascia, and corticosteroid injections.

All articles generated from the EBSCOHost search were reviewed independently by both authors. Inclusion criteria included articles that pertained to plantar fasciitis as well as ultrasound or sonography. Articles that were excluded but pertaining to plantar fascia and ultrasound were ones that included plantar fascia release or other surgical methods. Other articles were excluded if they did not include the use of an ultrasound device despite pertaining to the treatment of plantar fasciitis. Inclusion criteria for an article was that it must have either ultrasound/sonography guidance and plantar fascia/fasciitis. Articles were excluded if treatment included fascia release or other surgical procedures. After the inclusion and exclusion methods were performed, ten articles of literature were left for review, with seven of them being included in the data shown below.

Results

According to Ang et al., steroids were found to be effective for treatment of plantar fasciitis for a brief period of 4 to 12 weeks.[4] The findings from the systemic search showed no clear consensus favoring the use of ultrasound guidance during steroid injections. Of the ten articles reviewed, three articles recommended the use of ultrasound guidance and are discussed below. Summary of the results are shown in Table 1. No studies were found recommending against the use of ultrasound guidance for steroid injections in the treatment of plantar fasciitis.

In a study performed in 2013 by N. Chen et al., the authors found that the use of ultrasound guidance showed better results when looking at tenderness and pain after three months than with palpation guided injections. [6] According to Tsai et al., it was determined that ultrasound guided steroid injections lead to a lower recurrence of heel pain.[7] Tatli et al. performed a study in 2008 determining whether or not steroid injections are effective in the treatment of plantar fasciitis.[8] This article found that steroids are effective when combined with conservative methods but also recommended the use of ultrasound guidance during injections. McMillian et al. performed a randomised control study in February of 2011 that showed that ultrasound guided dexamethasone treatments were effective for relieving pain for up to four weeks.[10] The 188 subjects either had ultrasound guided dexamethasone injections or a placebo. While it showed that there were little complications, there was no group that had dexamethasone injections that were not assisted with ultrasound guidance. Other articles were reviewed that did not recommend the use of ultrasound over palpation guided injections. Yucel et al. in 2009 found that there was no significant difference in plantar fasciitis pain between ultrasound guided injections, palpation guided injections, and scintigraphy guided injections at follow up 25 months after treatment.[11] The authors suggested the use of both ultrasound guided injections and palpation guided injections but not scintigraphy guided injections. The authors stated that this was due to ultrasound being more precise than scintigraphy. While the authors recommended the use of ultrasound over the use of scintigraphy, they did not specify differences between ultrasound guidance and palpation guided injections except that ultrasound guidance allows for a more accurate localization of the injection.

Schulfer in 2013 also found that dexamethasone ultrasound guided injections were beneficial for reducing pain for four weeks and swelling for up to 12 weeks.[12] As with the McMillan et al. study, there were no subjects in the literature

that had non-ultrasound guided injections. Another article was reviewed that showed that ultrasound can be used to determine the long-term progression of plantar fasciitis with treatment by steroid injections.[13] This article recommended the use of ultrasound in the therapy of plantar fasciitis as opposed to using it merely as a guide.

Articles showing benefits of US guidance	3
Articles showing complications of US guidance	0
Articles showing no preference to US vs non-US guidance	2

Table 1: Results of literature review regarding recommendations for US guided injections

Discussion

The majority of the articles reviewed were favorable for the use of ultrasound guidance. As of current, the consensus for ultrasound guidance being more effective than palpation guided injections is still under review by many clinicians. The studies reviewed suggested that no complications or limitations were associated with the use of ultrasound. One setback found during this review was a lack of studies pertaining to the use of ultrasound guidance as compared to palpation guidance. Of the studies that directly compared ultrasound and non-ultrasound guided procedures, the studies showed no complications or side effects for ultrasound guidance relative to non-ultrasound guidance. Therefore, there were only positive or neutral studies found for the use of ultrasound guidance. Only one study found during the review showed no significant difference in the patient's pain assessments post injections when contrasting ultrasound guided with palpation guided. While there were no negatives outcomes found in the studies pertaining to the use of ultrasound, more studies should be performed to come up with a clearer consensus of the effectiveness of using an ultrasound device during injections. Regarding the cost to benefit ratio of ultrasound, more studies should also be performed to look at the cost and accessibility of ultrasound in comparison with palpation guided injections.

Conclusion

This review sought to determine the reliability and effectiveness of ultrasound guided steroid injections for patients suffering from plantar fasciitis compared to non-us guided injections. Most of the literature suggests that there is either a benefit or no significant difference in results from using ultrasound during the guidance of an injection compared to non-ultrasound guided methods. More studies should be performed to determine the effectiveness of ultrasound use and provide a better consensus on the benefits of ultrasound use and whether the increased visualization leads to more effective treatment for plantar fasciitis. Further investigation on this topic may present and provide a more standardized first approach to steroid injections and reduce the number of complications and refractory cases of patients suffering from plantar fasciitis.

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Tackling the Opioid Crisis with HTX-011

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Abstract

Objective: In 2017, the United States announced a public health emergency due to the opioid crisis. In the search for alternatives to opioids, HTX-011 was created to reduce post-operative pain and decrease the need for opioid prescriptions. HTX-011 is composed of bupivacaine and meloxicam, which makes it more effective in pain management compared to local anesthetics alone. The purpose of this review is to analyze the research on HTX-011 as a possible solution for reducing the need for post-operative opioids.

Methods: All recent publications about HTX-011 were reviewed to better understand this alternative to opioid medication and determine if this can be a viable alternative for patients.

Results: HTX-011 has shown promise in clinical trials and was awarded the Breakthrough Therapy Designation from the Food and Drug Administration (FDA). Thus far, HTX-011 has been found to reduce opioid usage after bunionectomies showing its potential impact on the field of podiatry. It has also been studied in herniorrhaphy subjects and in pediatric patients. The use of HTX-011 has helped decrease patients' need for opioids postoperatively. Postoperatively, 17.3% of patients administered HTX-011 did not need opioids while only 8.0% of patients who were administered bupivacaine did not need opioids.

Conclusion: While studies about its safety and efficacy are currently ongoing, to date, HTX-011 has decreased the need for opioids and could be a promising solution to the current opioid epidemic that affects millions of patients each year.

Introduction

Chronic pain is defined as pain lasting greater than three months or past the normal time for healing. For people with chronic pain, the impact on their daily life is substantial. Though it is difficult to estimate the amount of people with chronic pain, the 2012 National Health Interview Survey estimated 11.2% of adults have daily pain and the National Health and Nutrition Examination Survey estimated 14.6% of adults in America have pain lasting over three months.[1] Postsurgical pain is pain lasting three to six months after a surgery and differs from the quality of pain prior to surgery. At least 450,000 people per year will develop persistent post-operative pain with chronic pain developing in 10% of these patients.[2]

One of the challenges of treating patients with chronic pain is that it is difficult to create an effective treatment plan. While searching for a treatment for chronic pain, many doctors began prescribing opioid medication to patients in the late 1990s. Some of the most common prescription opioids are oxycodone, hydrocodone, morphine, and methadone. Fentanyl, a synthetic opioid, is also regularly prescribed to patients. Heroin, a synthetic illegal opioid that has been increasing in the U.S. among both genders and all socioeconomic levels, is more likely to be abused following the use of legally prescribed opioids.[3]

The use of opioids has increased since 1999 with about 11.4 million people in the U.S. using opioids.[4] Although opioids are proven to relieve pain, there are negative side effects to the prescription drugs such as drowsiness, nausea, vomiting, and constipation. More severe side effects include physical dependence, tolerance, increased sensitivity to pain, respiratory depression, and death.[4] According to the U.S. Department of Health and Human Services, more than 130 people die per day from overdosing on opioids. It has been estimated that 2.1 million people in the U.S. have an opioid use disorder.[3] From 1999 to 2016, more than 350,000 deaths in the U.S. have been caused by opioid overdose. As a result of the widespread misuse and overdose of opioids, in 2017, the Health and Human Services declared that the opioid crisis is a public health emergency.[3]

Deaths from opioids have increased in three waves, as can be seen in Figure 1.[4] The first wave started in the late 1990s when pharmaceutical companies reassured medical professionals that patients would not become addicted to opioids. It has now been proven that opioids are largely addictive and patients can experience withdrawal symptoms such as muscle pain, anxiety, and irritability. Consequently, the amount of opioid prescriptions increased as well as overdose deaths involving prescription opioids. In 2010, the second wave of overdose deaths took place with the increase of illegal opioid use such as heroin. The third wave started in 2013 with an increase of deaths from synthetic opioids such as illicitly manufactured fentanyl (IMF). IMF continues to increase in prevalence and has been found to be combined with heroin, counterfeit pills, and cocaine.[4]

The Center of Disease Prevention has worked to prevent opioid overdose by collecting data and tracking trends, partnering with public safety

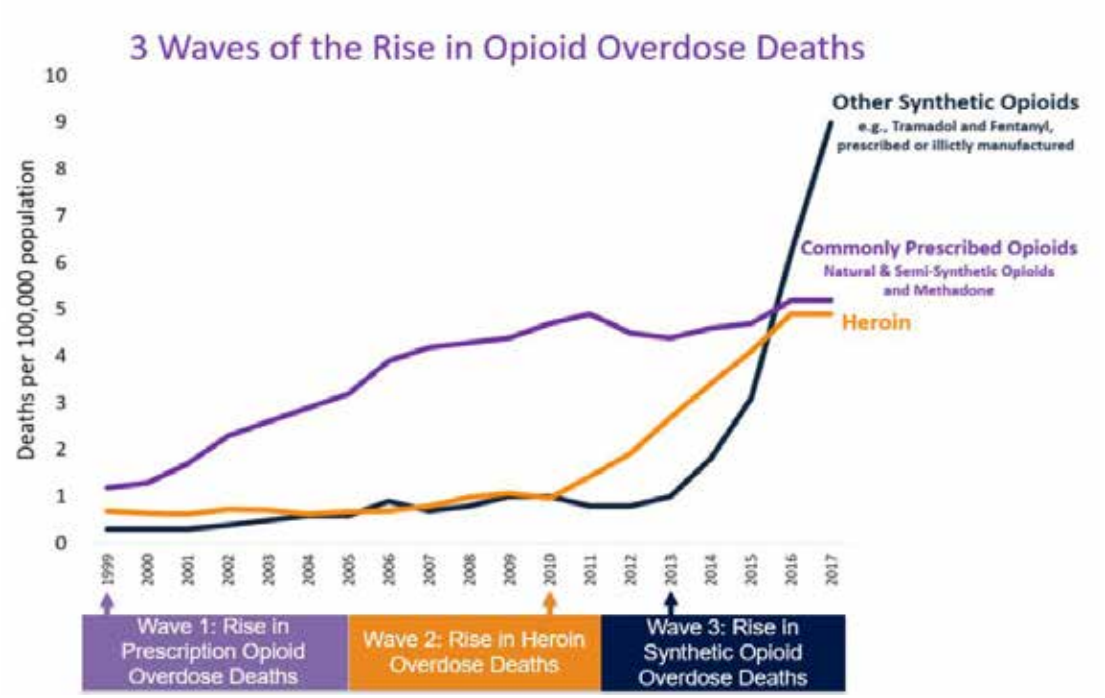

Figure 1: Opioid overdose deaths represented in three waves from 1990 to 2016. Adapted from the Center for Disease Control and Prevention: Opioid Overdose.[4]

officials such as law enforcement, helping providers and health systems by educating on how to improve prescriptions, raising awareness, and creating prevention efforts.[1]

In California, the Controlled Substance Utilization Review and Evaluation System (CURES) has been created for prescribers and dispensers. It is mandatory as of October 2, 2018 to utilize the CURES program statewide. The program includes patient safety alerts, compacts, and peer messaging for providers. The intention is to reduce prescription drug abuse without jeopardizing patient care.[5] Due to the opioid crisis and the need to reduce opioid use, providers and patients have been searching for a new solution to decrease pain while avoiding opioids.

Pathophysiology of HTX-011

In the search to reduce the prescription of opioids, Heron Therapeutics created a drug to attempt to reduce both postoperative pain and the need for opioids. The drug, HTX-011, was created as a combination of bupivacaine and meloxicam. Bupivacaine is a local anesthetic commonly used in operative and clinical settings while meloxicam is a nonsteroidal anti-inflammatory. Adding meloxicam to bupivacaine reduces the acidic environment and reduces inflammation caused by surgical trauma.[6] This reduction increases the action of bupivacaine by allowing for greater penetration.

While local anesthetics are typically injected in the surrounding area of the surgical site and might require multiple injections, HTX-011 is administered only once into the surgical site. Furthermore, as depicted in Figure 2, HTX-011 is not injected into the skin, but rather it is administered without a needle into the surgical site before it is sutured. This method decreases the amount of injections a patient receives, reduces the risk of puncturing intravascular structures, and provides an easier application method for physicians. With the use of HTX-011, the company's intent is to reduce post-operative pain for 72 hours, decreasing the need for opioids and therefore, decreasing the risk of opioid addiction and overdose.

Methods

Data was gathered through PubMed using the keywords "HTX-011," "Exparel," and "Liposomal Bupivacaine." Data was also collected directly from the Huron Therapeutics website.

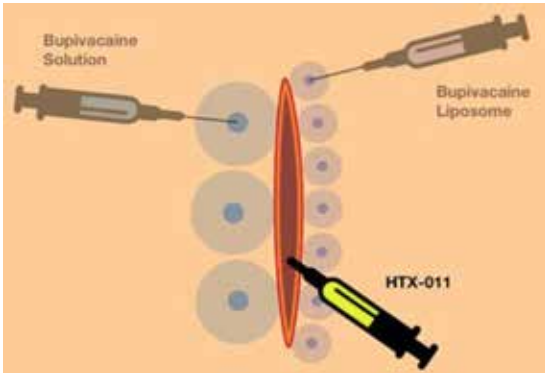

Figure 2: HTX-011 being administered without a needle into the surgical site releasing its ingredients simultaneously. Adapted from Heron Therapeutics.[6] When administered by itself, bupivacaine only has analgesic effects for up to 24 hours; when administered with meloxicam, its efficacy is greatly increased to 72 hours.[6]

Inclusion criteria included any study where HTX-011 or liposomal bupivacaine was used post-operatively. Since HTX-011 is a recent advancement in pain management, no exclusion criteria was specified to ensure that all information regarding HTX-011 could be reviewed.

Research

HTX-011 is not currently FDA approved but is on the Fast Track Designation from the FDA and Heron Therapeutics recently submitted a non-disclosure agreement (NDA).[6] Exparel, a similar product that functions as an extended release liposomal bupivacaine, is currently on the market and has shown promise in recent pain management studies.

In a 2018 study conducted by Day et al., extended release bupivacaine was used for pain management in 27 patients post-palatoplasty.[7] Patients of an average age of 10.8 months were given 1.3% liposomal bupivacaine to determine the safety and efficacy of liposomal bupivacaine as an alternative for pain control.[8] Of the 27 patients in the study, only 7.4% had emesis and 3.7% had pruritis which are symptoms associated with opioid use. According to Day et al., liposomal bupivacaine is a safe pain management drug in pediatric patients.

HTX-011 shows advantage over Exparel by creating a synergistic effect between bupivacaine and meloxicam, which creates a greater reduction in pain than individual bupivacaine extended release or meloxicam extended release. While extended release bupivacaine is limited to 24 hours, HTX-011 can reduce pain for up to 72 hours- three times the duration of Exparel.[6]

A phase 2 open-label study conducted by Heron Therapeutics studied the safety and efficacy of HTX-011 after a bunionectomy.[9] This study observed the effects of HTX-011 in 30 patients as it is applied to the surgical site. As seen in Figure 3, patients who were administered HTX-011 reported less pain when compared to patients who were administered a saline placebo or bupivacaine HCl.[9] This study is ongoing and expected to be completed by the end of 2019.

While HTX-011 has the potential to be a groundbreaking solution for opioid-free pain management, more studies are needed to determine its safety and efficacy.

A 2018 study by Viscusi et al., observed the synergistic effects of HTX-011 in patients post bunionectomy and herrniorrhaphy.[10] This study observed the use of HTX-011 in 234 bunionectomy cases and 179 herniorrhaphy subjects. For all the patients in this study, HTX-011 alleviated pain within the first three days after surgery without serious adverse effects. As seen in Figure 4, within 0-72 hours, patients who were given 300 mg of HTX-011 had the lowest amount of total opioid consumption. However, patients who were given the saline placebo had the highest postoperative opioid use. In these patients who were treated with HTX-011, the amount of opioid medication used post bunionectomy and herniorrhaphy was reduced compared to patients who were not given HTX-011 after surgery. pain management drug in pediatric patients.

Conclusion

The United States is currently facing an opioid epidemic due to increased prescriptions,

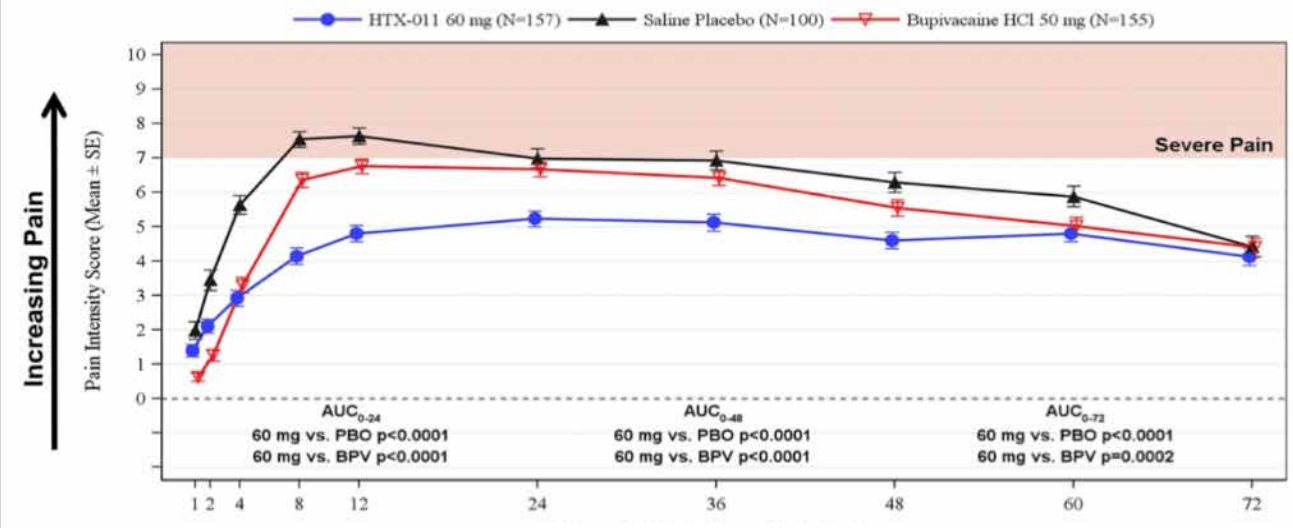

Figure 3: The effects of HTX-011 on pain management post bunionectomy showing the increased pain reduction from HTX-011 compared to the placebo or liposomal bupivacaine. Adapted from Heron Therapeutics Phase 3 HTX-011 Studies.[6,11]

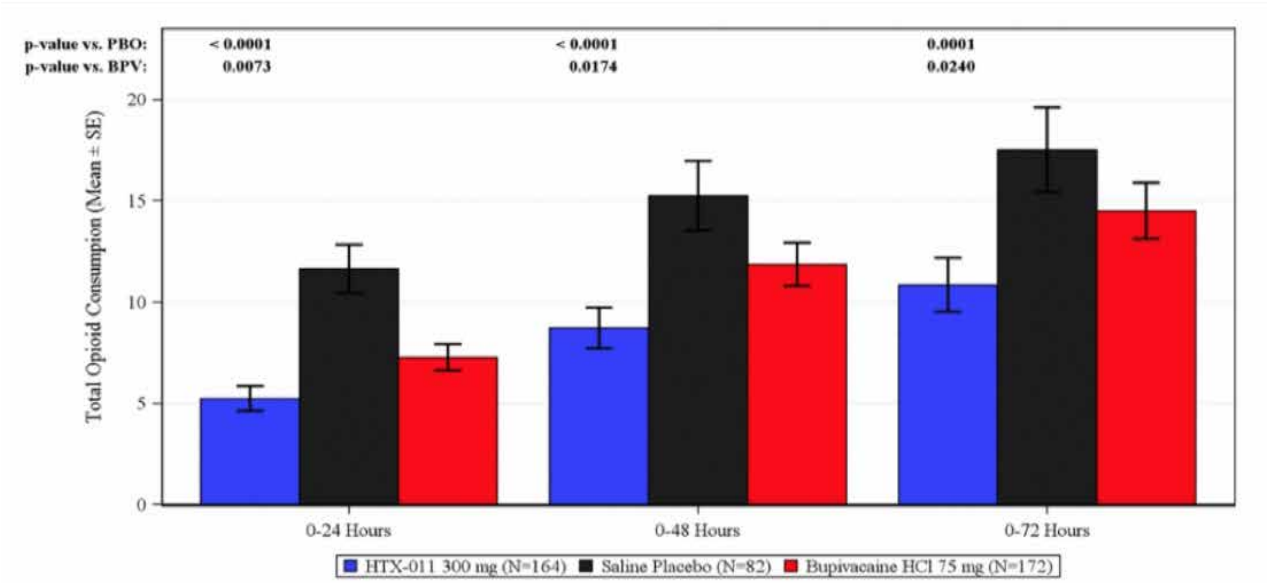

Figure 4: HTX-011 significantly reduces total opioid use vs. bupivacaine and placebo. Adapted from Heron Therapeutics Phase 3 HTX results.[6,10]

misuse of medication, and the addictive property of opioids. According to the Department of Health and Human services, 11.4 million people misused prescription opioids in 2017.[3] One way to better tackle this crisis is by developing and prescribing alternative non-opioid medication.

Currently, HTX-011 is being considered as an alternative to opioid medication. HTX-011 is a combination of bupivacaine and meloxicam used for postoperative pain management. It is administered only once to the surgical site and has proven to be more effective than local anesthetics alone. Studies examining the use of HTX-011 after a bunionectomy and herniorrhaphy have shown that the use of HTX-011 does reduce the patient's need for opioid pain medication.[10] The safety and efficacy of HTX-011 is currently being studied; however, based on the current research, HTX-011 has been shown to be safe for use in both adult and pediatric patients.

Although HTX-011 can be a promising alternative to opioids, more research on its safety and efficacy needs to be conducted. However, based on current research, HTX-011 can be a promising solution to the opioid epidemic that is currently affecting millions of Americans.

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Achilles Tendon Rupture: Conservative Versus Nonconservative Treatment

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ABSTRACT

Objective: The goal of this research is to assess the efficacy of treating patients with Achilles tendon ruptures conservatively or surgically.

Methods: Meta-analyses that utilized randomized controlled trials were primary analyzed as they prevented author bias.

Conclusion: Achilles tendon rupture is one of the most common and debilitating injuries an individual can sustain. Recovery to full activity can take up to six months. Up until 2010, surgery was viewed as the most effective way to treat Achilles tendon ruptures. However, new evidence has emerged that suggests surgical treatment may not benefit the patient as much as conservative treatments. While surgery is still an effective method for treating Achilles tendon ruptures, new evidence is beginning to demonstrate that conservative methods of treatment are often times more effective and less risky than surgical intervention.

Introduction

The Achilles tendon is the most commonly ruptured tendon in the body, often in men in their thirties.[1] It occurs in the most hypovascular portion of the gastrocnemius-soleus tendon complex, 2-6 cm proximal to its insertion at the calcaneus.[2] The main deliberation on managing ruptures is whether or not to use surgical methods. Non-surgical treatments include early weight bearing exercises on the ruptured tendon and early range of motion exercises.[3] Support for the use of non-operative techniques comes from the Zhang et al. meta-analysis which attempted to determine how to best treat Achilles tendon ruptures. The researchers concluded that if functional rehabilitation with early range of motion exercises was employed, the re-rupture rates between the surgical and non-surgical patients were much closer than previously reported.[4] While functional rehabilitation protocols are different at every facility, the protocols typically involve early weight bearing and range of motion exercises in conjunction with orthotic usage rather than a conventional cast.[4] While this research into re-rupture rates and functional rehabilitation outcomes is promising, the majority of podiatric surgeons and orthopedic surgeons still rely heavily on surgical means to solve all problems related to Achilles tendon ruptures.[5] The reason for this is two-fold: a surgeon can grant a patient rapid results if the tendon is repaired in the operating room as well as a faster recovery. Additionally, a recent meta-analysis concluded that the rate of re-rupture ranged from 3.5% to 4.3% in the surgical group, to 8.8% to 9.7% in the non-surgical group.[6] According to Jhang et al., the benefits of surgery outweigh the risks, leading surgeons to believe that surgical treatment of a ruptured Achilles tendon was the best method of treatment. However, new research is beginning to highlight the benefits of nonoperative treatment.

With surgery comes the increased risk of complications. Major risks related to surgery include deep vein thrombosis, infections, or neural damage.[7] In a recent systematic overview of meta-analyses done for the treatment of Achilles tendon ruptures, it was determined that surgery had such potential risk that it posed no actual benefit to the patient. [7] This should lead podiatric and orthopedic surgeons alike to reevaluate how they treat Achilles tendon ruptures.

Results

The study conducted by Willits et al. was one of the first studies to assess operative versus nonoperative methods of repairing Achilles tendon ruptures.[3] The researchers determined that of the two treatment groups, there was no clinically important difference between groups with regard to strength and range of motion.[3] There were nearly double the amount of complications in the operative group as compared to the nonoperative group, with the largest difference being the increased number of soft tissue related complications in the operative group.[3]

In 2012, Soroceanu et al. conducted a meta-analysis to determine whether or not conservative treatments for ruptured Achilles tendons were effective. The researchers used rigorous selection criteria that produced 10 studies.[4] The first item that the researchers examined was the rate of re-rupture. Upon pooling the ten studies together, it was determined that the risk of re-rupture was 5.5% less in the surgical group than in the non-surgical group.[4] However, because there was significant heterogeneity among the studies, the researchers explored factors that might be responsible for the heterogeneity with the use of meta-regression.[4]

The use of functional rehabilitation was found to be the significant cause of heterogeneity in the studies. With this information, Soroceanu et al. conducted a stratified analysis of re-rupture rates to

determine how functional rehabilitation might affect eventual healing outcomes. The results are listed in Figure 1.

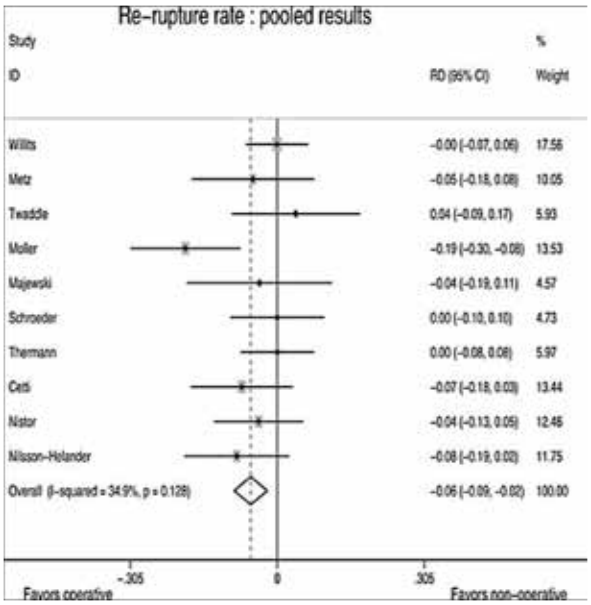

Figure 1: Results from the initial analyses of the 10 studies. Results skewed to the left of the solid center line indicate favorable results when surgery was performed. Results skewed to the right indicate favorable outcomes in the absence of surgery. This chart shows risk differences are skewed to the left in favor of surgery. Adapted from Journal of Bone and Joint Surgery.[4]

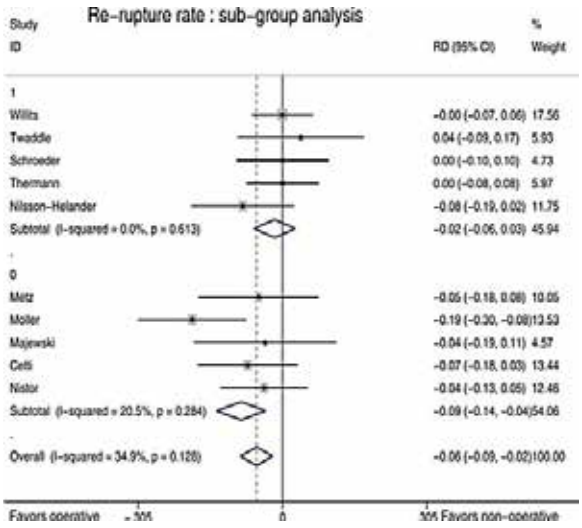

Figure 2: The upper portion of the table includes data from Willis, Twaddle, Schroeder, Thermann, and Nisson and Helander. These studies utilized functional rehabilitation and early range of motion in the operative and non-operative groups. The lower portion of the table includes data from Metz, Moller, Majewski, Cetti, and Nistor. These studies did not incorporate functional rehabilitation and early range of motion. Note in the upper potion data reflects an operative score of 0, indicating a favorable outcome without surgery. Adapted from Journal of Bone and Joint Surgery.[4]

The results of their stratified analysis illustrated that if a functional rehabilitation protocol with early range of motion was used, the re-rupture rate between the surgical and non-surgical group were nearly identical (absolute risk difference = 1.7%), suggesting that no absolute risk reduction was achieved by performing surgery.[4] In the group that did not perform functional rehabilitation and early range of motion (the lower half of Figure 2), surgery had an 8% lower amount of re-rupture than non-operative techniques.[4] This indicates conservative measures are recommended over surgical ones.

The researchers determined the prevalence of other complications as a result of surgery. These include: infections pertaining to deep and superficial wounds, necrosis of skin and tendons, fistulas, damage to the sural nerve, deep vein thrombosis, decrease in ankle motion, and pulmonary embolus.[4] The meta-analysis indicated that the risk difference was 15.8% in favor of nonsurgical treatment, meaning that surgery was associated with a 15.8% increase in risk for complications.[4] Patients whose Achilles' tendon rupture was repaired surgically were able to return to work 19.16 days earlier than those who underwent non-surgical treatment.

In 2017, in response to the paper published in 2012, one of the largest and most comprehensive meta-analysis studies done to determine the efficacy of different treatment modalities for Achilles tendon ruptures was carried out. Deng et al. surveyed over 1500 studies and due to their rigorous criteria, only 8 papers eventually made it into the meta-analysis.[8]

It was determined that re-rupture occurred 3.7% of the time in surgically treated patients and 9.8% of the time in non-surgically treated patients.[8] The overall rate of wound infection was 5.0% (range 1.7% to 12.2%) in the surgical group.[8] It was also determined that the non-surgical group generally required more time to return to normal activities.[8] No significant heterogeneity was detected in the rate of re-rupture.

Conclusion

The study done by Zhang, et al. illustrates the need for podiatric and orthopedic surgeons to consider more conservative measures when treating Achilles tendon ruptures.[4] This research also suggests that health care facilities need to offer patients functional rehabilitation opportunities and access to early range of motion because both demonstrate the ability to enhance healing and recovery.

While there are some potential drawbacks to taking a non-surgical route to repairing a ruptured Achilles tendon, primarily, a longer time to heal (19.16 days approximately), there are more benefits that can be offered to patients.[4,8] The biggest benefit is the reduction in risk associated with surgery as stated prior. In addition to the decrease risk in surgical complications there is also an increase in plantar flexion strength associated with conservative treatment.[3]

In a 2017 Meta-Analysis, Deng states the benefits from surgery outweigh the negatives. However, this study failed to account for many of the factors that the meta-analysis in 2012 accounted for. The Deng Et al. meta-analysis failed to account for the benefits of functional rehabilitation and early range of motion in determining the efficacy of whether to treat patients with surgery or not.[4,8] Due to this bias, it would appear that more conservative approaches coupled with functional rehabilitation and early range of motion are the most beneficial to patients that have more time to allow for healing.

Overall, it is difficult to truly say that conservative treatment or operative treatment is better than the other. However, there is evidence now that supports the assertion that nonoperative treatment should be considered before putting a patient under the knife. Patients and their providers should always consider the least invasive and most effective measure when considering how to proceed with an Achilles tendon repair.

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Recent Advances in Maggot Debridement Therapy in the Enhancement of Wound Healing in Diabetic Foot Ulcers

Adam Chan, M.S., Dy Chin, M.S., Spencer Sterling, B.S.

ABSTRACT

Objective: Diabetic foot ulcers which present as chronic wounds that rarely heal without intervention are a major health concern among diabetic patients. The larvae of the green bottle blowfly (*Lucilia sericata*) has been used extensively throughout history to treat different types of wounds. Much of the evidence for the use of maggots in wound healing has been anecdotal or reported as individual case reports. There has been a recent emergence of cellular and molecular evidence that lends support to those previous studies. The purpose of this review is to provide recent advances in the literature for the use of maggot debridement therapy as a method of wound healing.

Methods: Our literature review utilized the PubMed search engine to query the MEDLINE journal database. Query terms included "diabetic foot ulcers AND wound healing", "wound healing AND maggot debridement therapy", "maggot debridement therapy AND (excretion OR secretion) products", and "maggot (excretion OR secretion) AND molecular pathways". The results of the searches yielded publications that provided background information to begin our review.

Results: The excretion and secretion products from the maggots promote wound healing by modulating immunity, inflammation, and angiogenesis. Excretion and secretion products contain several proteases and glycosaminidases that prevent the formation of biofilms. NF-κB, a major inflammatory pathway, was shown to be inhibited by these products. Finally, excretion/secretion products have been shown to promote angiogenesis at the wound site by upregulating vascular endothelial growth factor (VEGF).

Conclusion: Maggot debridement therapy is an effective alternative method for wound healing. This review has elucidated some of the recent advances in the molecular and cellular evidence supporting the benefits of maggot debridement therapy. In addition, the benefits are reiterated in a case series, a meta-analysis, and a novel case report demonstrating the angiogenic effects of excretion/secretion product.

Introduction

Diabetic Foot Ulcers

Diabetic foot ulcers (DFU) are a major health concern affecting diabetic patients.[1] Among the population with diabetes, up to 6% are affected with DFUs and approximately 25% may develop a DFU during their lifetime.[2] Risk factors for developing diabetic foot ulcers include vascular disease and foot deformities.[3] Because of the impaired healing of these foot ulcers, lower limb amputations are an unfortunate consequence. The prevalence of a lower limb amputation is approximately fifteen times greater in a diabetic patient compared to a non-diabetic patient.[3]

The primary cause of DFUs is peripheral neuropathy coupled with poor foot mechanics causing increased focal pressure.[4] A key characteristic for this type of foot ulcer is arrestation of the wound healing process in the inflammatory phase, resulting in chronicity.[5] Hyperglycemia seen in diabetic patients was noted as a potential cause for impaired wound healing.[6]

Diabetes is associated with changes in connective tissue metabolism. This could be seen as the contributing factor for why these patients have significant issues of poor wound healing. One such connective tissue is collagen. Research has shown that diabetic patients have remarkably low collagen formation during wound healing. The loss of collagen can be due to either a decrease in synthesis, an increase in breakdown, or a combination of these two processes.[7] Persistent inflammation is also noted in diabetic wounds which may contribute to the prolonged healing process.[8] During early wound healing, type III collagen is predominantly produced. It is replaced by type I collagen as the wound healing progresses, resulting in fully healed scar tissue.[9]

Debridement and Wound Management

The primary goal of wound care management aims to promote re-epithelialization of the ulcerative wound. The overall steps to achieve healing are: debridement of any nonviable tissue found at the wound site, managing inflammation and infection associated with the wound, moisture control, and assessing environmental conditions and the potential for epithelialization.[10] The debridement step is a major component in the wound healing process. It removes devitalized tissue (slough, necrotic, or eschar) at the wound bed preparing it for the next stage of healing. The presence of devitalized tissue and necrotic tissue forms an ideal environments permitting bacteria and microbes to thrive off of; therefore, it is imperative to minimize these conditions.[10]

The current standard for debridement of DFUs is known as the sharp method. This method can be divided into two categories: surgical and non-

surgical. Surgical debridement is more aggressive and must be performed in an operative room. Non-surgical debridement can be performed in an office setting.[11] Both of these methods can be very effective for debriding wounds; however, the overall outcomes often depends on the skill of the practitioner to be able to distinguish between viable versus non-viable tissue.[12]

There are also several other types of debridement techniques that can remove devitalized tissue. Autolytic debridement is a conservative method which utilizes the body's natural immune response to phagocytose and breakdown necrotic tissue. In non-infected wounds, this process can be effective and restore the wound with normal healthy tissue.[10] Enzymatic debridement is a slower debridement process that uses exogenous proteolytic enzymes to debride the infected wound. This method, however, is generally used when specific conditions are indicated. Mechanical debridement can also be used to remove devitalized tissues and debris by using mechanical forces such as wet-to-dry, pulsatile lavage, or irrigation. Lastly, biological debridement, such as larval therapy, can be an effective and painless treatment in removing devitalized tissues. This process utilizes the secretions and excretions of proteolytic enzymes released by the larva.[10] The current review seeks to elucidate recent advances in larval therapy and understand the molecular and cellular processes which makes it viable option for wound debridement and healing.

Maggot Debridement

History

Maggot debridement therapy (MDT) involves the use of the larvae of the green bottle blowfly (*Lucilia sericata*) to remove necrotic tissue and improve ulcerative wound healing. The use of maggots to debride tissue has been recorded as far back as over one thousand years in human history. The first doctor to report the benefits of maggot debridement therapy was Ambroise Pare, a French surgeon in the 16th century. Pare's original study promoted a great deal of interest in using maggots as a medical treatment. His study also influenced many publications and articles describing its use and therapeutic application.[13] A significant benefit of MDT is that it does not disturb any healthy tissue at the wound site, whereas surgical debridement with a scalpel blade frequently removes healthy tissue that is associated with the wound.[14]

Excretion and Secretion Products

In addition to the biomechanical method of feeding on devitalized tissue, MDT can also promote wound healing through bioactive elements that are either excreted or secreted by the larvae. Recent studies have shown that there are several signaling pathways involved in wound healing that are activated by these excretion/secretion (ES) products. We will discuss the ES products that are contributory to immunity, inflammation, angiogenesis, and some antibacterial properties.[15]

Nuclear Factor-κB (NF-κB) is a transcription factor which regulates the expression of certain genes involved in the major pathway promoting immunity and inflammation.[16] Tombulturk et al. measured the effect of ES products of larvae on the expression of NF-κB as well as collagen types I and III. Their research found that the substrate p65 expressed by NF-κB was overexpressed in wounds of diabetic rats compared to wounds of non-diabetic controls, indicating a heightened level of inflammation. ES treatment appears to modulate this inflammation by decreasing the expression of NF-κB. Another effect of the ES treatment is that it promotes the synthesis of collagen type I while inhibiting the synthesis of collagen type III. Their results demonstrated that the increased expression of collagen type I induced by ES treatment may trigger accelerated wound healing in the diabetic rat model.[17]

During the wound healing process, angiogenesis is an important step for revascularization and promoting blood flow. Following an injury, activated macrophages assist in the healing process by mediating angiogenesis through multiple chemotaxins, including vascular endothelial growth factor (VEGF).[18] This method for increasing wound healing with MDT may be supported by the study of cells treated with ES products resulting in an increase production of VEGF.[19]

In a different study, human microvascular endothelial cells (HMEC-1) treated with ES products demonstrated an increase in cell migration that resulted in increased wound healing by approximately 30% over those that were not treated.[20] An increase in activity of PI3K/AKT1 signaling from the ES is credited to the increase.

ES products from maggots have been shown in multiple studies that it has the ability to block and prevent biofilm formation from different bacterial colonies such as *S. aureus* and *P. aeruginosa*.[21] Studies have shown that ES products contain a variety of proteases and glycosaminidases which can break down certain biofilms and make the microbes more susceptible to conventional antibiotic treatment.[19, 21]

Maggot Debridement Therapy in Practice

Maeda et al. published a case report of a 78-year-old man presenting with severe ulcers on the right foot which required a transmetatarsal amputation of all the digits.[22] Following amputation, the wound remained unhealed likely due to worsening ischemia to the wound site. The skin perfusion pressure, an index of peripheral circulation, of the right foot was 12 mmHg dorsally and 17 mmHg on the plantar aspect. The presentation of the wound two months after the amputation is shown in Figure 1. The patient was given two rounds of MDT. After the second round of therapy, the skin perfusion pressure was increased 54 mmHg on the dorsal and 44 mmHg on the plantar surface. Maeda et al. attribute the healing of the ischemic wound due to the increased blood supply from the treatment using MDT. This case report demonstrates the angiogenic effects of maggot ES products. In addition, the authors note that the use of elevated skin perfusion pressure can be used to assess successful treatment contributed by local perfusion of the wound site.[22]

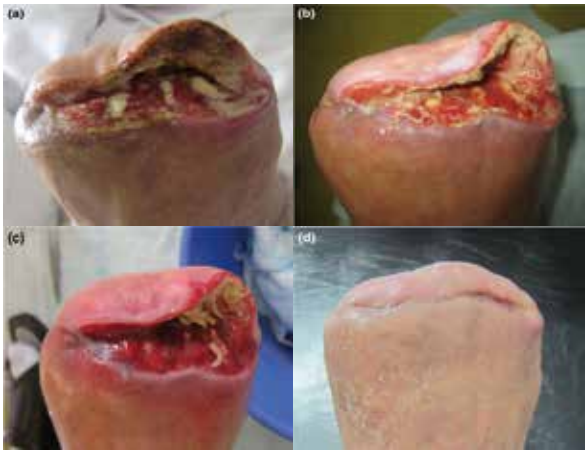

Figure 1. The patient was a 78-year-old man who initially presented with several ulcers requiring eventual amputation. a) Two months after the transmetatarsal amputation. b) initial treatment of maggots placed on the wound. c) 2 days after MDT. d) 6 months after therapy. Adapted from Clinical and Experimental Dermatology.[22]

A recent study from 2017 in Iran followed twenty-nine cases of non-treated wounds.[23] All the wounds had previously undergone attempts of medical and surgical debridement, 45% were believed to require some form of amputation of future surgery, and several had microbial pathogens that were resistant to multiple antibiotics. Following multiple rounds of MDT, all of the patients in the study were healed from their ulcerative wound. Two of the cases required a split thickness graft. In the three years of follow-up, none of the patients were diagnosed with recurrence of osteomyelitis and none required amputations.[23] One of the cases that was followed and documented in their paper is shown in Figure 2. The injury was a limb-threatening DFU with osteomyelitis. This patient was treated with maggot debridement therapy in the hospital. He was also treated with maggots as an outpatient every 3 days, receiving 32 rounds of maggot debridement over the course of 120 days. Finally, the wound was closed with a skin graft.

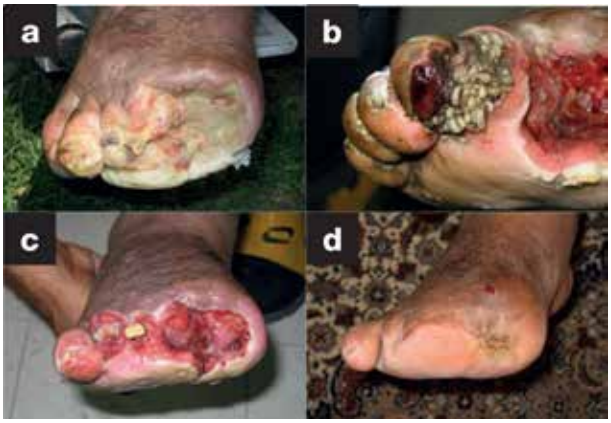

Figure 2. This patient was a 57-year-old patient who was at risk for amputation with an underlying osteomyelitis. Images a-d show the progression of the wound after treatment with maggot debridement therapy. In total, this patient received 32 cycles over 120 days of treatment. Adapted from Journal of Wound Care.[23]

In a meta-analysis, Sun et al. examined 12 studies that compared MDT to other conventional methods.[24] The outcomes measured were time to healing and costs of MDT. There were six randomized controlled trials, two prospective studies, and four retrospective studies. They showed that time to healing was significantly reduced in four studies. In addition, costs of MDT were nearly halved compared to hydrogel therapies.[24]

Conclusion

Maggot debridement therapy has been widely used as a treatment for wounds from early recorded history to the present day. Many studies and case reports have shown the benefits and improved outcomes for patients who present with persistent and chronic wounds. In the last decade, many studies have been published that finally expound the underlying mechanism of action and other cellular and molecular evidence of how maggot debridement therapy can increase the effectiveness of wound healing attributed by the maggot excretion/secretion products. Maggot debridement therapy is increasingly used to treat chronic and stubborn

wounds. Problematic diabetic foot ulcers fall in this category and may benefit from maggot debridement therapy. Furthermore, molecular research into the excretion and secretion products can help identify new benefits. New randomized controlled trials that investigate the effects of the ES products can further solidify the evidence presented here in cell and animal models. This review has elucidated the underlying mechanisms of how maggots and their ES products can influence and improve wound healing as well as reiterated the advantages for its use in practice.

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Non-Surgical Treatment Modalities for Plantar Fasciitis: A Review of Current Literature

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ABSTRACT

Objective: Current literature about the non-surgical treatment modalities for plantar fasciitis is broad. The purpose of this review is to compare the effectiveness and implementation of stretching, corticosteroid injections, and platelet rich plasma (PRP) injections using current literature.

Methods: The studies used in this review were retrieved by searching the Cochrane Library, PubMed, and EBSCOhost. Specific searches were conducted for corticosteroid injections, PRP, and stretching. All studies reviewed were all published from the years 2008-2018 to keep the information current.

Results: Stretching is a preferred method amongst many clinicians and surgeons. Stretching and controlled training are non-invasive and have been proven effective. However, stretching is up to the diligence of the patient and may have decreased compliance. Corticosteroid injections have been used for nearly 70 years and have excellent short-term treatment value. However, corticosteroid injections are not as useful in cases of chronic plantar fasciitis. PRP is a very safe treatment option and adequately reduces the thickness of the fascia. However, the PRP injections are costly and minimal research has been done to determine the exact results of long-term therapy.

Conclusion: Even though research has been conducted on controlled training, corticosteroid injections, and PRP injections, it is difficult to conclude which treatment is the most effective. Future studies with the direct comparison of these non-surgical treatment modalities should be conducted in order to make a definitive conclusion on their efficacies. This would enable clinicians to better determine a more acceptable first line treatment for plantar fasciitis and perhaps come up with a combination of therapies that have proven long-term results.

Introduction

Nearly 1 million new cases of plantar fasciitis are seen every year in the United States. It is a disease process that is poorly understood, with debate as to whether plantar fasciitis is either an inflammatory or a degenerative process.[1] It is common to approach new cases of plantar fasciitis conservatively at first, as many cases resolve spontaneously. It is estimated that 20% of cases progress to chronic plantar fasciitis.[1] Numerous studies have been conducted to analyze the effectiveness of non-surgical and invasive therapies.

Conflicting results can easily be found when analyzing these studies. A review on plantar fasciitis is important to understand any changes in understanding of the disease process, and to see what can be agreed upon between the many conflicting studies. The objective of this review is to compare the efficacy of controlled training (stretching and exercise), corticosteroid injections, and PRP injections to one another using current literature since they individually have many studies claiming their superior efficacy.

Controlled Training with Stretching and Exercise

Controlled training with stretches and exercises is a mainstay in non-surgical plantar fasciitis treatment. Controlled training includes stretching and strength training prescribed by a physiotherapist or physician. In the study by Johansen et al., patients were instructed to perform three strengthening exercises three times a week daily.[1] There are different modalities for exercise and stretching, but it is common to prescribe a patient a home-based routine with regular follow-up with the prescribing physician.

These exercises commonly include plantar and calf-plantar fascia stretches, foot-ankle circles, toe-curls, and unilateral heel raises with toe dorsiflexion (see Figure 1).[2] It is important to identify the risk factors that are specific to the patient when prescribing a regimen for stretching and exercising. For example, patients presenting with plantar fasciitis often have obesity, pes planus or cavus deformities, and limited ankle dorsiflexion which can make it difficult to comply with therapy. It is important to consider weight loss along with the lower extremity physical therapies as obesity is one of the most common modifiable risk factors for patients with chronic plantar fasciitis.[3]

A survey from 2008 of 116 orthopedic surgeons who specialize in foot and ankle surgery, showed that 74 of the 116 surgeons preferred plantar fascia-specific stretching and supervised physical therapy over anti-inflammatory or corticosteroid injection therapy.[3] Evidence for strength exercises and stretching for the long-term treatment of chronic plantar fasciitis has shown statistically significant reductions in plantar pain.[1,4] For clinicians, it is worthwhile to consider prescribing exercises and stretching as part of the first line treatment of plantar fasciitis. Often, methods of stretching are different

depending on the patient, practitioner, and individual needs of the patient. Although there are some mixed results, it has been shown that either weight bearing or non-weight bearing exercises show significant reduction in pain after an average of 8 weeks.[5]

It is advisable to start first line therapy with stretching and exercises for new cases of plantar fasciitis, as there is virtually no medical risk to performing these exercises, and the reduction in pain is significant. Controlled training treatments require further studies and a standardized method of treatment for comparison so that an adequate conclusion can be made to its long and short-term effectiveness.[6]

Figure 1. Stretching exercise for plantar fasciitis. Adapted from MyHealth.Alberta.ca.[2]

Corticosteroid Injection Therapy

Methylprednisolone acetate is a synthetic glucocorticoid with potent anti-inflammatory activity commonly used to treat plantar fasciitis by injecting it beneath the fascia, often with the guidance of ultrasonography.[7] This therapy has shown some short-term effectiveness when other non-surgical therapies have failed to produce results. Common non-surgical therapies involve NSAIDs, stretching, taping, reduced activity, and supportive footwear.[2]

In a study by Johannsen and colleagues, corticosteroid injection with controlled training is compared against corticosteroid alone, or controlled training alone. As there is no accepted best practice for plantar fasciitis, comparing three modalities is not enough to justify such a wide sweeping conclusion. A more valid conclusion from their study would be that corticosteroid injection with controlled training is better than either therapy alone.

One criticism of corticosteroid injections is that there is a significant decrease in efficacy in mid and long-term study periods.[8,9] According to Sankarapandian and Chatterjee et al. in 2017, there is indication that steroid injection compared with other therapies may slightly reduce heel pain.[8] This is hypothesized to be due to the strong anti-inflammatory effects of the steroid, and evidence shows that corticosteroids can inhibit fibroblast proliferation and ground substance proteins, which may be helpful in the healing process.[8]

One method used to evaluate plantar fasciitis objectively is fascial thickness on ultrasound or MRI. The thickness of the fascia is an important consideration because patients with plantar fasciitis are 100 times more likely to have a thickened fascia compared to healthy individuals.[10] The fascia thickness in patients injected with methylprednisolone decreased from an average of 8.05 mm to 6.13 mm within three months of the injection as discussed in the study by Jiménez-Pérez et al. from 2018.[11] However, after six months, the thickness was measured at an average of 6.9 mm. This supports the idea that corticosteroids are helpful in the short-term but may not be as effective for long-term treatment of chronic plantar fasciitis. One argument against using corticosteroids for the treatment of plantar fasciitis is that the disease may lack an inflammatory process.[12] This is especially true when considering whether plantar fasciitis is more related to a degenerative or an inflammatory process.[13] The histologic evidence is important because it has been concluded that the use of corticosteroids may predispose the patient to fascial rupture. The histological effects of corticosteroid on plantar fascia, include deposits of artifacts, can be seen in Figure 2.[13] Therefore, a consideration for the use of corticosteroids in the treatment of chronic plantar fasciitis should be reevaluated.[13]

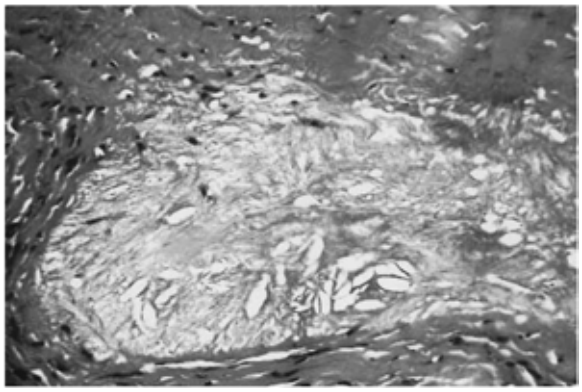

Figure 2: Artifacts within fascia representing areas of previous corticosteroid injections (H&E x40). The artifacts contribute to the weakness of the fascia after repeated therapy. Adapted from Plantar Fasciitis: A degenerative process without inflammation.[13]

Platelet-Rich Plasma Therapy

PRP is a therapy in which a supersaturated concentration of autologous platelets augments the natural healing response of fascia.[12] This concentration of platelets possesses bioactive components of the blood that increases the

concentration of growth factors responsible for increased healing in various tissues. A common hypothesis of the effects of PRP is that platelets release cytokines to inhibit anti-inflammatory COX-2 enzymes.[12] PRP solution is prepared by collecting the patient's own blood. The blood is then separated via centrifuge to allow for collection of the buffy coat layer that contains a high concentration of platelets and/or leukocytes.[14] The solution is injected into the site of injury. There are other formulations of PRP such as leukocyte-rich, leukocyte poor, and activated or non-activated solutions.[14] Of these different PRP solutions, minimal research has been conducted to differentiate their efficacy.

This method has been studied with interest in the possibility that PRP also aids the regeneration of tissue that has low or prolonged healing potential.[11] It has been studied in the setting of many musculoskeletal conditions like joint osteotomy, ACL repair, arthroplasty, Achilles tendinopathy, and degenerative spine disease.[15] There is still much to learn about PRP therapy, but the current literature alludes to a bright future for research and clinical uses for PRP. The advantage to PRP is that it is autologous and relatively safe for the patient, as it is easily recognized by the body. It is not a low-cost method, however, as it averages $1,755 per injection.[15] Like corticosteroid, PRP has considerable uncertainty concerning its effectiveness compared to other treatment methods. Notwithstanding this uncertainty, PRP is still used as a treatment option as approximately 86,00 athletes are treated annually with PRP injections for various musculoskeletal conditions.[14]

In a study from 2018 by Jiménez-Pérez et al., PRP demonstrated positive results for the treatment of chronic plantar fasciitis when measuring relief of pain using the visual analog scale.[11] Patients reported changes from an average of 8.25 mm to 1.85 mm. The same study indicated that ultrasound measurement of the fascia decreased from an average 7.90 mm to 4.32 mm after 3 months post-injection. The change in thickness was maintained after 6 months from the start of PRP therapy.[11] PRP is a safe treatment option that is effective in the long term, showing superior results compared to corticosteroid injections.[6,12] Most cases of plantar fasciitis are acute and resolve relatively quickly therefore, implementing PRP as a first line treatment is not necessary. However, it may be useful in cases of chronic plantar fasciitis. More research will yield results that may prove beneficial when combining this therapy with another non-surgical treatment.

Discussion

The most common measurements utilized throughout the literature was the visual analog scale for pain. Alternatively, ultrasound measured fascia thickness was another common measurement used. A study by Cenk et al. indicates that the thickness of the fascia is not predictive of the outcome of treatment of plantar fasciitis.[16] They suggest fascia thickness to be reserved for diagnosis, not prognosis.

A 2018 study by Johansen et al. indicates that corticosteroid injections combined with controlled training is the best treatment for plantar fasciitis and should be considered as the first-line therapy for new plantar fasciitis cases.[1] However, a study released in the same year by Jiménez-Pérez et al. suggests that PRP has better long-term results than corticosteroid treatment.[11] This disparity suggests that there is not a common consensus to the first line treatment for plantar fasciitis. It is evident that cases of chronic plantar fasciitis are treated differently than acute cases, which resolve spontaneously in about 85% of cases.[1] It is of note that there is much research ongoing concerning plantar fasciitis. As the disease processes for plantar fasciitis becomes better understood, treatment plans can be better specified for the individual.

Conclusion

Stretching, corticosteroid injections, and PRP injections are all independently useful treatment options for plantar fasciitis, each with their own disadvantage. Stretching is a useful modality in both the short and long term and is highly recommended amongst orthopedic surgeons. The fact that the treatment is dependent on patient compliance means monitoring patient progress can be difficult. Corticosteroid has been used for many years, is effective in the short term, and cost effective. One drawback is the possibility of recurrence with the long-term effectiveness in doubt. Though rare, corticosteroids may predispose the patient to fascial rupture which further complicates treatment. PRP injections are effective short and long term therapies, are patient independent, and are effective in reducing inflammation. However, PRP is most likely not to be recommended as a first line treatment because it is a novel treatment on the market and can be costly.

Between the three non-surgical treatment modalities discussed, it is safe to conclude that starting with the least invasive and working towards the most invasive is the best clinical application. This is advantageous especially in cases of acute plantar fasciitis, as it has been shown that most cases resolve spontaneously. As the plantar fasciitis persists, drastically reducing inflammation with corticosteroids is most likely the concluding step in

treatment. However, in cases when the fasciitis becomes chronic, different modalities, such as PRP may be appropriate to reduce the thickness of the fascia long term. During the entire course of treatment, stretching and exercises should also continue to create an optimal environment for recovery.

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Case Report: Kohler's Disease Appears in Monozygous Twins

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Abstract

Kohler's disease is a rare type of idiopathic osteochondrosis arising from avascular necrosis of the navicular bone. Kohler's disease occurs most often in children less than ten years of age. This article serves to present evidence of a genetic predisposition and to promote awareness of Kohler's disease. This article discusses an unusual case of Kohler's disease seen bilaterally in monozygous male twins. The case discussed in this article comes from research that reviewed the development of bilateral Kohler's disease and promoted awareness of bilateral Kohler's disease in monozygous twins due to the absence of the occurrence in the literature. Kohler's disease has a predisposition for male patients despite females typically being diagnosed earlier than males. Radiologic evaluation is needed for clinical diagnosis, often depicting flattening, sclerosis, and fragmentation of the navicular bone, distinguishing the clinical progression of the disease, and differentiating it from other plausible diseases. Moreover, due to Kohler's disease occasionally presenting with the cardinal signs of inflammation, it is commonly misdiagnosed as osteomyelitis, which is important to differentiate from as the prominent treatments differ.

Introduction

German radiologist Alban Kohler was the first to describe the bone disease referred to as Kohler's disease. Kohler's disease occurs when the navicular bone transiently loses blood supply leading to avascular necrosis (osteonecrosis) resulting in bone collapse.[1] Approximately 25% of patients that present with Kohler's disease develop it bilaterally.[1] The onset typically occurs during childhood from the ages of four through nine.[1] This disease disproportionately affects males more than females with faster onset in females due to an earlier ossification process.

The exact etiology is currently unknown, although some theories propose an unknown genetic disposition. This article seeks to propose a plausible genetic mechanism for the etiology of Kohler's disease.

Vascular endothelial growth factor (VEGF) plays a pivotal role in angiogenesis and has been postulated in the regulation of blood vessels in the primary spongiosa.[2] While normally expressed in chondrocytes at the growth plate, VEGF's absence in mouse models illustrates a profoundly decreased vascular invasion and concomitant trabecular bone formation.[2] Factors affecting VEGF expression may be present in pathological states where low oxygen tension or hypoxia manifests such as myocardial infarction, cancer, and stroke.[2] Recent research proposes that fetal skeletal development, as well as cell differentiation, is hindered in this reduced oxygen state.[2] A potent and critical moderator of hypoxia and VEGF is the hypoxia-inducible factor (HIF).[2]

Expression and subsequent circulation of VEGF occurs due to production of HIF in oxygen deficient conditions.[2] On epithelial cells, VEGF binds to specific receptors to induce angiogenesis. HIF activity is modulated by post-translational modification.[2] Under hypoxic conditions, normal physiology compensates by stimulating the production of HIF to increase expression of VEGF and subsequently an increase in angiogenesis.[2] The ubiquitin protease pathway degrades HIF under normal physiologic conditions, although HIF degradation is prevented under hypoxic conditions.[3] Therefore, we propose two events that can lead to the rise of Kohler's disease. First, a significant deficiency in VEGF or HIF can lead to decreased angiogenesis. Second, a significant increase or elevation in ubiquitin results in the degradation of HIF, which lowers the expression of VEGF.

Some theories suggest since the navicular bone is the last tarsal bone to develop an ossification center, Kohler's disease may be related to micro-injuries and stress surrounding the navicular bone.[4] The ossification process starts at 18 months to two years in females, compared to two-and-a-half years to three years in males.[4] The navicular bone is impacted by weight-bearing pressures such as weight gain, an early onset growth spurt, or forces from turning and twisting. Late bone ossification results in structural weakness of the navicular bone causing compression of the blood vessels supplying the navicular bone to transient avascular necrosis.

The navicular bone has a dual-vessel vasculature supplying the dorsal and plantar aspects. The dorsal aspect is supplied by a branch of the dorsalis pedis artery whereas the plantar aspect is supplied by the medial plantar branch of the posterior tibial artery. Both vessels penetrate the navicular bone, branching to feed the medial and lateral thirds of the bone and leaving the central one-third avascular.[5] These vascular foramina are located on plantar, dorsal, medial, and lateral aspects of the navicular bone.[5] Theoretically, significant compression of any tiny surrounding vascular foramina may result in reduced blood flow,

subjecting the navicular bone to avascular necrosis.[5] The differential diagnoses for Kohler's diseases include osteomyelitis, tarsal coalition, symptomatic os navicular, pediatric flexible flatfoot, and stress fracture.

Case Presentation

Two identical twin brothers of Caucasian descent, aged eight-and-a-half with no significant medical history, presented for assessment of bilateral dorsomedial midfoot pain radiating up the tibia. The twin brothers experience pain for one year and it progressively worsened over the next three weeks. The pain worsened after a long day of strenuous physical activity. Nothing alleviated the mild, aching pain. The complaints were identical for both twin brothers.

Upon physical examination, the twins were well-developed and displayed normal growth. Both patients experienced pain and tenderness to palpation upon grazing the dorsomedial aspect of their midfoot, with the left side being more prominent. The patients had full range of motion in all directions, although both patients' pain was exacerbated with both active and passive inversion and eversion forces. No dermatological changes were noted and both patients were neurovascularly intact. An extensive neurological exam showed no abnormal findings. A thorough vascular exam displayed no pathologic findings and thyroid hormones were within normal limits in both patients. The diagnosis of Kohler's disease was made clinically based on history and a high degree of suspicion.

Radiological assessment exhibited flattening, collapse, and fragmentation of both navicular bones, indicating the presence of bilateral Kohler's disease (Fig.1, 2).[7] The right navicular bone for one of the twins (Patient 1; Fig. 1) was more apparent compared to the other twin (Patient 2; Fig. 2), who had approximately equivalent involvement of both naviculars. Nonetheless, the left navicular bone produced more significant clinical symptoms in both patients.

For treatment, both patients were given a below-the-knee walking cast for the left lower extremity. Only the left lower leg was cast due to increased clinical manifestations isolated at the navicular bone and to maintain adequate mobility. Three weeks after their initial hospital visit, the casts were removed. The symptoms had decreased as indicated by a normal physical exam and clinical presentation. In addition, each patient was treated with flexible, soft, medial longitudinal arch shoe support.

In the months following, both twins encountered bouts of recurrent and persistent symptoms paralleling each other clinically. Additionally, each twin was treated conservatively with arch support shoe inserts. This lasted until the clinical manifestation increased promptly, creating the need for casting and refraining from all strenuous physical activity. The twins also developed gastrocnemius-soleus complex tightness for which they underwent physical therapy. The gastrocnemius-soleus complex plantarflexes the foot at the ankle joint, thus demonstrating they developed gastrocnemius-soleus equinus.

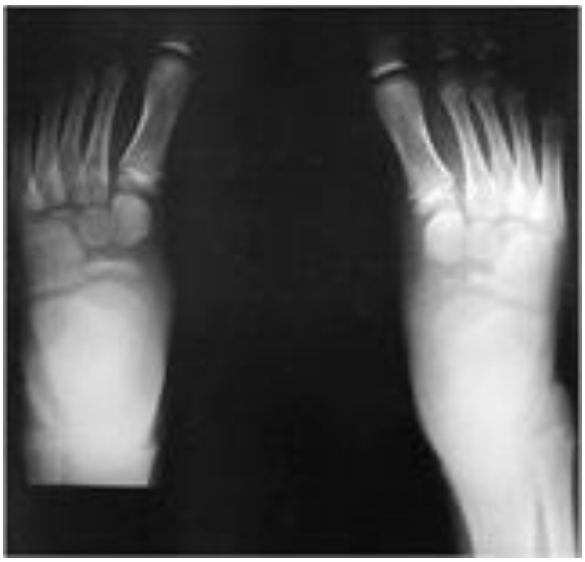

Figure 1. *Radiologic Findings for Patient 1.* Adapted from Clinical Orthopaedics and Related Research.[7]

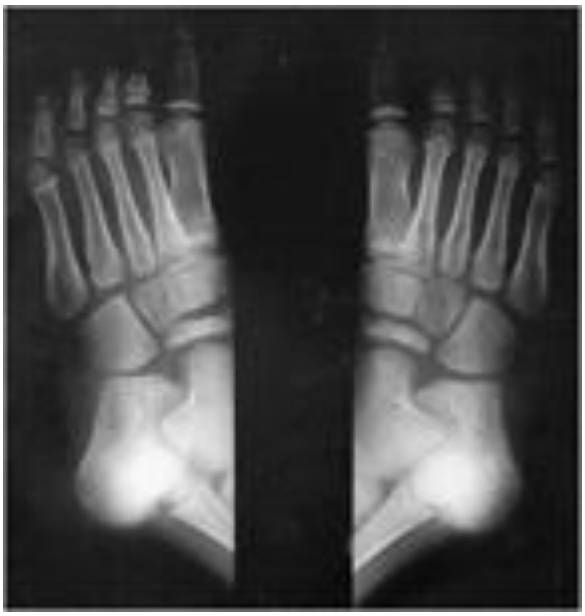

Figure 2. *Radiologic Findings for Patient 2.* Adapted from Clinical Orthopaedics and Related Research.[6]

Many cases of Kohler's disease spontaneously resolve between 18 months and three years, some even as early as six months from the initial diagnosis.[7] During a follow-up visit 18 months after the initial diagnosis, the twins both displayed a normal physical exam. Both twins resumed participation in strenuous physical activities with no complaints or symptoms. Four and a half years after the initial onset of symptoms, the twins proclaimed to be physically fit and completely free from any recurring symptoms.

Discussion

Two main points make this case unique. First, clinical manifestation and progression of Kohler's disease presented similarly in both twins. Second, both patients had a bilateral presentation, suggestive of an underlying genetic predisposition because Kohler's disease is typically unilateral. As with most cases of Kohler's disease, the patients fit the typical patient demographic consisting of young male children.[8] Due to the rarity of Kohler's disease, there are several limitations involving this case report, as this sample size may not be representative of the general population.

While the cardinal signs of inflammation commonly present in Kohler's disease clinically, osteomyelitis shares a similar presentation of increased pain, erythema, temperature, and swelling and can often result in the misdiagnosis of osteomyelitis.[9] Osteomyelitis is a bone infection developing from two different mechanisms. The first mechanism is the invasion of microorganisms as commonly seen in trauma. The second mechanism is through the hematogenous spread, which commonly affects pediatric patients with open physes similar to the patients in this case presentation. Therefore, differentiating between both diseases is vital as the primary treatment differs. Osteomyelitis can be easily differentiated from Kohler's diseases through laboratory analysis of the patient's white blood cell count, C-reactive protein, and erythrocyte sedimentation rate, which should all be elevated.

Imaging plays a crucial role in differentiating Kohler's disease from other more prevalent bone lesions. Radiographs and magnetic resonance imaging can differentiate Kohler's disease from other diagnoses such as tarsal coalition, os navicular, and fractures. Typically, Kohler's disease presents radiologically as flattening, sclerotic changes, and fragmentation of the navicular bone.

Kohler's disease is treated non-surgically and contingent on clinical progression. For mild cases that may be self-limiting, a navicular bone cut-out supportive orthotic with padding may be enough. For moderate to severe cases, below-the-knee weight bearing casts should be worn for approximately six to eight weeks. Additionally, the foot may benefit from being placed in a slightly plantarflexed and inverted non-weight bearing position to alleviate the symptoms that occurring due to the tibialis posterior muscle. General orthotics may provide symptomatic relief, although there is no evidence indicating a reduced duration of symptoms. The only indicated pharmacologic intervention would be NSAIDs supplemented with rest and ice for mild cases. Although Kohler's disease is typically self-resolving, patients with non-surgical treatment experience relief of symptoms at three months rather than 15 months.[10] Additionally, in cases where Kohler's disease does not self-resolve, patients may encounter sustained pain or damage to the surrounding area.

Conclusion

This article analyzed a unique case of bilateral Kohler's disease in identical twins. Initially, both patients had a severe onset of Kohler's disease and were instructed to wear a weight bearing cast for six to eight weeks. Shortly afterward, both patients' symptoms subsided allowing them to wear a navicular bone cutout with medial arch support. Both twins had extremely similar clinical presentations and radiologic findings, highly suggests influence of genetic or environmental factors. The pathogenesis of Kohler's disease is poorly understood, and future investigations are needed to identify genetic, vascular, bone, and biomechanical predispositions for developing this disease. Despite the rarity of Kohler's disease, physicians must be keen to correctly identify this pathology in clinical practice and implement the appropriate treatment.

Understanding the genetic mechanism for Kohler's disease is important for not only treating and preventing Kohler's disease but for other osteochondroses as well. Both Kohler's disease and Freiberg's disease are considered rare true osteochondroses that may stem from the same genetic root. Future research may include clinical trials monitoring the levels of VEGF, HIF, and ubiquitin. Additionally, stem cell research may yield benefits to further enhance the complex mechanism between VEGF, HIF, ubiquitin, and other factors possibly interacting.

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Case Report: Coral Reef Aorta with Hypercalcemia

Jin Lee, B.A.

ABSTRACT

Objective: The purpose of this case report is to highlight an atypical feature observed in a patient diagnosed with coral reef aorta and to present a physical finding that may aid clinicians in early detection of coral reef aorta.

Methods: A 59-year-old female who presented to the emergency department with severe lower extremity ischemia and later diagnosed with coral reef aorta was followed for 10 days. Her serum calcium levels were obtained throughout her hospital stay.

Results: Although cases of coral reef aorta have been associated with normocalcemia, this patient showed fluctuations in her serum calcium levels with gradually increasing hypercalcemic values throughout most of her hospital stay. This patient also had abdominal tenderness upon palpation along the midline which correlated with the course of her calcified aorta.

Conclusion: Obtaining consecutive serum calcium values for patients with coral reef aorta will help delineate if fluctuations in serum calcium are involved in the pathogenesis of coral reef aorta. Assessing for abdominal tenderness in the context of visceral and lower extremity ischemia may be an effective screening tool for coral reef aorta.

Introduction

Before 1984, cases of coral reef aorta (CRA) were documented as aortic ossifications. The term CRA was coined by Qvarfordt et al. due to its "rock-hard, irregular, gritty, and whitish luminal surface strongly resembling a coral reef."[1,2] Although its etiology remains unclear, it has been found to be most common among middle-aged female smokers reported to have normal serum calcium levels despite the heavily calcific nature of CRA. Severe calcification causes luminal obstruction of the descending aorta and its branches, this results in lower extremity claudication and visceral ischemia. Symptoms can include renal hypertension, abdominal pain, and weight loss. This report is about a patient who presented with CRA but with fluctuating levels of serum calcium. Despite the possibility that her hypercalcemia was likely paraneoplastic secondary to an elevated parathyroid hormone-related peptide (PTH-rp) from her lung malignancy, this case raises questions of how fluctuating calcium levels affect the pathogenesis of CRA and whether this is a regular feature in CRA development. This report will also highlight the importance of identifying abdominal tenderness on patients presenting with lower extremity ischemia as it may be a key physical finding for this rare disease.

Case Report

A 59-year-old female presented to the emergency department (ED) with worsening lower back and bilateral lower extremity pain upon exertion with greater severity on the right. Her history was notable for chronic obstructive pulmonary disease, degenerative joint disease, migraine headaches, tobacco use, and hypertension that was controlled with two different anti-hypertensive medications.

To relieve the pain, the patient would sit down on the couch with her lower extremities flexed and knees twisted, using pillows to support this position. She would remain in this position until these symptoms gradually improved, but when it failed to help, she decided to go to the ED.

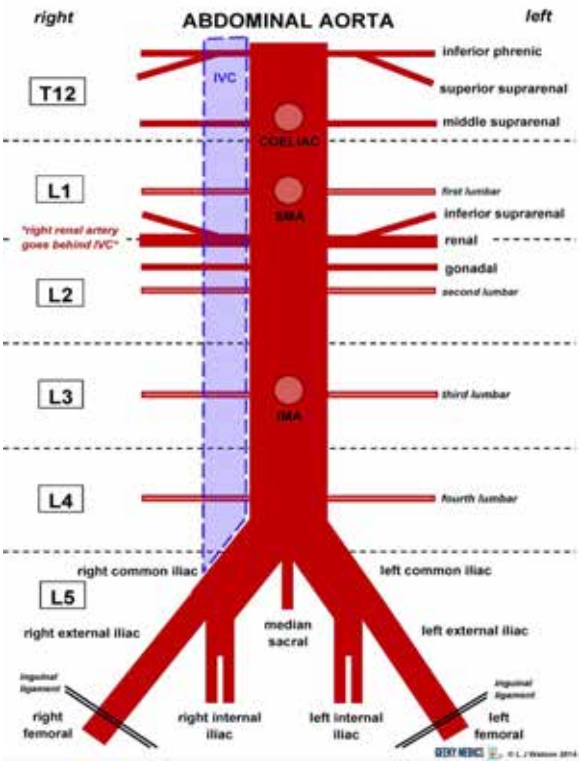

Figure 1 (adapted from Geeky Medics). Branches of the abdominal aorta.[3]

On physical exam, the muscle strength of her lower extremities was 5/5 bilaterally across knees and hips but she could not push for long as her legs would quickly fatigue. Reflexes and gross sensation

were intact. Most of the physical exam was unremarkable, except for 7/10 abdominal pain with deep palpation along the midline. Patient denied urinary symptoms and tests were negative for signs of an infection. However, a computed tomography (CT) angiogram showed multifocal atherosclerotic vascular calcifications of the abdominal aorta, directly deep to the supra-pubic and peri-umbilical regions corresponding to the lower lumbar vertebra, L3-L5 (Fig. 1), and these levels correlated with her abdominal tenderness. The CT angiogram also showed a complete occlusion of the right common iliac artery and a near complete occlusion of the left common iliac artery (Fig. 2), explaining her lower extremity ischemia.

The other pertinent physical exam finding was diminished breath sounds over her left lower lung, consistent with the location of her lung cancer. The patient's calcium levels were followed along with other metabolites due to her cachexia. Her serum calcium was 10.6 mg/dL (normal range: 8.5 to 10.2 mg/dL) in the ED, but normalized the next three days (9.9-10.2 mg/dL) of her hospital stay. However, even with the decrease in her calcium intake, her serum calcium steadily trended up to 12.2 mg/dL by the day of her discharge. Labs showed an intact parathyroid hormone (PTH, 10.63 pg/ml) that was decreased and an elevated PTH-rp (29 pg/ml), likely paraneoplastic to the squamous cell carcinoma that was diagnosed following a left lower lung biopsy. Although the patient had presented for lower extremity ischemia, surgical re-vascularization of the aorta for declaudication, a common surgical treatment for CRA, had to be postponed to prioritize the staging of her lung malignancy. As the patient desired to continue the rest of her work-up for the lung malignancy and begin outpatient cancer treatment, the patient was treated with Zoledronate, a bisphosphonate for her hypercalcemia prior to her discharge and was provided a rollator to help her ambulate short distances. The patient was referred to a pulmonologist but lost to follow-up.

Discussion

Coral reef aorta is a rare obstructive atherosclerotic calcification of the descending aorta. CRA is most commonly found among middle-aged female smokers, but has a wide age distribution (4-82).[7] Policha et al. suggested that the 1.6:1 female-to-male preponderance found in their literature review may be associated with a drop in estrogen among perimenopausal women.[2] The lower estrogen levels may lead to excessive calcification via protein mediators; receptor activator of nuclear factor κB ligand (RANKL) and protein-2 have been implicated.[11] Despite its calcific nature, patients have been reported to have normal serum calcium levels. It is unclear whether this is an abnormally normal finding as low serum levels of calcification inhibitors, such as fetuin-A and uncarboxylated matrix Gla protein (ucMGP) have been implicated.[9,7] The one limitation that Schlieper et al. acknowledged

Author (Year)	No. cases	Sex	Age	Location	Serum Calcium
Qvarfordt[1] (1984)	9	F (9)	48-67 (51 mean)	Suprarenal (6) Both (3)	Normal (9)
Schulte[4] (2000)	21	F (11) M (10)	54.6 (mean age)	Suprarenal (5) Infrarenal (2) Both (12)	Normal in several with hyperplastic bone formation (?)
Pulli[5] (2001)	1	F (1)	50	Suprarenal (1)	Normal (1)
Minnee[6] (2005)	3	F (2) M (1)	52, 56 62	Suprarenal (2) Both (1)	Normal (3)
Grotemeyer[7] (2007)	70	F (46) M (24)	14-81 (59.5 mean)	Suprarenal (6) Infrarenal (15) Both (43)	
Kopani[8] (2009)	1	M (1)	73	Both (1)	Normal (1)
Schlieper[9] (2010)	10	F (6) M (4)	39-77 (54.8 mean)		Normal (10)
Policha[2] (2013)	1	F (1)	54	Both (1)	
Ishigaki[10] (2017)	1	M (1)	82	Both (1)	Normal (1)
Our patient (2018)	1	F (1)	59	Both (1)	High, normal, then high (1)

Table 1. Analysis of literature on coral reef aorta, comparing sex, age, location and serum calcium levels with our patient.

was that a single analysis of calcium serum levels might fail to identify fluctuating events that lead to the development of calcifications.[9] Due to her cachexia, our patient's serum calcium was followed consecutively and the patient showed up-trending values after a few days of normocalcemia. There is uncertainty whether the fluctuating event was due to the mildly elevated PTH-rp (29 pg/ml, normal range 14-27 pg/ml) or if this fluctuating event is a regular feature in CRA development.

The physical examination may prove to be a good screening method particularly for thin patients such as ours. Lederle et al. recommended that persons over the age of 50 undergo a careful abdominal palpation every two to three years for the early detection of abdominal aortic aneurysms.[12] Our patient did not have an aneurysm but consistently reported 7/10 abdominal pain with deep palpation along the midline.

Symptoms vary depending on the location of the calcification within the descending aorta. Isolated suprarenal involvement is more common than an isolated infrarenal involvement, while involvement of both suprarenal and infrarenal segments appear most frequent, as was seen in this case. (Table 1) Qvarfordt et al. reported that all nine of his patients had diminished femoral pulses and 8/9 had aortic bruits, but neither was assessed on this patient.[1] The most common symptoms among 70 patients with CRA who were seen in a single center included renal hypertension (31/70), intermittent claudication (27/70), and chronic visceral ischemia (15/70) usually with abdominal pain, diarrhea, or weight loss. Among those with intermittent claudication, 20/27 had pain-free walking distances less than 200 meters.[7] Similarly, our patient presented for claudication associated with walking short distances as well as hypertension, but the cause of her hypertension was not expounded. The suprarenal and infrarenal involvement seen in her CT angiogram does suggest the possibility for bilateral renal artery involvement. Our patient denied symptoms of diarrhea but had abdominal tenderness with palpation as well as weight loss. However, her lung malignancy was also likely contributory to her weight loss.

CRA is usually diagnosed with abdominal CT or magnetic resonance imaging (MRI). MRI does not contribute to more specific findings but Doppler flow studies or a CT angiogram can be used to determine the severity of the occlusion.[8] The treatment is surgical, involving re-vascularization or stent-graft placement yet these involve potentially serious complications including embolization of atherosclerotic debris.[13]

Conclusion

Coral reef aorta is a rare and severe form of calcification that can lead to visceral and lower extremity ischemia. Pathogenesis remains uncertain, but low serum levels of calcification inhibitors have been implicated. This case study showed levels of hypercalcemia throughout most of patient's hospital stay but serum calcium levels in previous studies have been reported as normal. The patient's hypercalcemia may have been a paraneoplastic source secondary to her squamous cell carcinoma. It is not clear how much of an influence serum calcium fluctuations have on the development of CRA or if it is a normal feature of CRA pathophysiology. Future studies on CRA pathogenesis should consider following serum calcium levels on a consecutive basis. Similar to the abdominal tenderness found in patients with abdominal aortic aneurysm, clinicians should carefully do an abdominal exam deep palpation along the midline in those presenting with visceral and lower extremity ischemia as it may provide an advanced indication for CRA prior to imaging.

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Madura Foot: Case Report and Review

Karanjot Kaur, B.S., Emily Shibata, B.S., Samantha Zandowicz, B.S., Elizabeth Oh, B.S.

ABSTRACT

Objective: The purpose of this article is to review the features that allow for early identification, proper treatment, and overview for the diagnosis of Madura foot.

Conclusion: Mycetoma or "Madura foot" is a chronic granulomatous disease of the skin and underlying tissues that affect the foot. There are multiple different fungi and bacteria that cause this condition but primarily Mycetoma is caused by the bacterium, *Actinomycotic Mycetoma* and fungus, *Eumycetoma*. This condition of the foot is commonly found in countries within the "Mycetoma belt" such as India, Mexico, and Sudan. Despite the majority of the United States lying outside of the region, a few cases such as this case report, have been documented.

Introduction

Mycetoma is the general term for a chronic subcutaneous fungal or bacterial infection of the skin and soft tissue. It has a high predilection for the lower extremity, with 80% of cases reported in the feet and 6% in the legs.[1,2] Other names for this disease are *Eumycetoma*, *Actinomycotic Mycetoma*, and Madura foot; these names refer to the fungal origin, bacterial origin, or its geographic identification in Madura, India, respectively.

This infection has been identified worldwide in regions of tropical and subtropical conditions, often referred to as the "Mycetoma Belt" (Figure 1).[3] Countries within this region include India, Mexico, Sudan, Venezuela, Somalia, and Chad. Despite the United States distance from the Mycetoma belt, there have been a few case reports of Mycetoma within the Midwest of affected individuals who migrated from such tropical countries.

There is a high prevalence seen between the ages of 20-40 years old and a ratio of 3:1 between men and women. Working in agriculture, inhabiting an endemic rural location, or being in an immunocompromised state have been identified as risk factors.[1]

Surveillance and prevention data of Mycetoma is lacking in literature since it is not mandatory to report this disease. Awareness of this condition over the last few years has improved after it was added to The World Health Organization's Neglected Tropical Disease list in 2013, but further investigation is needed.

One of the major cautions of Mycetoma is its prognosis; if left untreated, it may lead to secondary infection, dissemination, lifelong disability, and possibly mortality. Functional concerns are also a concern as a study reported 39.7% of the sample patient population suffered from limited mobility. [25] The goal of this paper is to help spread awareness, discuss features of Madura foot, and present a case report that will guide clinical suspicion to reduce delayed diagnosis, secondary infections, permanent disability, or fatality. [8,9]

Figure 1: Global map highlighting the Mycetoma belt in light green with countries reporting cases of Mycetoma in dark green. [3] Adapted from the Centers of Disease Control and Prevention.

Case Report

A 40 year-old male with a history of diabetes presented complaining of painless "tumors" on his right foot that were present for at least 15 years and reported that they have gradually increasing in size. He recalled stepping on a corn husk while working in the field in Mexico several years prior to moving to the United States. He had not sought out medical treatment for the issue previously because he did not have health insurance and he did not note any significant pain with the worsening condition. During his initial visit, the denied fever, chills, nausea, vomiting, and weight loss. On physical exam, multiple nodules were present on the dorsal and plantar aspect the of the right foot with 2 open lesions measuring 0.4x0.3x1.0cm and 0.2x0.2x0.8cm respectively (Figure 2). Moderate drainage was noted from these lesions containing yellow pebble-like material. No erythema or malodor was noted to the right lower extremity. His left foot and proximal regions of legs and thighs had no significant findings.

Radiographic imaging revealed multiple lytic lesions affecting the calcaneus and midfoot of the right foot with radiolucent lesions present in the soft tissue. The radiographs indicate bone involvement, while soft tissue lesions correlated clinically to the nodules identified in the physical examination. Culture biopsies revealed the presence of yellow grains.

The patient was diagnosed with actinomycotic mycetoma upon final report of culture results and was subsequently started on Bactrim and doxycycline for long term antibiotic treatment. The patient is currently one year post-diagnosis and has been on antimicrobial therapy for the past one year.Patient is showing gradual improvement within the soft tissue and reports back to clinic every 6 months with an MRI for management purposes. Due to a delayed diagnosis and initial onset of treatment, the prognosis for our patient is poor. Imaging revealed diffuse bony and soft tissue involvement of the right foot. Treatment for our patient will aim to stall the progression of disease rather than cure due to the severity of bony and soft tissue involvement. The patient will need a lifelong antibiotic regimen in order to stall the progression of disease and even then, there is a high probability for progression and high possibility of either a below the knee or below the ankle amputation for a better quality of life.

Background

Initial infection of mycetomas occurs when the microorganism is introduced into the skin or subcutaneous tissue by traumatic inoculation regularly from a contaminated thorn prick, splinter, or stone cut. Soil is the known natural reservoir for these organisms with thorns serving as the mechanical vectors.[5,10] The trauma may be a minor event and commonly not recalled by patients.[11,12] If the organisms are not eliminated by an initial neutrophil mediated response, aggregates of organisms form, often referred to as “grains”. Presence of these grains induces a chronic inflammatory state resulting in fibrosis and edema.[13,14] As replication and inflammation continue, painless indurated tumors are formed from the coalescence of smaller nodules, eventually, evolving into necrotic abscesses with draining sinus tracts. [15] These findings are recognized as the classic clinical triad of mycetoma, soft tissue swelling, draining sinus tracts, and macroscopic grains. [16]

Mycetoma can be diagnosed clinically with the presence of the classic triad alone; however, a more definitive diagnosis is achieved through biopsy with presence of grains, seen in Figure 3, and a microbiological examination for species identification.[17] The color of grains may be helpful in distinguishing the underlying etiology of the infection and help guide initial treatment. Yellow to white grains are nonspecific, whereas black grains are specific for a fungal etiology.[18]

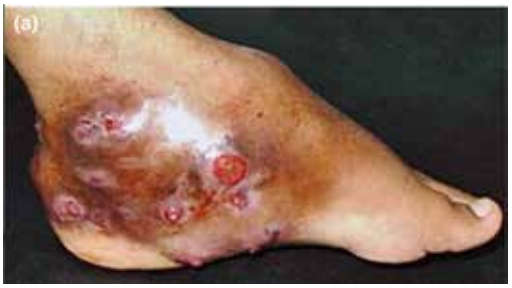

Figure 2: Example of classic Madura Foot with multiple nodules. Adapted from Trop Infectious disease.[16]

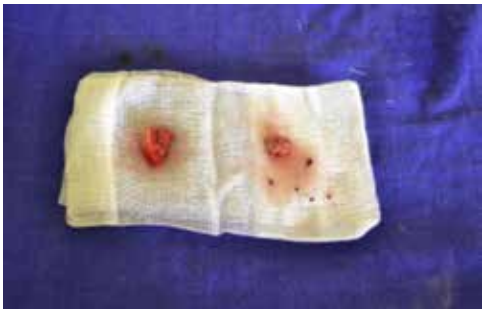

Figure 3: Macroscopic black grains seen in tissue biopsy which are typically seen with fungal etiology.[17] Adapted from the Journal of Dermatology and Dermatologic Surgery.

Imaging modalities can also assist in diagnosis as well as determine the severity and extent of the tissue and osseous involvement.[19] A 27 patient study by Czechowski et al. utilized different modalities to report features of mycetomas. They found MRI provided accurate diagnostic information in about 75% of cases, 80% of which were found to have a small lesion consisting of grains, aiding in differentiation of mycetoma from other infections and tumors.[17] The “dot in circle” sign observed on MRI and ultrasound is highly specific of Madura foot and provides a noninvasive early diagnostic alternative to biopsy. Furthermore, Sarris reported MRI findings of ill-defined mass containing multiple discrete high intensity spherical lesions with a tiney central low-signal focus consistent with dot-in-circle sign on T2-weighted images, Figure 3. This finding is caused by inflammatory granulomata grains surrounded by a fibrous matrix.[19] MRI is utilized to monitor this disease and the efficacy of treatment by evaluating for reduction of inflammatory tissue and bony destruction.[18]

Radiographic findings consistent with mycetoma are soft tissue edema, "punched out'' bone lesions with periosteal reaction, and osteoporosis, as seen in Figure 4.[20,21]

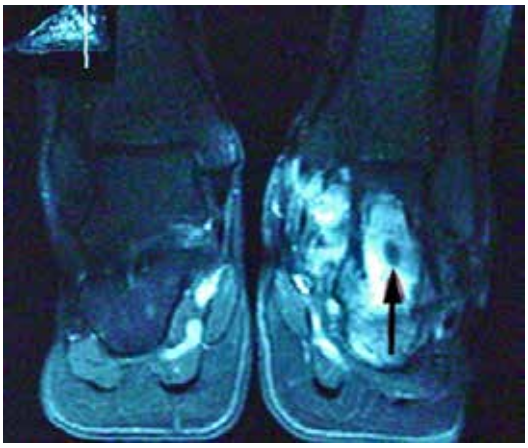

Figure 4: T1-weighted MRI with intravenous gadolinium and fat suppression of a pedal mycetoma after two years of treatment. Arrow points to bone cavitiy. Adapted from Skeletal Radiology, example of "dot in circle".

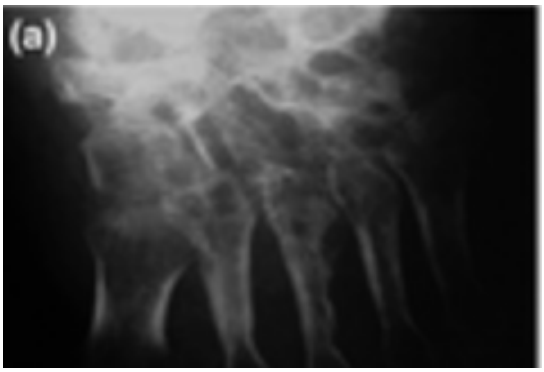

Figure 5: Example of punched out lesions on plain radiographs. [21] Adapted from Int J of Dermatol.

Current treatment is guided by the underlying pathogen and may consist of antimicrobials, surgical intervention, or a combination of the two. If surgical intervention is indicated this may include wound debridement, advanced excision, or amputation. [23,24]

Actinomycetomas are largely treated with antimicrobials alone with rare cases requiring surgical intervention.[22] The medications most commonly reported for treatment include Sulfa drugs, Tetracyclines, Amikacin, and Rifampicin. Combinations, dose, frequency, and duration varies widely. The minimal reported duration of therapy was 4 months and a maximum of 6 years with no recurrence.[24] Bendl et al. recommend at least 12 months of therapy but treatment may be required for longer periods of time if there is bone involvement, indicating poor prognosis.[24] Unfortunately, support for one regimen over another is limited based on the studies evaluation methods and the number of subjects.

Eumycetomas are more likely to require surgical intervention than actinomycetomas but resolution is attainable with antimicrobials in the Azole class alone, including Ketoconazole, Voriconazole and itraconazole. Salim and colleagues reported treatment with azole derivatives drugs for eumycetoma has a resolution of disease in 88% of patients. Comparatively, when antimicrobial therapy was integrated with surgery, complete resolution of 95.7% was observed. Involvement of surgery was initiated at different points of treatment and recommended management remains unclear. [24]

Discussion

This patient fits many of the characteristics seen in the classic presentation of Madura foot. At the time of injury, he was working on a farm in Mexico, one of the most endemic locations for this disease. The use of protective equipment such as shoes and gloves should be prompted in the setting of contact with soil.

Due to delayed diagnosis for 15 years post injury, patient presented with classic triad of soft tissue swelling, draining sinuses and macroscopic grains. Despite being diagnosed treatment was delayed due to inconclusive yellow-white grains observed on biopsy. Therapy was initiated after cultures grew bacteria susceptible to bactrim and doxycycline. The prognosis for this patient is poor due to the long standing nature of disease. The abundance of fibrosis and osseous involvement makes the infection difficult for antimicrobials to fully eradicate due to impeded penetrance. [25] Surgical intervention may be needed in the future if improvement does not continue on the biannual MRI monitoring. Further education of individuals especially within endemic or bordering countries, could have changed the outcome for this individual by making eradication more likely with earlier presentation and less extensive disease.

Conclusion

It is important to recognize and treat Madura foot in the early stages of disease manifestation. Additionally, spreading awareness by educating healthcare professionals working in endemic areas will allow them to recognize and treat mycetoma promptly before progression to advanced disease. Further research is needed to recognize important factors resulting in significant delay, and effective treatment options for delayed diagnoses among populations need to be assessed.

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Jones Fractures in High-Level Football Players

Artin Shakhbandaryan, B.A.

ABSTRACT

Objective: This paper aims to explore the treatment options that produce the best outcomes among high-level football players suffering a Jones fracture in current evidence-based literature.

Methods: Articles were found using the PubMed search engine which primarily accesses the MEDLINE database. Search terms used were "Jones fracture," "Jones fracture treatment," "Jones fracture athletes," and "Jones fracture football." Inclusion criteria included papers about the Jones fracture in high-level football players. Exclusion criteria included studies of patients with systemic diseases.

Results: Research shows that high-level players treated conservatively suffer from refracture 50% of the time compared to 12% among those treated surgically with an intramedullary screw. Players treated surgically with an intramedullary screw returned to activity by about 8.7 weeks compared to 15 weeks in those treated conservatively.

Conclusion: A surgical approach is the treatment of choice among elite football players suffering a Jones fracture due to a quicker recovery and a superior outcome.

Introduction

A metaphyseal-diaphyseal fracture of the fifth metatarsal, known as a Jones fracture, is a common injury affecting high-level football players. A Jones fracture typically occurs as a result of forced inversion of the foot and ankle with axial loading. Patients present with pain on the lateral aspect of the foot and on physical exam, swelling is usually present on the lateral midfoot region. The patient will also communicate sharp pain upon palpation of the fifth metatarsal base.

Athletes often report pain with cutting (rapid changes in direction while transferring their body weight to the involved foot), rolling up on the lateral side of the foot, or landing on the lateral side of the foot.[1] These movements are common for elite football players. Rarely is the fracture a result of a direct contact or a crush injury.

The Jones fracture comprises 17.8% of all foot fractures in the NFL compared to only 0.7-1.9% in the general population.[2] Imaging modalities can diagnose and classify fractures at the base of the 5th metatarsal; each classification correlates with a different course of treatment. The purpose of this article is to review the course of treatment that would produce the best outcome among high level football players suffering from a Jones fracture.

Imaging and Classification

Radiographic imaging is a key component in diagnosing a Jones fracture. Anteroposterior, lateral, and oblique views are preferred to identify and classify the fracture. An oblique view is optimal for isolating the base of the fifth metatarsal and any pathology that may be present (Figure 1). Jones fractures appear as a zone of radiolucency oriented perpendicular to the long axis of the 5th metatarsal, with cortical disruption about 1.5 cm distal to the styloid process on radiographic images.[3] In rare cases where the radiographic series does not show the fracture clearly, magnetic resonance imaging (MRI) or computed tomography (CT) may be used.

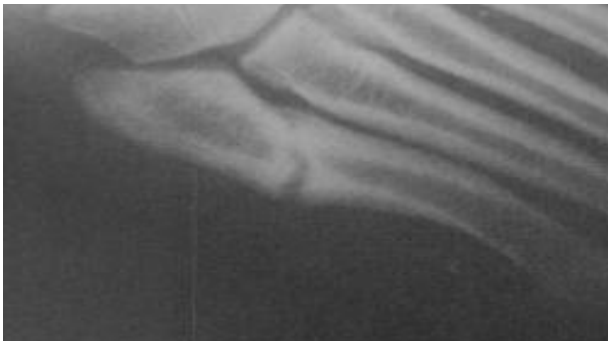

Figure 1: Oblique view of Jones fracture, showing sclerosis and persistence of the fracture incurred six months prior. Adapted from Bilateral Jones Fractures in High School Football Player.[4]

The term "Jones fracture" is often used inconsistently to describe all fractures of the 5th metatarsal base. Several classification systems exist to describe fractures at the base of the 5th metatarsal such as the Lawrence and Botte classification, Stewart classification and the Torg classification. It is important to correctly classify each type of fracture to assist with treatment.

One of the more commonly used classification systems was authored by Lawrence and Botte in 1993.[5] This classification system differentiates between three different fractures at the base of the 5th metatarsal. The distinguishing factors between the three include: location, mechanism of injury, treatment, and prognosis (Figure 2).

A zone 1 (avulsion) fracture describes both intraarticular and extraarticular fractures of the tuberosity. This occurs due to an increased pull from

the peroneus brevis tendon and the lateral band of the plantar fascia during inversion injuries. A zone 2 fracture is often referred to as a true Jones fracture. These fractures occur at the metaphyseal-diaphyseal junction and extends into the 4th and 5th intermetatarsal junction. Zone 2 injuries are a result of forefoot adduction with the hindfoot in plantarflexion.[6] Zone 3 fractures are located at the proximal diaphysis distal to the 4th and 5th metatarsal base articulation. These fractures are caused by acute or chronic overloading of the region as in a stress fracture.[6]

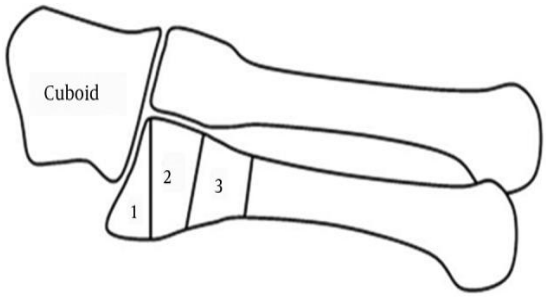

Figure 2: Lawrence and Botte's Classification of Proximal 5th Metatarsal Fractures (Zone 1, 2, and 3). Adapted from Proximal Fifth Metatarsal Fractures: Anatomy, Classification, Treatment and Complications.[6]

The Torg classification further classifies Jones fractures that take place in zones 2 and 3 (Figure 3).[7] A type 1 has a narrow fracture line without intramedullary sclerosis. Type 2 has widening of the fracture line with evidence of intramedullary sclerosis. Type 3 (non-union) consists of complete obliteration of the medullary canal by sclerotic bone.[7] Both Torg types 2 and 3 involve both cortices.

Type	Activity	Radiographic Findings
1	Acute	Narrow fracture line without intramedullary sclerosis
2	Delayed Union	Widened fracture line with intramedullary sclerosis
3	Non-Union	Complete sclerotic obliteration of the intra-medullary canal

Figure 3: Torg classification for 5th metatarsal fractures in zones 2 and 3. Adapted from Fractures of the base of the fifth metatarsal distal to the tuberosity.[7]

Treatment

Treatment for the Jones fracture has changed throughout the years. Zone 1 fractures are the most common and can be treated conservatively with good outcomes. For nondisplaced fractures, most authors recommend a conservative approach that includes immobilization in a posterior splint and strict non-weight bearing; icing and elevation are also recommended in the first three to five days.[8]

Zone 2 and 3 fractures typically require a surgical approach. Zones 2 and 3 are not treated conservatively due to the increased likelihood of delayed union or non-union.[7]

In previous years, the treatment of choice for Torg types 1 and 2 fractures had been nonoperative. For a Torg type 3, either a bone graft, or an intramedullary screw is the treatment of choice. Intramedullary screw fixation is now the standard for all three Torg fracture types (Figure 4).[6] A conservative approach is not commonly used as the only form of treatment except after reinjury of a stable screw fixation.[1] Whether the patient is an athlete or not also plays a role in treatment. In athletes, a surgical approach with open reduction and internal fixation yields excellent results; for those in the general population, the patient should participate in the discussion and choice of treatment techniques.[8]

Although intramedullary screw fixation is widely agreed upon, there is still disagreement about screw selection among surgeons. The length of the screw should allow it to cross the fracture line and engage the diaphysis distally. Some studies suggest that when it comes to the diameter of the screw, the largest screw that can fit tight within the medullary canal should be chosen. On the other hand, a cadaveric study looking at 4.5-mm and 5.5-mm screws suggested that maximizing screw diameter did not improve fixation rigidity.[9] In a study by Porter and colleagues, 20 fractures were fixated with a 5.5-mm screw and 24 were fixated with a 4.5-mm screw. The mean return to sports time with the 5.5-mm screw was 9.3 weeks whereas the group with the 4.5-mm screw returned in 7.5 weeks.[10] Although both screws compare favorably to other sized screws, there is no significant difference between the 4.5-mm and 5.5-mm with regards to returning to activity. The advantage of the 5.5-mm screw is its superior bending strength. There were no bent screws in the 5.5-mm group compared to about 6-8% of screws bent in the 4.5-mm group. Of the patients in the 5.5-mm group, three suffered reinjury where none suffered reinjury in the 4.5-mm group. At final follow up, all fractures in both groups healed clinically.

The average follow-up for the 5.5-mm group was 16.5 months and that of the 4.5-mm group was 19.8 months. Although both groups experienced similar favorable outcomes, the study was unable to show significant improvement in the 5.5-mm group over the 4.5mm group.

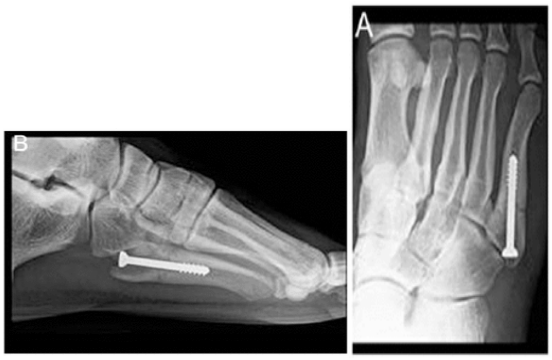

Figure 4: X-rays of football player postoperatively after open reduction internal fixation of 5th metatarsal Jones fracture with 5.5-mm screw. Adapted from Fifth Metatarsal Jones Fractures in the Athlete.[1]

Return to Activity

Return to high level activity is priority when considering treatment for high level athletes. Conservative treatment can sideline an athlete for several months and up to 50% of Jones fractures treated conservatively can result in nonunion or refracture.[11] According to findings of Lareau et al., the average return to activity for 25 NFL players with a Jones fracture treated surgically was 8.7 weeks.[12] Of the 25 players treated surgically, 12% of the group experienced refracture.[12]

Data taken from NFL.com looked at Combine (pre-NFL draft tryout) participants and evaluated how effectively those with a Jones fracture repair returned to activity.[2] Out of the 1,311 participants, 40 had a Jones fracture repair using an intramedullary screw. Seventy percent of those with the Jones fracture repair were drafted compared to 66% of those without the repair. The number of NFL games played in the following season for the group with the Jones fracture repair was 8.8 ±6.8 compared to 7.4±6.6 for those without the repair.[2] Although not significant, this study also suggests that appropriate treatment of a Jones fracture does not diminish NFL participation.

Recurrent Jones fractures are common among professional athletes, there can be a 50% recurrence in professional athletes when trying to play in the same season as injury.[13]

Discussion

This study looked at existing literature to compare treatment options for football players suffering a Jones fracture based on outcomes and recovery time. Not all fractures at the base of the 5th metatarsal are Jones fractures, hence the use of radiographs to diagnose and classify each fracture is crucial in planning treatment.

Although common among football players, the Jones fracture is not an injury that affects players long term. It can be expected that once a player recovers, there will not be much of a drop off in performance.[2] Also important to note is that reinjury is not common if the player takes the appropriate time off and does not attempt to return the same season the injury occurred.

Conservative treatment for a Jones fracture includes splinting or some form of casting, and immobilization until the fracture has healed. Conservative treatment is not recommended for high-level football players trying to minimize the time they are away from competition.[13] Among those suffering a Jones fracture in the general population, a discussion should take place between the patient and the physician to plan treatment. The patient, with the help of the physician, should choose the treatment option best suited for their lifestyle. The verdict is still out as to whether a surgical or conservative approach is best for non-athletes. It is not uncommon for patients not involved with high-level athletics to opt for conservative planning and not deal with the risks and stress associated with surgery. More research can be done to arrive at a more definitive, reproducible solution for those in the general population suffering a Jones fracture.

Conclusion

In conclusion, open reduction and intramedullary screw fixation is the treatment of choice for high-level football players suffering a Jones fracture. Most studies show a recovery period of about 8 weeks and close to a 12% refracture rate among high-level football players treated surgically. Both the refracture rate, and the time to recovery are superior to the results obtained with conservative treatments.

Several areas can be further studied when it comes to the Jones fracture. For one, there remains a disagreement as to the operative technique and the different sizes of hardware used. Whether a 5.5-mm screw produces better results than a 4.5-mm screw is still debatable and the results from literature inconclusive. With that being said, the Jones fracture is not as feared of an injury as it once was due to advancements in treatment and operative techniques.

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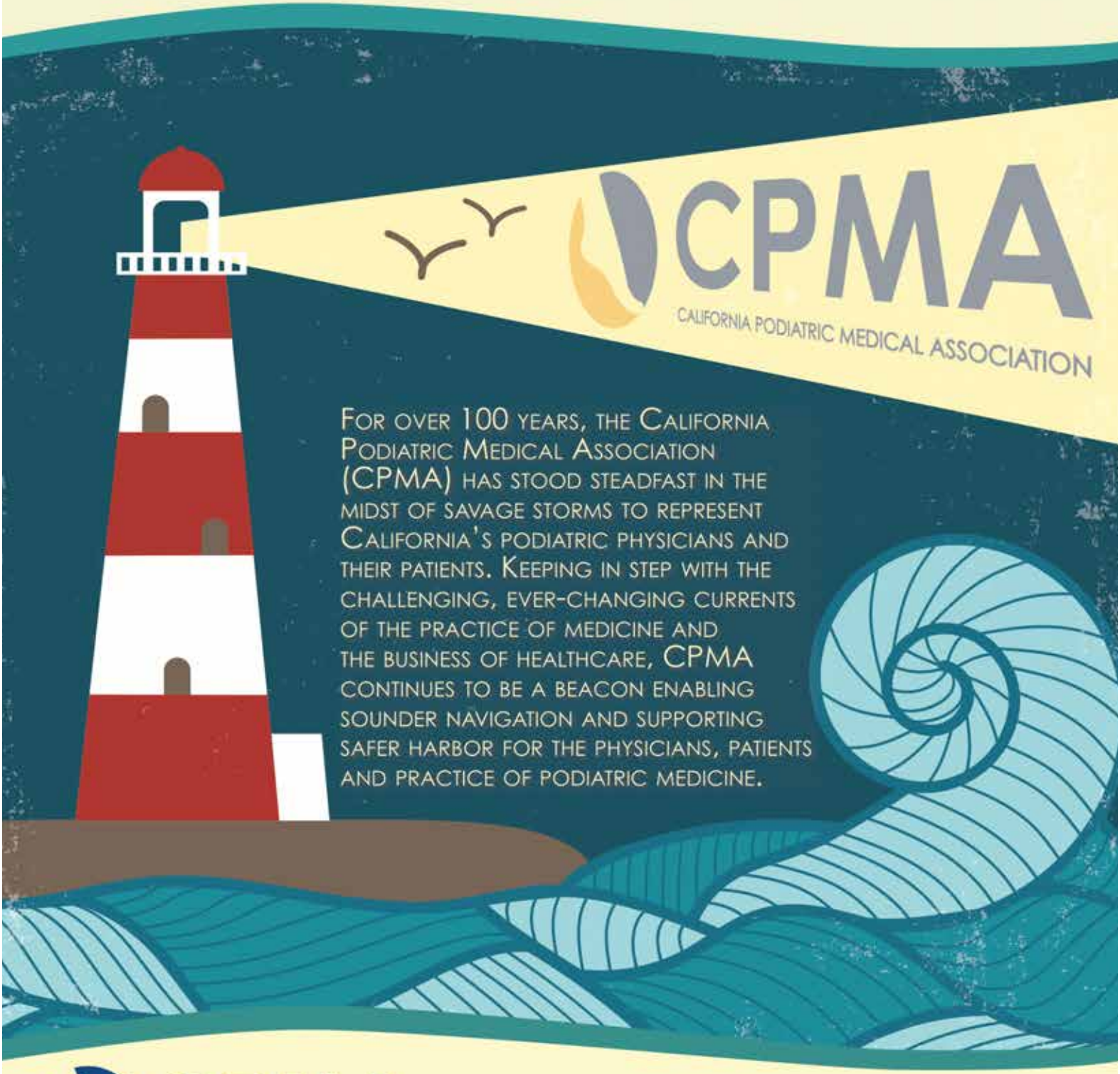

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