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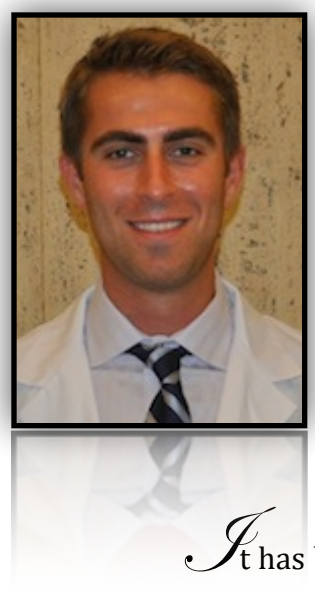

A Note from the Editor

It has been three years since the *Podiatric Medical Review* made a return to the NYCPM campus, and in that short time the journal has grown in scope, size, and quality. This was an especially rewarding year for the editorial board, receiving a record number of proposals for the 2015 journal. As a result of an inaugural lecture mini-series designed to educate and guide students through the often tedious research process, the editorial board was able to open a dialogue with the authors in order to discuss literature reviews and properly formatting research manuscripts.

This year's accomplishments are a product of both the editorial staff's vision and the passion our student body possesses for the advancement of podiatry and research.

Research is our profession's most powerful asset to further strengthen our standing in the medical field. One can see the broadened scope of podiatry in the research that was performed in this year's journal, which ranges from dermatology to vascular pathologies to complex limb salvage and reconstructive surgeries.

My hope is that students take what they have learned as a result of contributing to the journal on with them as they advance in their careers and that they continue to push their own boundaries as well as those of Podiatry as a field. Furthermore, I want readers to sense the passion and effort that was put into creating this student run publication and to use its contents to strengthen their own knowledge and to improve the care of their patients.

Michael T. Rossidis, BS
Editor-in-Chief

A Comparison on the Effective Treatment of Various Skin Grafts on Diabetic Foot Ulcers: A Systematic Review

Hye Jin Yoo, BS, Maria C. Cifone, BS, and Shivani H. Panchal , BA

Abstract

Introduction
It has been shown that among the diabetic patient population, 1 in 4 patients will eventually develop foot ulcers. Unfortunately, underlying conditions such as peripheral vascular disease, neuropathy and poor blood glucose management in the diabetic patient results in higher recurrence rates of foot ulcers despite the efforts of conventional treatments. Failure of such treatment can lead to cellulitis, osteomyelitis, wound chronicity, and ultimately to amputation. Newer treatments such as skin replacement products have improved the efficacy of healing diabetic foot ulcers. Currently, the three widely used skin grafts are Apligraf, EpiFix, and Dermagraft. The purpose of this literature review is to assess the clinical outcomes and effectiveness of each type of skin graft by evaluating recurrence rate, healing times, cost effectiveness, and the mechanism of action of each skin graft.

Study Design
Qualitative Systematic Review of the Literature

Methods
Pubmed and Cochrane database searches were performed on the treatment of diabetic foot ulcers. Inclusion criteria consisted of articles with subjects as follows: age 18 or older; type I or type II diabetes; chronic ulcer size >1.0 cm2 and <25 cm2; full thickness and does not extend to bone, muscle, or tendon; adequate circulation at the ankle of affected leg; no clinical signs of infection. Exclusion criteria consisted of articles with subjects as follows: diagnosed with cancer and is undergoing chemotherapeutic agents or radiotherapy; suspected malignancy of current ulcer; HIV+ or AIDS; any connective tissue diseases; pregnant or breast-feeding; prescribed immunosuppressant, and non-English articles. Six articles were chosen in this qualitative review due to same authorship on several papers with similar data.

Discussion
Comparative analysis of skin grafts showed that EpiFix is superior to Apligraf and Dermagraft in terms of healing time, cost effectiveness, recurrence, and mechanism of action.

Conclusion
Apligraf, EpiFix, and Dermagraft were evaluated for their effectiveness in treating chronic diabetic foot ulcers. Evaluation of such skin graft products is necessary for providing the most effective and optimum treatment for diabetic patients with chronic foot ulcers. It was determined that EpiFix is superior over Apligraf and Dermagraft. However, a consistency in post-operative evaluation is needed to better understand the efficacy of skins grafts.

Key Words
Diabetic foot ulcer (DFU), Apligraf, Dermagraft, EpiFix

*Level of Evidence***:** 4

INTRODUCTION

As the prevalence of people with diabetes increases worldwide, so does the prevalence of complications secondary to this disease. An individual with diabetes faces a lifetime probability of developing a diabetic foot ulcer (DFU's) estimated at 15%.[1] Non-healing DFUs are defined as those that failed to proceed through an orderly and timely reparative process.[2] It is reported that ulcer duration of more than 30 days is independently associated with a 4.7-fold increase in infection. An infected foot ulcer increases the risk of hospitalization by nearly 56 times, and risk for amputation by nearly 155 times.[3] These DFU's may lead to further complications which may ultimately result in amputations. Both complications and the inability to properly treat or prevent the recurrence of DFUs pose a profound economic burden to the society. The cost of treatment for diabetic foot ulcers accounts for $9 billion to $13 billion annually.[4] The wound healing society guidelines recommend the consideration of advanced wound therapies (skin grafts) if a diabetic ulcer does not reduce in size by 40% or more after 4 weeks of standard therapy.[5] Standard therapy consist of debridement, dressing changes, and off-loading.[5] The purpose of this paper is to assess three of the most popular skin graft treatments (Apligraf, EpiFix, and Dermagraft) for diabetics with chronic foot ulcers.

Before one can understand the effectiveness of a skin graft, it is important to understand the processes necessary for wound healing, and how the diabetic state can negatively affect this repair process. Wound repair generally consists of three phases: inflammatory, proliferative, and remodeling. According to Lev-Tov, during the inflammatory phase, cytokines and lymphocytes, such as neutrophils and macrophages, are recruited to the wound; during the proliferative phase, fibroblasts are recruited and angiogenesis takes place when granulation tissue and keratinocyte proliferation are observed; during the remodeling phase, the wound is trying to restructure itself with myofibroblast proliferation in order to increase its strength. [6] Non-healing ulcers in diabetic patients result from hyperglycemia that adversely affects the normal healing process. Hyperglycemia causes an increased level of advanced glycation end products, which in turn inhibit normal extracellular matrix (ECM) deposition and up-regulate activity of matrix metalloproteinases (MMPs).[7] Diabetic patients with ulcerations also experience a decreased response to growth factors because of decreased proliferative fibroblasts in DFUs.[7] Therefore, the impaired ECM in DFUs is a potential target for skin grafts to promote rapid and complete healing to decrease the risk for infections and further complications.[7]

To aid the poor wound healing process in many diabetic foot ulcers, many conventional treatments can be implemented. The conventional treatment regimen for diabetic foot ulcers includes removal of all necrotic or devitalized tissue by mechanical, chemical, surgical and autolytic debridement.[5] Diabetic foot ulcers should be cleansed at each dressing change, using a non-irritating and non-toxic solution.[5] In addition to this, many diabetic foot ulcers are off-loaded to prevent pressures on the foot

from negatively affecting healing time. Also, non-healing diabetic foot ulcers must be eliminated of all bacterial infections before a skin graft is placed. Bacterial infections in diabetic foot ulcers are considered to be "failure or lack of the epithelialization of the ulcer within two weeks of debridement, in addition to offloaded therapy." [5] Thus, diabetic foot ulcers with bacterial infections should be treated with antibiotics. Studies have shown that topically applied antibiotics are more effective for treating diabetic foot ulcers than systemic antibiotics, as they do not effectively decrease bacterial levels in granulation tissue.[5] It is suggested that patients who fail to show a reduction in ulcer size by 40% or more after four weeks of therapy should be re-evaluated and other treatment options such as skin graft should be considered.[5] Apligraf, EpiFix, and Dermagraft stand to be the more novel skin grafts used for the treatment of chronic non-healing diabetic foot ulcers.

Apligraf is tissue-engineered skin made up of cultured living dermis and epidermis.[3] The tissue is derived from neonatal foreskin. Four components make up the composition of Apligraf: extracellular matrix, viable allogenic dermal fibroblasts, epidermal keratinocytes, and a stratum corneum.[8] The extracellular matrix (ECM) contains type I bovine collagen, which is organized into fibrils and fibroblast-produced proteins. The ECM promotes the in-growth of cells, provides the scaffold for Apligraf, and provides mechanical stability and flexibility. The dermal fibroblast component contributes to new dermal tissue by producing growth factors to stimulate wound healing, and additionally this layer also helps to maintain the epidermis.[8] The epidermal keratinocytes layer produces growth factors to stimulate wound healing and form the epidermis. The stratum corneum provides a barrier to infection, wound desiccation, and mechanical damage.[8] Apligraf is supplied in a sealed bag at 20-23°C.[7] The product must be ordered at least 1-2 business days before use and it has an expiration date of fifteen days after initial packaging.[7]

EpiFix is dehydrated human amnion/chorion membrane allografts (dHACM), which contains important biological molecules such as collagen, connective tissue, cytokines, and various types of growth factors.[9] Such growth factors include: the platelet derived growth factors alpha and beta (PDGF-α and PDGF-β) which promote cell proliferation in connective tissue; the epidermal growth factor (EGF) promotes proliferation of epithelial cells; the transforming growth factor (TGF) promotes normal wound healing; and the fibroblast growth factor (FGF) promotes cellular proliferation.[9] In addition, cytokines such as tissue inhibitors of metalloproteinase (TIMPs) regulate the matrix metalloproteinase (MMP) activity, which is crucial for extracellular matrix remodeling.[10] Significantly, in vitro and in vivo experiments have demonstrated that EpiFix contains one or more soluble factors capable of stimulating mesenchymal stem cell migration and recruitment.[10] EpiFix is available in multiple sizes and may be stored at room temperature for up to five years.[9]

Dermagraft is a cryopreserved human fibroblast-derived dermal substitute composed of viable newborn foreskin fibroblasts, seeded onto a bioabsorbable polyglactin mesh.[6] In other words, the fibroblasts from a qualified cell bank (after being screened for infectious agents) are utilized and allowed to proliferate to fill the

interstices of polyglactin mesh scaffold; where the fibroblasts can secrete collagen, other extracellular matrix proteins, growth factors, and cytokines.[6] As a result, Dermagraft does not contain other cell types found in skin such as macrophages, lymphocytes, endothelial cells or keratinocytes.[11] The product is supplied frozen (−75°C) in a clear bag containing a 2 inch × 3 inch matrix and requires a 20-step process of thawing and rinsing the product prior to application to the wound.[6]

In this qualitative review the effectiveness of Apligraf, EpiFix, and Dermgraft, as an alternative treatment for non-healing diabetic foot ulcers were assessed in terms of healing time, cost effectiveness, recurrence rate, and the mechanisms of actions.

METHODS

The systematic search was performed using PubMed database and Cochrane library database, respectively. The initial search on the Pubmed database was conducted using the Boolean operator "and" for the terms "Diabetic Foot Ulcer" AND "Apligraf". The first search yielded 37 articles. The second search was performed employing the boolean operator "and" for the terms "Diabetic Foot Ulcer" AND "Dermagraft" and yielded 30 articles. The third search was also done employing the Boolean operators "and" "or" for the terms "Diabetic Foot Ulcer" AND "EpiFix" or "Dehydrated Human Chorion Membrane Allograft". The third search yielded 8 articles. Inclusion criteria consisted of articles with subjects as follows: age 18 or older; type I or type II diabetes; chronic ulcer size >1.0 cm^2 and <25cm^2; full thickness and does not extend to bone, muscle, or tendon; adequate circulation at the ankle of affected leg; no clinical signs of infection. Exclusion criteria consisted of articles with subjects as follows: diagnosed with cancer and is undergoing chemotherapeutic agents or radiotherapy; suspected malignancy of current ulcer; HIV+ or AIDS; any connective tissue diseases; pregnant or breast-feeding; prescribed immunosuppresant, and non-English articles. The Pubmed Database search yielded 75 articles. After analyzing the papers for proper inclusionary and exclusionary properties, 22 were chosen from the Pubmed database.

The systematic search was also conducted using the Cochrane database. The same Boolean operators as Pubmed database were applied for each graft. As a result, the search for Apligraf yielded 9 articles. The second search for Dermagraft yielded 8 articles. Lastly, the search for EpiFix yielded 2 articles. The Cochrane database yielded total of 17 articles. After applying aforementioned inclusion and exclusion criteria and accounting for overlapping articles with Pubmed database, 2 articles were selected from the Cochrane database. Due to the same authorship on several papers with similar data, 6 out of 24 articles were chosen for this qualitative review.

DISCUSSION

Various studies on skin grafts in the treatment of chronic diabetic foot ulcers have emphasized the need for efficient wound healing. Previous studies have shown the skin grafts are much more effective for treating chronic diabetic foot ulcers than standard wound care alone.[12]

Treatment	Source 2: *Fetterolf et al.*	Source 6: *Zelen et al.*
Standard Care	N/A*	35%
EpiFix	81%	95%
Apligraf	35%	45%
Dermagraft	15%	N/A*

Table 1. Rates of complete healing at 6 weeks of chronic diabetic ulcers of the lower extremity.
*N/A - Data not available in the literature.

Healing time

A study conducted by Zelen et al., compared Apligraf, EpiFix, and standard wound care strategies in a prospective, randomized controlled multicenter study.[7] The result of the study conducted by Zelen et al. found EpiFix had significantly greater rates of complete healing and more rapid time to healing than wounds treated with Apligraf.[7] Apligraf and EpiFix were both more efficient treatments for chronic diabetic foot ulcers compared to standard wound care. Zelen et al. further supported the findings of a retrospective study performed by Fetterolf et al. Fetterolf and colleagues compared EpiFix, Dermagraft, and Apligraf. Research analysis completed by Fetterolf et al. also supported EpiFix to be the most efficient in the treatment chronic diabetic foot ulcers. The results from both studies are presented in Table 1.

The study conducted by Zelen et al. showed an overall increased healing rate for EpiFix (95%) and Apligraf (45%) when compared to the data collected in the retrospective study by Fetterolf et al., (Table 1). Zelen et al. suggested various factors influence the difference in healing rates at 6 weeks between these two published works. These factors include: more aggressive debridement of the foot ulcer and offloading, as well as differences in frequency and quantity of graft application. In regards to the work conducted by Fetterolf et al., it is important to note that by 12 weeks (as opposed to 6 weeks), the rates of complete healing increased for each of the three skin grafts analyzed; EpiFix (92%), Apligraf (56%), and Dermagraft (30%). Rates of healing were not assessed further than 6 weeks in the study by Zelen et al. Overall, both studies support EpiFix to be the best for treatment of chronic ulcers of the lower extremity in diabetic patients in terms of complete healing at 6 weeks. Note that both of these studies had the same inclusion and exclusion criteria.

Cost Effectiveness

When considering the economic impact of advanced wound care products, advanced wound care products can increase short-term spending. However, long term results such as increased healing rates, faster healing time, and reduced incidences of infections and amputations allows cost saving to be achieved in the long run. According to Fetterolf et al., the Centers of Medicare and Medicaid Services (CMS) calculates the cost of each of

	Apligraf	Dermagraft	EpiFix
Mean number of grafts per patient	3.9	5.7	2.4
Total product (sq. cm) utilized	172	214	14
Cost of product used per patient	$7,097	$11,881	$3,091

Table 2. Comparison of quantity and estimates cost of products used per patient.

the three allografts. The overall cost of Apligraf was estimated to be $794,992 or $7,097 per patient.[13] The overall cost of Dermagraft was estimated to be $1,544,499 or $11,881 per patient. And the overall cost of EpiFix was estimated to be $197,819 or $3,091 per patient.[13] Table 2 shows the mean number of grafts used per patient, the total amount of product used in square centimeters, and the cost of product used per patient. The most expensive product for treatment was Dermagraft. The second most expensive skin graft was Apligraf, and the least expensive product used for treatment was EpiFix. Although the price per square centimeter of product for EpiFix is higher compared to the price for Apligraf and Dermagraft, the ultimate treatment cost per patient is least expensive. [13] This is due to the various sized availability of the graft and rapid healing times, resulting in less waste of graft material. [13] In addition, EpiFix is operationally efficient compared to Apligraf and Dermagraft. EpiFix can be stored up to 5 years at ambient temperature, whereas Apligraf and Dermagraft must be stored in specific conditions and require immediate use once packaged. [9, 6, 7] This may potentially save the cost of wasting graft from both damage and expiration.

Recurrence

It is important to consider the recurrence of an ulcer, after product application, to assess

Table 3. Comparison of recurrence incidence of diabetic foot ulcers.

Recurrence Incidence	Apligraf	Dermagraft	EpiFix
Veves et. al.	12.5% at 4 months 2% at 5 months 5.9% at 6 months		
Fetterolf et. al		26% at 8 months	
Marston et. al.		19% at 8 months	
Zelen et. al.			5.6% at 9-12 months

the durability of the product. Each product studied by Fetterolf et al. had different healing times and patients were assessed every certain number of weeks and months to see if the ulcers were completely healed, or if the ulcers had recurred. Ulcer recurrence is defined as ulcers that healed by week 12 and re-opened on or before week 32, according to Fetterolf et al. Table 3 shows recurrence incidence of Apligraf, Dermagraft and EpiFix according to Veves et al., Fetterolf et al., Marston et al., and Zelen et al. Patients treated with Apligraf were reassessed at 4, 5, and 6 months after the ulcers initially healed after 12 weeks. The reported incidence of recurrence was 12.5%, 2%, and 5.9% at 4, 5, and 6 months respectively.[12] Two separate studies showed results for recurrence incidence among patients treated with Dermagraft. The first study by Fetterolf et al., showed that ulcer recurrence was 26% at 32 weeks (8 months) while the second retrospective study showed that ulcer recurrence was 19% at 32 weeks.[14] Patients treated with EpiFix actually showed a full healing rate of 94% following primary healing.[10] These percentages support that patients treated with EpiFix had the lowest rate of ulcer recurrence, followed by Apligraf and finally Dermagraft.

Comparison of Mechanisms of Action in Advanced Wound Care Products

One factor, which plays a role in the difference among these three allografts, is the method by which they are processed. The method by which each skin graft is processed influences the mechanism of action in treating chronic diabetic foot ulcers. Various methods have been developed for processing human allografts. Generally, most methods completely remove cells, DNA, soluble macromolecules, as well as the antigenic and immunogenic macromolecules; leaving only an extracellular scaffold for tissue regeneration to occur.[7] The method by which EpiFix is processed greatly differs from the preparation methods used for both Apligraf and Dermagraft. EpiFix (or dHACM) contains both amnion and chorion from donated placental tissue following scheduled Caesarean sections.[7] Since EpiFix is primarily composed of both amnion and chorion tissue, and not neonatal foreskin (found in both Apligraf and Dermagraft), it can be developed with the PURION® process.[7] The PURION® process is a gently cleansing and dehydration process used to both preserve and maintain biological activities and natural growth factors in native amnion.[7] Since EpiFix is processed in this manner it is assumed to have more growth factors, cytokines, interleukins and other endogenous factors which make it more effective for wound healing. For instance, a study by Koob et al. reported various growth factors that are eluted from EpiFix, after 24 hours in saline solution shown in Figure 1. [7] The growth factors in EpiFix range from 62% (EGF) to 6% (PDGF-BB).

In addition to the growth factors preserved in EpiFix, various interleukins and tissue inhibitors of metalleoproteinases (TIMPs) are maintained by the PURION® process as well. Koob et al., suggests that the maintenance of such factors in EpiFix has a major role, specifically at the molecular level, in the treatment of chronic diabetic foot ulcers. This statement has been supported by the previously discussed results on healing rate by Zelen et al.

Despite the molecular advantages EpiFix has to offer in the treatment of chronic diabetic

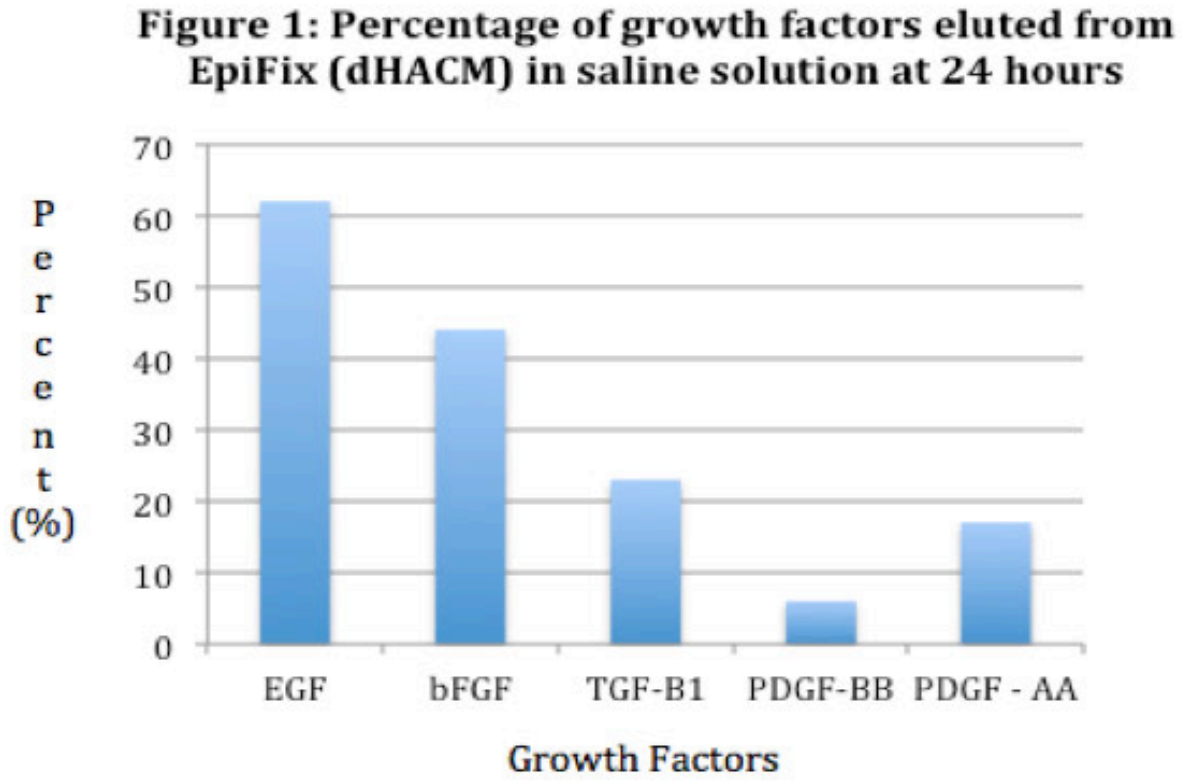

Figure 1. Variety of growth factors available to patients who receive EpiFix.

foot ulcers, it does have its setbacks. Previous studies have shown that significant levels of growth factors *alone*, are required to reach clinical effectiveness for treating chronic DFUs, specifically 10-1000 µg of growth factor treatment.[15,16] While the growth factor concentrations present in dHACM are much lower than clinically reported value (10-1000µg) for effective treatment, EpiFix still has its many other factors, in addition to the level of growth factors available, which still allow for effective treatment.[17] Specifically, EpiFix still contains many cytokines, interleukins, TIMPs, and other endogenous growth factors which all allow all for successful treatment of chronic diabetic foot ulcers.[17]

Finally, one differentiating factor between Apligraf and Dermagraft is Apligraf has been shown to contain tissue inhibitors of metalloproteinases (TIMPs) similar to EpiFix.[10] Since both Apligraf and EpiFix contain TIMPs, this allows for the potential to modulate off-target destruction known to occur in diabetic wounds because of metalloproteinase activity.[18] Since Apligraf contains TIMPs, it could suggest the reason for Apligraf to have greater healing rates compared to Dermagraft's healing rates.

Limitations

One limitation of this qualitative review exists in the selection of the articles analyzed, as several papers used here present results from clinical trials sponsored by pharmaceutical companies that distribute the grafts used. While the authors attempted to limit the biased perspectives of these papers, the underlying implication remains that the

reported graft efficacies can be overestimated. Future reviews will depend on additional clinical studies that are unbiased and also compare these advanced grafts with traditional wound care products. Another limitation was the various offloading devices used in each study. For instance, the data reported by Fetterolf on post-operative standards for skin graft care include: Apligraf-treated patients used crutches or a wheel-chair for the first 6 weeks and then were fitted for a tridensity sandal;[12] Dermagraft patients were allowed to be ambulatory using extra-depth diabetic footwear with custom inserts or healing sandals;[14] and EpiFix patients wounds were offloaded using a removable cast walker (Active Offloading Walker; Darco, Huntington, W.V.).[10] However, in the most recent study by Zelen, non-adherent dressing (such as Adaptive Touch), a moisture-retentive dressing, a compressive dressing and a diabetic cam walker were used for off-loading purposes after treating both Apligraf and EpiFix study groups.[19] Zelen et al. emphasized this method of offloading played an important factor in increasing rates of complete wound closure, as well as the healing rate of diabetic ulcers. Therefore, a uniform offloading device type is recommended for future studies. In addition to this, patient compliance with offloading devices is another factor influencing the rate of healing in chronic diabetic foot ulcers.

CONCLUSION

It is important to continually analyze and assess both the treatment options and opportunities for more efficient wound healing, especially with chronic diabetic foot ulcers. The technological and biological advancement of wound care products such as Apligraf, Dermagraft, and Epifix have certainly aided in better and quicker healing rates compared to standard wound care treatment. In this paper, collective studies indicated that patients treated with EpiFix showed the highest rates of complete healing and quickest wound closure when compared to those treated with Apligraf and Dermagraft. One reason EpiFix has higher healing rates and more efficient wound closure, is due to its molecular advantages. The PURION® process by which EpiFix is prepared allows for increased availability of growth factors, interleukins, and TIMPs; all of which benefit the treatment of chronic diabetic foot ulcers. Apligraf contains TIMPs, therefore allowing for more effective treatment against chronic DFUs compared to Dermagraft. Apligraf and Dermagraft are not processed by the PURION® method, and therefore are not as efficient in the treatment of chronic DFUs as EpiFix. In addition, EpiFix is the most cost effective allograft as it requires the least number of grafts to achieve complete healing, in addition to its availability to use in a closest size to the wound. In regards to ulcer recurrence, EpiFix was shown to have the least chance of recurrent ulcers, followed by Apligraf and then Dermagraft. In conclusion, EpiFix stands to be the superior product of the three most popular allografts used today for chronic diabetic foot ulcers.

AUTHORS' CONTRIBUTIONS

HJY and MC equally conceived the design of the study, performed the database advanced search and evaluated abstracts. SP supplemented the research. The authors designed figures, read, and approved the paper.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest.

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Classification, Diagnosis, and Treatment of Lisfranc Injuries: A Systematic Qualitative Review

James H. Chung, BS, Sam Mark, BS, and Danielle E. Boyle, BS

Abstract

Introduction
The purpose of this study is to evaluate the current diagnostic imaging and surgical treatment options for patients with Lisfranc injuries. A literature review was conducted to assess the efficacy and limitations of current surgical treatment options, specifically screw fixation, plate fixation, and arthrodesis.

Study Design
Qualitative Systematic Review of the Literature

Methods
An English language literature search was conducted using PubMed. Articles pertaining to the classification and radiographic diagnosis of Lisfranc injuries were found using the search terms "Lisfranc joint" OR "tarsometatarsal joint" AND "classification." Articles pertaining to surgical treatment options for patients with Lisfranc injuries were retrieved using the inclusion criteria consisting of adult human subjects and the keywords "Lisfranc joint" OR "tarsometatarsal joint." The search was narrowed using the terms "screw," "plate," and "arthrodesis." The exclusion criteria for both searches consisted of non-English articles, articles published prior to 2004, and cadaveric subjects. Ultimately, 17 articles were obtained through the PubMed database that met the criteria for the study.

Results
Quenu and Kuss were the first to describe Lisfranc injuries into a classification system, but the classification systems used currently in clinical practice are the Myerson and the Nunley-Vertullo classification systems. Diagnosis is assisted by clinical examination, conventional plain film radiography, computed tomography, and magnetic resonance imaging. Treatment options include conservative measures and surgical measures. Surgical measures include closed reduction under fluoroscopy, open reduction and internal fixation, and arthrodesis.

Conclusion
While the Myerson classification system describes high-grade Lisfranc injuries, the Nunley-Vertullo classification system is specific for low-grade Lisfranc injuries. Conventional plain film radiography is commonly used as the initial imaging modality to assess midfoot fractures and sprains, while magnetic resonance imaging is recommended for the evaluation of soft-tissue and ligamentous injuries. Conservative treatment is suggested for stage I Lisfranc injuries. Closed reduction with fluoroscopy is indicated for stage II or III injuries that were diagnosed in a timely manner. Open reduction and internal fixation is indicated for stage II and stage III Lisfranc injuries that have persisted for an extended time frame, or after failed attempt at closed reduction.

Key Words
Lisfranc joint, tarsometatarsal joint, Lisfranc injury, midfoot injury

Level of Evidence: 4

INTRODUCTION

The Lisfranc, or tarsometatarsal, joint complex is the articulation between the midfoot and forefoot. The joint is named after Jacques Lisfranc de Saint-Martin (1787–1847), Napoleon's French army field surgeon who described an amputation of the forefoot through the tarsometatarsal joint.[1,2] The osseous configuration of the Lisfranc joint provides inherent primary stability and is comprised of the five metatarsal bones distally and four of the seven tarsal bones proximally, which include the cuneiforms medially and cuboid laterally.[3] Of importance is the base of the second metatarsal and its

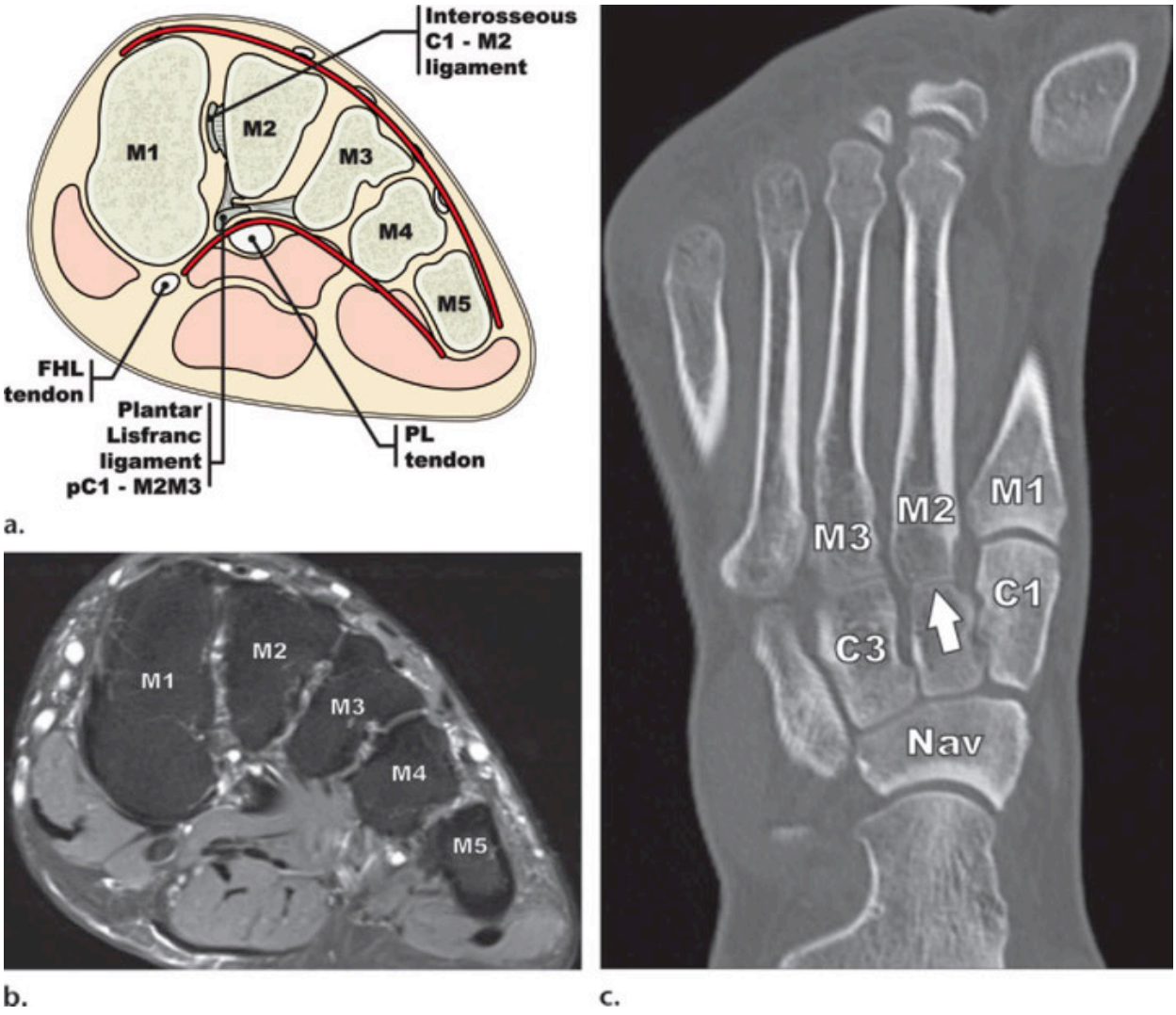

Figure 1. Normal osseous anatomy of the Lisfranc joint complex **(a)** The normal transverse midfoot arch (curved red lines). The keystone shape of the middle three metatarsal bases helps stabilize the alignment. *M1-5* = metatarsal bases, *PL* = peroneus longus, *FHL* = flexor hallucis longus, *C* = cuneiform, *p* = plantar. **(b)** Short-axis proton-density–weighted MRI of the left midfoot through the metatarsal bases (M1–M5) reveals the keystone shape of the middle three metatarsal bases. **(c)** Long-axis reconstructed CT image of the midfoot shows the mortise-and-tendon arrangement formed by the second metatarsal base (M2; arrow) recessed position between the medial and lateral cuneiforms (C1 and C3) that helps preserve joint alignment. *NAV* = navicular.[5] (Reprinted with permission from *Radiographics,* Siddiqui N, Galizia M, Almusa E, Omar I, Evaluation of the Tarsometatarsal Joint Complex Using Conventional Radiography, CT, and MR Imaging / Musculoskeletal Imaging, 514-531, Copyright (2014))

recessed position in between the medial and lateral cuneiforms in the coronal plane, creating a mortise and the "keystone" of a classic Roman arch.[3] This skeletal configuration plays a critical role in stabilizing the joint complex and supporting the transverse arch of the midfoot (Fig. 1).[4]

Additional stability is provided indirectly by ligamentous connections between the tarsometatarsal, intertarsal, and intermetatarsal articulations.[5] The strongest ligaments of the Lisfranc joint are involved in the Lisfranc ligament complex, which is composed of dorsal, plantar, and interosseous components oriented obliquely.[3,5] The interosseous Lisfranc ligament, known as the Lisfranc ligament proper, is the largest and strongest of the interosseous ligaments and is found between the medial cuneiform and the base of the second metatarsal.[5,6] The dorsal Lisfranc ligament connects the dorsal aspect of the medial cuneiform and the base of the second metatarsal, while the plantar Lisfranc ligament connects the plantar aspects of the medial cuneiform and base of the second metatarsal. Anatomic studies suggest that the interosseous and plantar ligaments provide the most stability to the Lisfranc joint as opposed to the dorsal ligaments.[7]

The literature classifies Lisfranc joint injuries into injuries resulting from high-impact trauma, termed *Lisfranc fracture-displacements*, and injuries resulting from low-impact trauma, termed *Lisfranc injuries* or *midfoot sprains.*[8,9] Although Lisfranc joint injuries are relatively rare in the general population, accounting for 0.2% of all fractures with a reported incidence of 1 per 55,000 people in the United States annually, they are the second most common foot injury in athletes.[10-12] These injuries can be difficult to detect at physical examination and imaging, resulting in an estimated 20% of Lisfranc injuries initially undiagnosed clinically.[13,14] Lisfranc joint injuries that are undiagnosed or treated improperly can lead to significant complications resulting from midfoot instability, planovalgus deformity, and osteoarthritis.[15] The goal of this study is to evaluate the current diagnostic imaging and treatment options for patients with Lisfranc joint injuries, as well as classification systems used to describe Lisfranc joint injuries. Furthermore, this review of the literature aims to assess the efficacy and limitations of current treatment options specifically screw fixation, plate fixation, and arthrodesis.

METHODS

An English language literature search was conducted using PubMed. Articles pertaining to the classification and diagnostic imaging of Lisfranc injuries were found using the search terms "Lisfranc joint" OR "tarsometatarsal joint" AND "classification." Articles that were non-English language and published prior to 2004 were excluded. The search yielded 23 total articles, of which three were selected. The three articles selected provided the most detailed understanding of the Lisfranc classification systems. Articles pertaining to surgical treatment options for patients with Lisfranc injuries were retrieved using the inclusion criteria consisting of adult human subjects less then 19 years old and the keywords "Lisfranc joint" OR "tarsometatarsal joint." The search was narrowed using the terms "screw," "plate," and "arthrodesis." The exclusion criteria consisted of non-English language articles and articles published prior to 2004. A total

of 60 articles were found and, after reviewing the abstracts, 14 articles were selected.

Ultimately, a total of 17 articles were used for this systematic qualitative review. Selected articles presented various classification systems, diagnostic methods, and treatment options specific to Lisfranc injuries.

RESULTS

In 1909, Quenu and Kuss were the first to describe Lisfranc injuries into a classification system based on their three column concept, specifically high-grade Lisfranc fracture-displacements.[16] Injuries were classified into three types based on incongruity and direction of displacement, without regard to mechanism of injury: homolateral, isolated, and divergent. Homolateral Lisfranc fracture-displacements were described as demonstrating complete incongruity of the tarsometatarsal joint and displacement of all five metatarsal bases in the same direction. These were found to be the most common injuries. Isolated injuries display only partial incongruity with displacement of one or two of the metatarsal bones and are the least common. Divergent Lisfranc fracture-displacements are similar to homolateral injuries as they both exhibit complete incongruity, but the first metatarsal is subluxed or dislocated medially while the second-fifth metatarsals are displaced laterally.[5] The Quenu and Kuss classification system was later modified by Hardcastle et al., and then by Myerson et al.[3]

The Myerson classification is the most common classification system used today.[17] Like the Quenu and Kuss classification, Myerson describes high-grade tarsometatarsal injuries and divides the injuries into three types: type A (homolateral complete), type B (homolateral incomplete), and type C (divergent). Type A injuries consist of complete incongruity and displacement of all five metatarsals in the same direction, either medially or laterally. Type B injuries are described by two patterns. Type B1 injuries display partial incongruity with isolated medial displacement of the first metatarsal. Type B2 injuries also display partial incongruity, but consist of lateral displacement of any of the lateral four metatarsals. Of all the types of injuries, type B injuries are reported to be misdiagnosed or under treated because it is the most subtle to detect clinically and radiographically.[18] Type C injuries are described as having a divergent pattern and are also divided into subtypes. Type C1 injuries demonstrate partial incongruity and involve the first metatarsal being displaced medially while any of the lateral four metatarsals are displaced in a lateral direction. Type C2 injuries demonstrate complete incongruity as the first metatarsal is displaced in the opposite direction of the lateral four metatarsals, which move as a unit .[5,19]

Nunley and Vertullo formulated a classification system to address the low-grade tarsometatarsal injuries frequently seen in athletes that are not described by Myerson or Quenu and Kuss (Fig. 2). The Nunley-Vertullo classification system takes into account clinical findings, comparative weight-bearing radiographs, and images from bone scans to classify the injuries into different stages. Stage I injuries display a low-grade sprain of the Lisfranc ligament complex, specifically a dorsal capsular tear and sprain, and have no diastasis between the

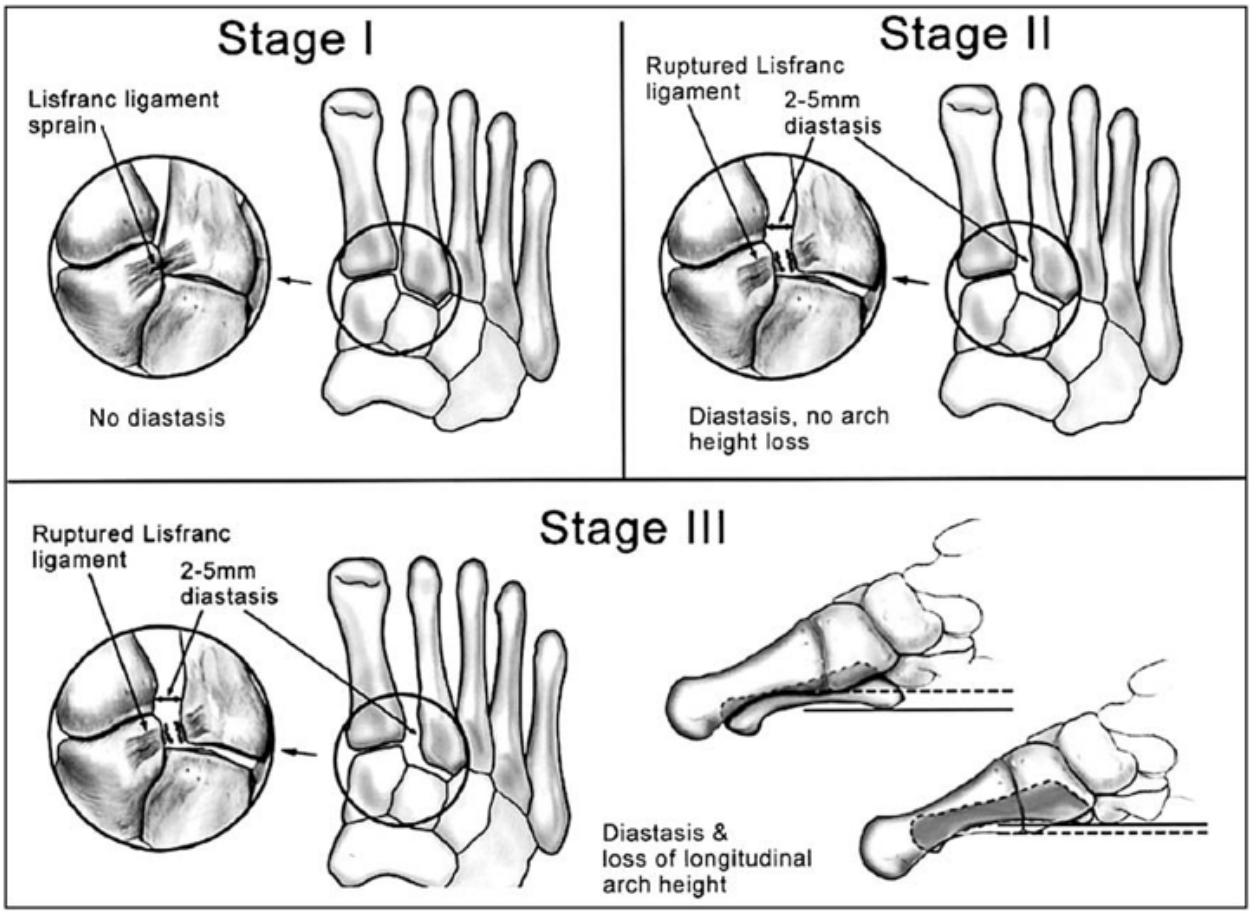

Figure 2. Nunley-Vertullo classification system for Lisfranc Injuries.[3] (Reprinted with permission from *Foot and Ankle Clinics*)

medial cuneiform and the base of the second metatarsal. There is no loss of arch height on weight-bearing with stage I injuries, but bone scans do show increased radiotracer uptake within the joint. Stage II injuries represent Lisfranc ligament insufficiency or disruption, but the plantar component of the Lisfranc ligament complex remains intact. Thus, stage II injuries have injured dorsal and interosseous Lisfranc ligaments with a 2-5mm diastasis between the medial cuneiform and the base of the second metatarsal. Like stage I injuries, stage II injuries have no loss of arch height. Stage III injuries involve disruption of the interosseous and plantar Lisfranc ligaments and display a diastasis greater than 5mm. There is a loss of arch height with stage III injuries when compared to the contralateral foot, demonstrated by a decreased distance between the plantar surfaces of the medial cuneiform and 5th metatarsal on a weight-bearing lateral radiograph. In cases of stage III injuries associated with more significant displacement, the Myerson classification should be used to describe the injury.[3,5,9]

Clinical examination, conventional plain film radiography, computed tomography, and magnetic resonance imaging are all used to assist in diagnosis.[5]

The current literature provides treatment options consisting of conservative measures

and surgical measures. Surgical measures include closed reduction under fluoroscopy, open reduction and internal fixation, and arthrodesis.[3]

DISCUSSION

Classification Systems

Quenu and Kuss

The Quenu and Kuss classification system is not used today in clinical practice due to its limitations, but it did formulate the groundwork for modern classification systems used currently. Because it is only useful in classifying high-grade Lisfranc injuries, it does not properly describe the full spectrum of Lisfranc injuries. It also neither provides treatment direction, nor insight into the prognosis of the patient.[5]

Myerson

The Myerson classification system is commonly used today because of its ability to provide a standardized approach for reportable injury patterns. This provides a high degree of interobserver reliability to communicate data. But like the Quenu and Kuss classification system, the Myerson classification system does not encompass low-grade Lisfranc injuries and does not provide treatment direction and is not a reliable predictor of clinical results.[5]

Nunley-Vertullo

The advantage of the Nunley-Vertullo classification system is in its capability to guide treatment of low-impact Lisfranc injuries or midfoot sprains. Based on their staging of Lisfranc injuries, Nunley and Vertullo hypothesized that injuries involving the Lisfranc ligament complex initially affects the dorsal capsule, with ensuing involvement of the interosseous and plantar aspects of the Lisfranc ligament complex as greater forces are imposed.[5] The Myerson and Nunley-Vertullo classification systems are currently used to described high-grade and low-grade Lisfranc injuries, respectively.[20]

Diagnosis

Clinical presentation and signs

The clinical presentation of a patient with Lisfranc injury is rather specific. The patient's chief complaints are often midfoot pain and discomfort. If the midfoot pain is a result of a foot trauma, a suspicion of Lisfranc injury is considered.[3] Further examination will reveal a swollen midfoot with plantar arch ecchymosis. There is usually tenderness and pain due to passive movements of the midfoot. A comparison with the contralateral foot is always performed because the injury is usually unilateral. However, bilateral injuries can occur, especially in windsurfers and parachutists.[3] In addition, the patient may present with a "gap sign," which is a separation of the first and second toes. Furthermore, it is important to assess for associated local neurovascular injury as well.[3]

Although these clinical presentations seem specific and easily identifiable, a significant portion of these injuries are misdiagnosed or mistreated due to the variability of the severity of the injury. High-impact injuries are apparent to diagnose with the aforementioned clinical presentations and signs. However, low-impact injuries are harder to detect and may be neglected by the patient, especially in athletes. They often believe that the pain is tolerable enough to

walk it off and will further delay proper treatments.[3]

X-ray

Conventional radiography is often used as the initial imaging examination for midfoot sprains. Non-weightbearing images of unilateral anteroposterior, lateral, and 30 degrees internally rotated oblique should be obtained. The sole indicator for Lisfranc fracture-displacements using non-weight bearing x-ray is the appearance of small chip fractures at the base of the second metatarsal and medial cuneiform, referred to as the fleck sign.[5] These chip fractures are usually the result of high-impact Lisfranc injuries and are seen in 90% of these injuries. However, Nunley and Vertullo found that 50% of lower-impact Lisfranc injuries appeared normal on non-weight bearing conventional radiograph. Therefore, weight bearing radiographs are indicated to better assess the injury. On the anteroposterior radiograph, a diastasis > 2mm between the bases of the first and second metatarsals and misalignment at the second tarsometatarsal articulation, with lateral displacement of the base of the second metatarsal with respect to the middle cuneiform, are indicators of Lisfranc injury.[5] When assessing the oblique view, loss of alignment between the medial borders of the fourth metatarsal and cuboid are consistent with Lisfranc injuries. Lastly, a loss of alignment between the plantar aspect of the fifth metatarsal and medial cuneiform on the lateral view is also consistent with Lisfranc injuries.[20]

Computed Tomography

In patients who are suspected of having Lisfranc injuries with normal conventional radiographic findings, CT or MRI can be used to better assess the injuries. Computed tomography is particularly helpful in finding high-velocity trauma and subtle osseous subluxations.[5] Moreover, reformatted 3D CT images are an ideal modality to be used for preoperative planning. However, CT imaging is not the best technique to show ligamentous integrity. Therefore, in low-impact injuries, which usually involve ligamentous injuries, MRI is suggested.[5]

Magnetic Resonance Imaging

MRI is optimal for the evaluation of soft-tissue and ligamentous injuries. Using the horizontal long-axis and short-axis planes on MR images, low-impact Lisfranc ligamentous injuries are best seen. Recently, the assessment of the Lisfranc ligamentous complex has been further optimized with the 3D fast spin-echo (SE) volumetric SPACE MRI.[5] Disruption and elongation of the ligament along with periligamentous edema in Lisfranc injury has been described. Injury to the deep peroneal (fibular) nerve can also be seen on MR imaging. Although MRI appears to be a far superior modality in accessing low-impact Lisfranc injuries, there are no true MRI-based grading schemes available in the literature. Nonetheless, the American College of Radiology Appropriateness Criteria guidelines slightly favor MRI over CT imaging in detecting Lisfranc injuries.[5]

Treatment

Conservative treatment

Conservative treatment is recommended for patients who have a low-grade Lisfranc ligamentous sprain, defined as a stage I (Nunley-Vertullo) injury. The standard conservative treatment is to use a non-weight bearing cast for 6 weeks. The cast is then replaced by custom-molded orthotics. If pain persists, an additional 4 weeks with a

removable boot should be considered.[3] Eleftheriou et al. suggest an initial 2-week protective period in a non-weight bearing cast before reexamination. If there is no longer tenderness on weight bearing, a return to activities is permitted as tolerated. If tenderness persists, then further immobilization is required.[20]

For all painful injuries that did not result in displacement of the bones, stress views should be repeated 10 to 14 days after the initial injury to check for stability. To maintain proper support, the foot should be immobilized in a short leg cast for 6 weeks. The short leg cast will act to keep the foot in a relaxed and slightly inverted position.[3]

For isolated ligamentous injuries, the foot should be held immobilized for up to 4 months to prevent displacement. Usually, physical therapy can begin at 3 months. One of the challenges that may result in a prolonged course of recovery is the patient's cooperation. The patient, especially an athlete, should understand that the ligamentous disruption may require a prolonged course of recovery after injury. Therefore, communication between the patient and the physician is crucial.[3]

Surgical Treatment

Current literature suggests Lisfranc injuries classified as stage II (Nunley-Vertullo) or greater be treated surgically, with an initial attempt of closed reduction under fluoroscopy.[3,20]

Closed Reduction (Percutaneous) with Fluoroscopy

Closed reduction with fluoroscopy is indicated for low-grade Lisfranc injuries classified as stage II or stage III on the Nunley-Vertullo scale and B1 or B2 on the Myerson classifications.[9] In a retrospective cohort study evaluating the outcome of treatments in athletes with Lisfranc injuries (n=15), Nunley et al. found that when surgery was needed, time to diagnosis was a key variable for determining whether closed reduction or open reduction was performed. The "time to diagnosis" can be defined as the amount of time the patient waited to seek medical attention post-injury. In the cases in which closed reduction was performed, the average time to diagnosis was 25 hours, whereas in the cases which open reduction was performed, the average time to diagnosis was 210 days.[9] Therefore, it is imperative to obtain a clear timeline of injury from the patient and to act quickly if surgery is indicated.

Unfortunately, a common complication with Lisfranc fractures and dislocation injuries is post-traumatic arthrosis, which could be caused by the soft tissue damage during the injury, during the time between injury and treatment seeking, and during the surgery.[21] Attempting a minimally invasive closed reduction prior to open reduction and internal fixation would be advantageous to the patient's healing process by limiting the amount of traumatic injury to the surrounding soft tissue structures.[22,23]

Open Reduction and Internal Fixation

Although closed reduction appears to be the ideal and safest surgical option, it is not always possible to fully resolve the Lisfranc injury by closed reduction. If closed reduction failed, open reduction and internal fixation is indicated for low-grade Lisfranc injuries classified as stage II or stage III on the Nunley-Vertullo scale and B1, or B2 on the

Myerson classifications.[9] Wagner et al. defined this closed reduction failure as either greater than 2 mm of residual tarsometarsal displacement, or greater than 15 degrees of persistent talo-first metatarsal angulation present after attempted closed reduction. Similarly, Gate et al. found that open reduction was performed when closed reduction under anesthesia had failed.[24] In addition, Richter et al. compared the efficacy of closed reduction and open reduction and found no significant difference in AOFAS score, gender, cause of the injury, or method of treatment.[25] Thus, open reduction still remains a vital form of surgical treatment for Lisfranc injuries.

Fixation choice

Cannulated Screw

Post-traumatic fixation of the Lisfranc joint has been performed with pins, plates, and cannulated screws, but screw fixation has demonstrated the most consistent and reliable results throughout the literature.[26,27] Traditionally, the medial column is fixed with screws to provide a stronger more stable construct, whereas the lateral column is fixed with k-wires to preserve its normal mobility.[24] Cannulated screws have been able to provide the stability that is essential for the proper functioning of the Lisfranc joint. However, the primary concerns associated with transarticular screw fixation are post-implantation damage to articular cartilage and screw breakage. There is no definite guideline for removal of the screws, but if there is no presenting symptoms post screw implantation, the screws are kept in. If symptomatic, screws are often removed anywhere from week 12 to year 3.[27,29] Despite these concerns, screw fixation remains the preferred fixation tool due to its efficacy and reliability.[28]

Plate

Plate fixation is an alternative to screw fixation in that it can theoretically increase postoperative range of motion while minimizing intraoperative damage to the articular surfaces of the tarsometatarsal joint.[9] Plate fixation can be applied extra-articularly using dorsal plates to avoid trauma to the articular surface.[30] Studies have shown that there is significantly less initial displacement and greater stability when using a plantar plate.[31] A significant advantage in using locked plate fixation is that it causes less irritation to the soft tissue. The screw heads are captured within the locked plate thus minimizing any friction between the plate and the bone to obtain structural stability.[32] Devries et al. reported a union rate of 98.5% (46 out of 47 subjects) and an average time of 7.8 weeks to return to full weight bearing when using plate fixation. In contrast, a union rate of 89.4% (88 out of 96 subjects) and an average time of 8.8 weeks to return to full weight bearing were reported when using screw fixation.[33] In another study performed by Garchar et al., a union rate of 96% (24 out of 25 subjects) was achieved with plate fixation.[31] Sorensen et al. reported a union rate of 100% (21 out of 21 subjects) when using plate fixation.[32] Thus, recent research has demonstrated that locking-plate fixation with or without lag screws resulted in a superior rate of union compared to standard crossed screw fixation, while allowing an earlier return to full weight-bearing.[33]

Arthrodesis

Although open reduction and internal fixation is the currently recommended treatment for Lisfranc injuries, it is still controversial

because it can result in chronic disability, such as the development of painful osteoarthrosis in some patients.[17,34] The current literature states that primary arthrodesis is not recommended for Lisfranc complex injuries, but instead should be reserved as a salvage procedure after failed open reduction and internal fixation, for a delayed or missed diagnosis, and for severely comminuted intra-articular fractures of the tarsometatarsal joints.[35] Other researchers such as Kuo et al. suggested that primary arthrodesis is a better treatment option for a subgroup of patients suffering from purely ligamentous Lisfranc injuries.[36] Ly and Coetzee conducted a prospective, randomized study to investigate primary arthrodesis compared with open reduction and internal fixation in the treatment of primarily ligamentous Lisfranc joint injuries. In the primary arthrodesis group, 95.2% (20 out of 21 subjects) of the subjects achieved initial anatomic reduction compared to the 90% (18 out of 20 subjects) in the open reduction and internal fixation group. At the 24 month postoperative follow-up, a mean AOFAS Midfoot score of 88 points was reported by patients treated with primary arthrodesis, while the patients treated with open reduction and internal fixation reported a mean AOFAS Midfoot score of 68.6 points ($p < 0.005$).[35] They found that the injuries being primarily ligamentous played a major role in the healing and outcome of these injuries. These primarily ligamentous injuries are characterized by a poorer healing potential of the ligament-osseous interface and a trend toward a higher rate of correction loss, increasing deformity, and degenerative arthritic changes. Therefore, Ly and Coetzee suggest that patients with a primarily ligamentous Lisfranc injury be treated with primary arthrodesis of the medial two or three rays and that performing immediate primary fusion helps patients to avoid several years of persistent pain and disability.[35]

Early Weight Bearing and Rehabilitation

Existing protocols for the post-operative treatment of Lisfranc injuries emphasize non-weight bearing for 4 to 6 weeks.[21] In a prospective case series (n=5) of patients who underwent open reduction and internal fixation, Brinsden et al. reported an average time to return to regular activities of 6 months.[37] In a similar study (n=19), Curtis et al. reported an average time to return to regular activities of 4.25 months.[38] In a retrospective study (n=15), Nunley and Vertullo reported an average time to return to regular activities of 3.6 months.[9] Wagner et al. found that patients were encouraged to bear weight as tolerated after the third postoperative week: initially using a controlled ankle movement walker boot or a stiff soled shoe while gradually moving into a more giving shoe. In this study, patients were able to return to their normal activities before 2 months. This could suggest that early weight bearing and rehabilitation could be a more significant determinant of Lisfranc injury recovery regardless of the chosen treatment regimen.

CONCLUSION

Lisfranc injuries are grossly underestimated, as 20% of Lisfranc injuries are clinically undiagnosed due to the subtlety of the injury. Even with prompt diagnosis and treatment, significant morbidity can result. There are two main classification systems used currently: Myerson and Nunley-Vertullo. The

Myerson classification describes high-impact injuries, but does not provide treatment direction and is not a reliable predictor of clinical results. The Nunley-Vertullo classification system describes low-impact injuries and helps guide treatment of low-impact Lisfranc injuries or midfoot sprains.

Various imaging modalities are used to diagnosis Lisfranc injuries. X-ray is better suited for high-impact injuries than low-impact injuries. CT imaging is also helpful for high-impact injuries and preoperative planning, but MRI is the optimal choice for low-impact soft tissue and ligamentous injuries.

Conservative treatment is suggested for stage I (Nunley-Vertullo) Lisfranc injuries. The patient is placed in a non-weight-bearing cast for 6 weeks, followed by physical therapy. If conservative measures are unsuccessful, surgical intervention must be considered. The primary goal of surgical intervention is anatomic reduction and stabilization. However, the controversy lies in the method of treatment. Closed reduction with fluoroscopy is indicated for stage II or III injuries that were diagnosed in a timely manner. Open reduction and internal fixation is indicated for stage II and stage III Lisfranc injuries that have persisted for an extended time frame or after failed attempt at closed reduction. Screws are the fixation choice currently preferred, but increasing research supports the use of plate fixation to minimize intraoperative damage. Arthrodesis has traditionally been reserved as a salvage procedure after failed open reduction and internal fixation, for a delayed or missed diagnosis, and for severely comminuted intra-articular fractures of the tarsometatarsal joints. However, recent research suggests that patients with primarily ligamentous Lisfranc injuries, primary arthrodesis provides superior short and medium-term outcomes as compared to open reduction and internal fixation.

A limitation to our research was that only one paper on using plate fixation with arthrodesis for Lisfranc injuries met our inclusion and exclusion criteria. This restricted our analysis of the efficacy of performing plate fixation with arthrodesis properly and opens up a question that requires further research to answer. An additional area of future research can be conducted to support primary arthrodesis as the preferred procedure for ligamentous Lisfranc injuries.

AUTHORS' CONTRIBUTIONS

The authors (JC, SM, and DB) equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors (JC, SM, and DB) declare no competing interests in relation to this manuscript.

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Surgical Correction of a Unilateral Rigid Pes Planovalgus Deformity in an Adult Post-Polio Patient: A Case Report

Loretta Cacace, BS, MPH, Caroline Fruge, BS, and Regina Fiacco, BS

Abstract

Introduction
While poliomyelitis has been almost eradicated from the world's population, sequela of previous polio infections remain evident within the adult population and presents as several pedal deformities such as pes equinovarus and pes planovalgus. Planovalgus deformity, or "flat foot", is a common presentation of post polio infection in the lower extremity, caused by atrophy of lower extremity muscles as a result of nerve damage. The resulting muscle imbalances cause deformity of the foot and greatly decrease quality of life and impact gait patterns in adults with prior polio infection. The current study is an evaluation of surgical technique in an adult patient with a rigid pes planovalgus deformity, secondary to convex vertical talus, as a result from a prior poliomyelitis infection.

Methods
A tendo-achilles lengthening (TAL), a triple arthrodesis of the subtalar joint (STJ), talonavicular joint (TNJ) and calcaneocuboid joint (CCJ), and a medial column fusion of the first metatarsal-cuneiform joint were all part of the surgical plan for this patient. Intra-operative complications were assessed, including the presence of osteopenic bone and allergic reaction to Vitoss bone graft.

Discussion
As a result of the current case report, the authors propose prior evaluation of bone stock as part of a patient's pre-operative evaluation for undergoing flatfoot reconstruction surgery in order to prevent post-operative complications similar to those encountered in this report.

Key Words
Poliomyelitis; Pes Planovalgus; Triple Arthrodesis; Flat Foot

Level of Evidence : 4-Case Report

INTRODUCTION

Poliomyelitis is an infectious disease caused by the poliovirus, a member of the genus *Enterovirus*. Clinical presentations of poliomyelitis vary widely, ranging from mild cases of respiratory and gastrointestinal illness to severe paralysis. In certain forms of the disease, damage to the anterior horn cells of the spinal cord occurs, causing limb paralysis.[1] While the Poliovirus has been almost completely eradicated throughout the world, it is not uncommon to see clinical manifestations of a prior infantile polio infection among patients. A common sequela of the virus is Postpolio syndrome, which presents as progressive muscle atrophy due to ongoing motor deterioration.[1] Other symptoms include diminished functional capacity, cold intolerance, and muscle and joint pain.[2] Furthermore, deformities can occur, especially in the lower extremity, due to muscle imbalances caused by muscle atrophy or flaccid paralysis.[3] Common pedal deformities as a result of poliomyelitis are equinovarus and planovalgus.

Planovalgus deformity, or flat foot, regardless of etiology, has been characterized as a foot having increased contact with the ground due to a decrease in longitudinal arch height. It is typically associated with a valgus rearfoot and is further characterized by a decreased calcaneal pitch and increased talar inclination and talometatarsal angles. Flatfoot secondary to neuromuscular disorders, such as polio, is typically induced by heel cord contractures (acquired equinus) and loss of function of the tibialis posterior muscle.[4] Acquired equinus limits dorsiflexory range of motion at the ankle joint during the stance phase of gait, leading to compensation at the STJ in the form of pronation (abduction, eversion, dorsiflexion). This increased pronation at the STJ further exacerbates a pes planovalgus deformity and leads to increased arthritic changes at the STJ.[5]

While conservative treatments of flatfoot exist, such as physical therapy and bracing, surgical interventions may be needed for treatment of flat foot secondary to neuromuscular disorder. The goal of these surgical interventions are to reduce the number of joints that are being controlled by weakened or paralyzed muscles. In children who had been affected by poliomyelitis, the Grice procedure is indicated for treatment of a pes planovalgus deformity. This procedure places bone grafts in the sinus tarsi to obtain an extra-articular arthrodesis of the subtalar joint, so as to avoid affecting subsequent growth of the foot.[6] However, after skeletal maturity is achieved, a triple arthrodesis can be performed in order to obtain the most effective control of the foot.[5] A standard triple arthrodesis procedure entails fusion of the talocalcaneal, calcaneocuboid and talonavicular joints in one surgical intervention in order to prevent detrimental pronatory forces through the mid-foot. Soft tissue procedures, such as tendon transfers and tendo-achilles lengthenings (TAL), are often done in conjunction with joint fusion procedures in order to increase the effectiveness of arthrodesis. Soft tissue procedures have previously been shown to improve outcomes related to flatfoot reconstruction.[7]

The current study aims to assess the surgical outcome of a triple arthrodesis, medial column fusion and a tendo-achilles lengthening in an adult demonstrating flatfoot due to neurological manifestations consistent with a prior childhood poliomyelitis infection.

METHODS

Pre-Operative Evaluation

The patient of the current case study was a 44 year-old otherwise healthy Hispanic female from Mexico whose chief complaint was diffuse pain in her left foot. She admitted the presence of muscle atrophy since age 3 with multiple visits to the hospital/doctors in Mexico, with no official identification of etiology. She reported difficulty with walking or standing for extended periods of time. The course of the deformity and pain had worsened over the years. She tried use of multiple conservative treatments including shoe-gear, padding, braces, pain medication and use of a cane, but all of which failed.

At her initial orthopedic evaluation, there was localized medial arch pain and deformity with severe tenderness to the TNJ and NCJ. There were increased callosities to the plantar aspect of these joints. There was lack of reconstruction to the medial longitudinal arch with the Hubscher maneuver. She was unable to perform double or single heel raise. There was elevation of the first ray from the NCJ with a plantarly subluxed hallux at the first metatarsophalangeal joint (MTPJ). The patient demonstrated a limb length discrepancy of a longer right lower extremity (>1cm). Range of motion at the ankle with the STJ in neutral and with the knee extended, as well as flexed, was decreased. Early heel raise and lack of heel purchase was evident on gait analysis.

Radiographic evaluation of the patient revealed a significantly decreased calcaneal

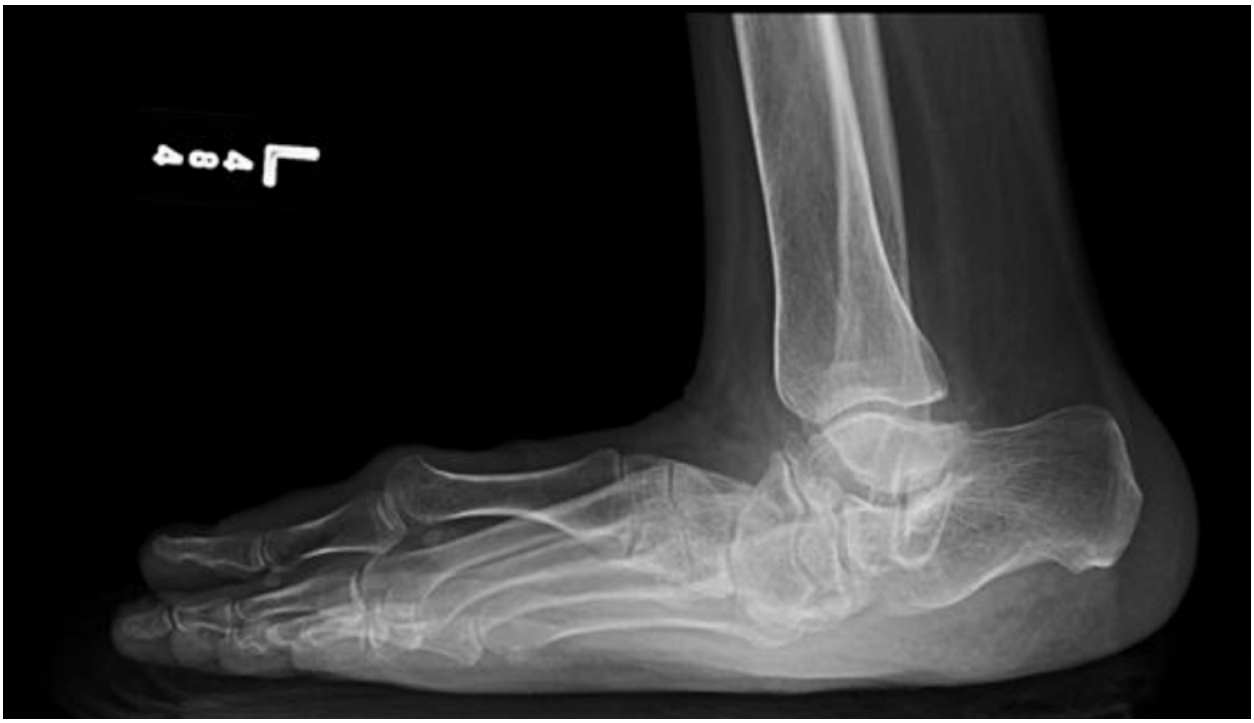

Figure 1: Pre-operative lateral X-ray.

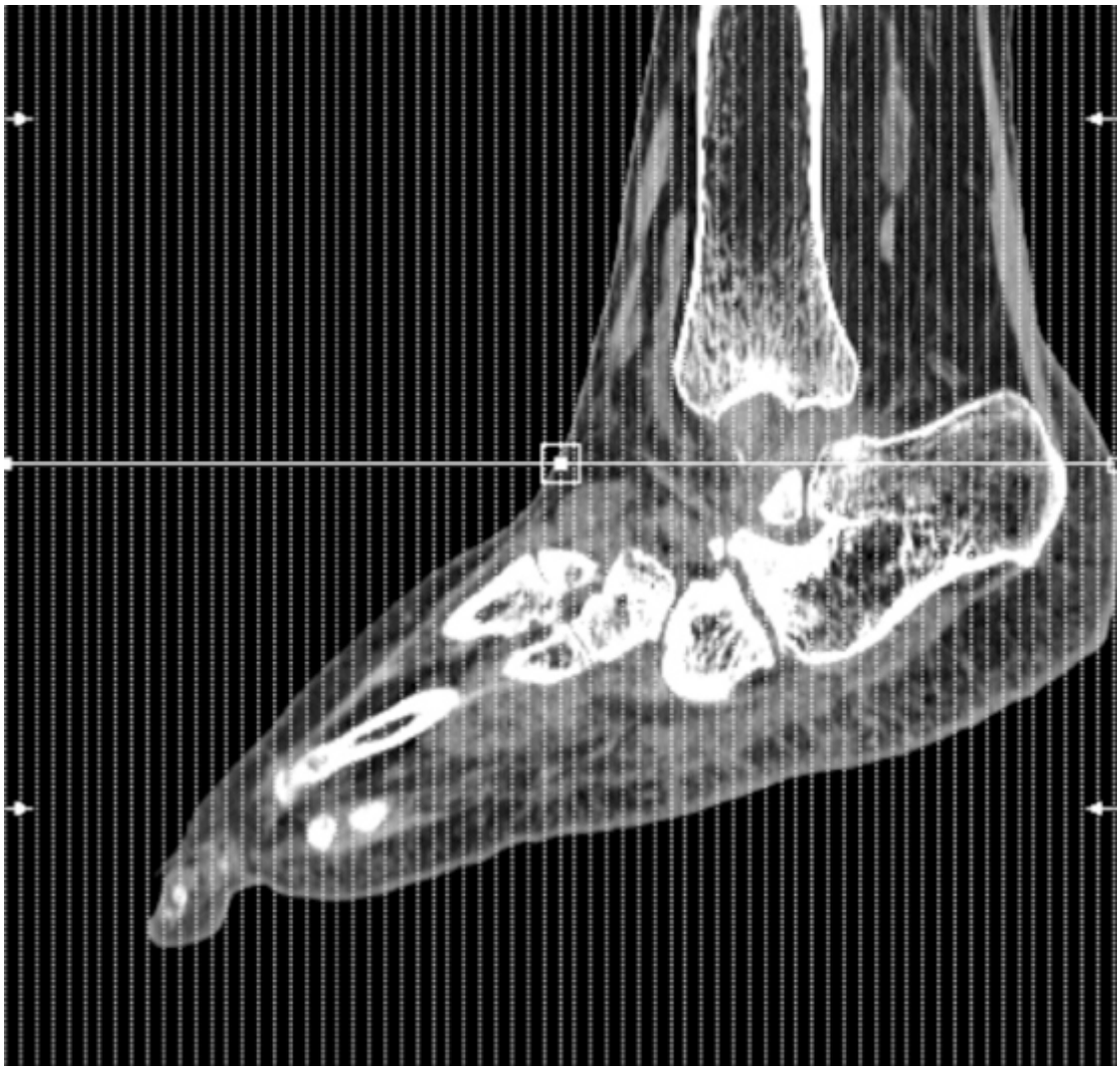

Figure 2: Pre-operative CT Scan (Sagittal View)

inclination angle. The calcaneus was also noted to be in equinus on lateral view. The talus was adducted and plantarflexed, assuming a superimposed position on the navicular. The talar declination was also markedly increased. The talar-navicular joint was indistinguishable on radiographic examination. Lateral view also demonstrated a plantarly displaced left navicular bone and a dorsally displaced first metatarsal. STJ arthritis was present at the area of the posterior facet of the talus. On examination of the dorsal-plantar view, the calcaneal-cuboid abduction angle was markedly increased and demonstrated increased midfoot abduction. 3-D CT scan was utilized to confirm radiographic findings and established the presence of a vertical talus of the left foot (Figures 1-3). There was no ankle arthrosis noted on a standard radiograph and CT scan, but there was evidence of the fibula abutting the calcaneus laterally.

Finally, a board certified neurologist also evaluated the patient. He performed EMG/ NCV studies to assess the nature of the

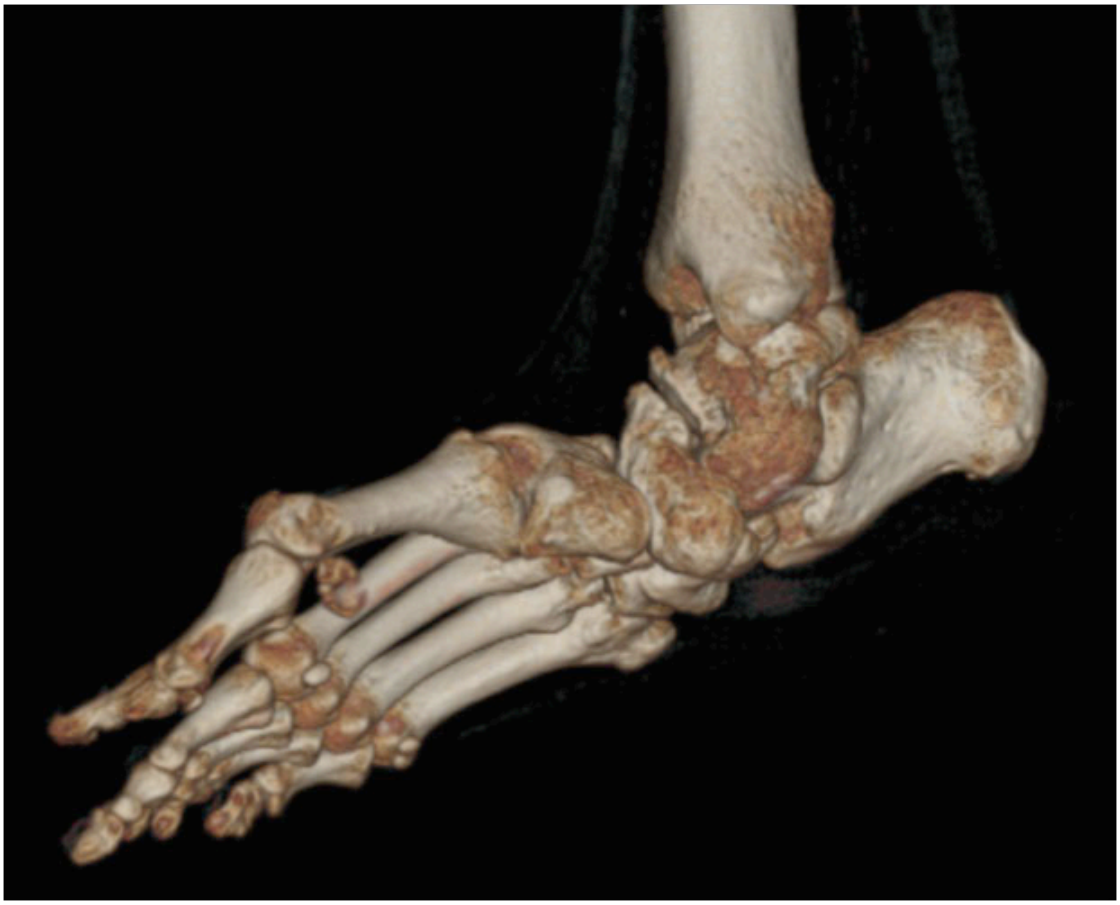

Figure 3: Pre-operative 3D CT Scan.

patient's neurological involvement. Results of the nerve conduction velocity exam were inconclusive but suspicious for unrecognized infantile poliomyelitis.

Surgical indications for this patient included failed conservative treatments as well as a rigid pes planus deformity with a vertical talus. The proposed surgical intervention was a staged left triple arthrodesis with medial column fusion, and tendo-achilles lengthening followed by a calcaneal slide osteotomy and second digit hammertoe arthroplasty in a follow-up procedure at a later date. Optimal realignment of the left foot requires plantarflexion of the first ray at both the navicular-cuneiform joint and metatarsal-cuneiform joint in order to allow for increased hallux plantarflexion. It also entails a decrease in the intermetatarsal angle, increased calcaneal inclination, and increased articulation of the talo-navicular joint. The goals were to eliminate motion at arthritic joints and to realign the foot as anatomically as possible to decrease pain or eliminate pain.

Surgical Technique: Tendo-Achilles Lengthening, Medial Column Fusion, and Triple Arthrodesis

The first procedure performed was a left foot triple arthrodesis with medial column fusion and tendo-achilles lengthening. A percutaneous Sgarlato Z-plasty technique was utilized to lengthen the achilles tendon by releasing the contracture of the gastroc-soleus

muscles. The anterior two-thirds of the tendon were incised distally from a lateral approach, followed by a medial incisional approach to the posterior proximal tendon.

The soft tissue procedure was followed by attempted medial column fusion of the first metatarsal-cuneiform joint, navicular-cuneiform joint and talonavicular joint. A dorsomedial incision was created in order to expose the first ray, including the TNJ, NCJ, MCJ, and first MPJ. Soft tissue dissections were carried out with care being taken to retract the neurovascular bundle and adjacent structures. Periosteal and capsular incision was made midline and reflected to expose the joint surfaces. Spurring had to be resected and osteophytes excised with rongeur and osteotomes to obtain adequate visualization. Severe periarticular adaptive changes and cystic lesions distorted the normal osseous anatomy. The use of Stryker Hintermann retractors assisted in joint distraction for increased exposure. The articular cartilage of the joints was resected in standard fashion and joint surfaces prepared with subchondral drilling and feathering techniques.

A lateral incision was made from just inferior to the distal tip of the lateral malleolus to the base of the 4th metatarsal. The STJ, CCJ, and lateral portion of the TNJ are thereby exposed. Care is taken to avoid branches of the sural, superficial peroneal nerves and to protect the peroneal tendons. The deep fascia was visualized through the entire course of the incision, and the extensor digitorum brevis (EDB) muscle belly was identified. An L-shaped incision was made through the deep fascia traveling along the course of the EDB insertion and distally across the CCJ. This releases the insertion of the EDB, allows access to the CC joint, and gives exposure to the sinus tarsi and Hoke tonsil. The EDB muscle belly was flapped distally, starting at its proximal lateral margin, giving excellent exposure to the CCJ and allowing eventual exposure to the lateral TNJ. All of the contents of the sinus tarsi were removed, including the interoessous ligament, to gain exposure to the anterior portion of the STJ.

A laminar spreader was placed into the sinus tarsi and used to open the STJ, vertically separating the talus from the calcaneus, but prior to this an adventitial joint formed between the calcaneus and fibula and was resected in order to free the talus on the calcaneus and to realign the socket on the navicular. Articular cartilage/osteophytes were then removed from the anterior, middle, and posterior facets of the calcaneus and CCJ with a curette and osteotome. The remaining subchondral bone was then fenestrated using a 0.062 K wire. This allowed vascular ingrowth through the subchondral plate and excellent bone preparation for fusion.

The foot was next manipulated into the corrected position and bone on bone contact at each joint was confirmed. Small gaps in joints/cystic lesions were filled with Vitoss bone graft substitute (Stryker, Mahway, NJ) to help ensure solid union. Once satisfied with the reduction the joints were temporarily fixated. A 70 mm cannulated, partially threaded screw was inserted in the posterior aspect of the calcaneus under fluoroscopy in order to fuse the posterior facet of the subtalar joint. The medial column was then fixated with staples and a 7-hole locking plate. The plate extended from the base of the first metatarsal across the medial cuneiform, navicular and talar head. A detachment of the tibialis anterior was performed to allow proper bone positioning and was reattached to

its proper insertion on the medial aspect of the base of the left first metatarsal and medial cuneiform prior to closure.

Post-Operative Course

An acceptable rearfoot and forefoot alignment was achieved post-operatively with an increase in declination of the left 1st ray and an increase in the calcaneal inclination angle from 0º to 5º degrees. The intermetatarsal angle and dorsal elevation of the first metatarsal were both corrected following fusion (Figure 4).

The patient was placed in a below-knee cast to avoid weight bearing and then stepped down to a posterior splint for the first 6 weeks. Pain was managed initially for the first two weeks with Tylenol #3 every four hours as needed and was given Keflex 500 mg TID prophylactically as hardware was inserted. All staples and sutures remained intact until 4 weeks post op when slight dehiscence was noted at the proximal aspect of the medial incision and lateral ankle incision. No drainage, malodor or clinical signs of infection were noted at that time. The sites of dehiscence were managed with Benzoin compound, steri strips, a betadine bandage and coflex compressive wrap, and the patient continued the use of a posterior splint. Prophylactic use of 300 mg Clindamycin BID for 10 days was administered to prevent infection. At six weeks, the patient was stepped down to a surgical shoe and crutches, and the second surgical procedure was postponed due to inadequate bone quality. Controlled weight bearing and dorsiflexion/plantarflexion exercises were implemented at this time. At eight weeks post operatively, all incision sites appeared intact with no signs of dehiscence or drainage and there was a slight pain with dorsiflexion/plantarflexion exercises. Patient was referred to physical therapy to strengthen her left limb and to improve range of motion and was given a CAM walker. At this time, the operating room was booked in four weeks with the surgical plan of a left calcaneal slide osteotomy with a 2nd toe hammertoe correction.

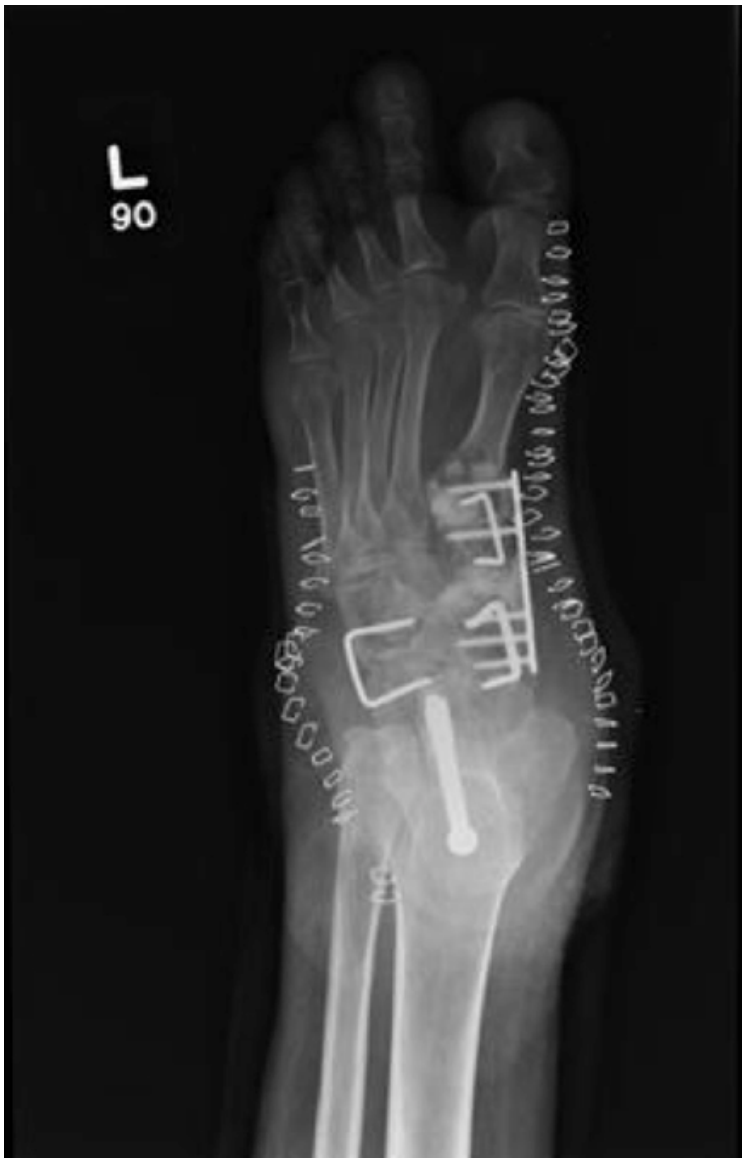

Figure 4: 1 week Post-operative DP x-ray.

Surgical Technique: Calcaneal Slide Osteotomy and 2nd Digit Arthroplasty

The second procedure was performed three months later. The goals of this procedure were to increase the calcaneal inclination angle via a medial displacement calcaneal osteotomy and to correct second digit hammertoe due to excessive elongated 2nd toe as compared to the hallux. Upon surgical dissection of the lateral aspect of the calcaneus, marked osteopenia was evident and a surgical fracture was iatrogenically created. It was decided to not proceed with the calcaneal slide osteotomy due to the osteopenic nature of the patient's calcaneal bone. The fracture site was packed with Vitoss bone chips and demineralized bone matrix to promote healing of the fractured osteopenic bone. Then, the second digit arthroplasty was performed on the patient's rigid hammertoe without any complications. The patient was placed in a posterior splint and advised to remain in non-weight bearing on the left foot.

RESULTS

Ultimately the procedure involved fusion of the CC joint, STJ posterior facet, TNJ, NCJ and first metatarsal medial cuneiform joint with a TAL. An acceptable rearfoot and forefoot alignment was achieved post-operatively with an increased declination of the 1st ray and increased calcaneal inclination angle from 0º to 5º. The intermetatarsal angle and dorsal elevation of the first metatarsal were both corrected following fusion. Excellent patient compliance was demonstrated as the patient remained non-weight bearing for a period of 6 weeks and kept the area clean and dry. At 8 weeks post-operatively adequate alignment was evident and physical therapy had been initiated to regain strength. The procedure achieved adequate bony alignment and significantly reduced pain on the visual pain analog scale from a 5/10 to a 0/10.

Unfortunately 13 weeks after the initial operation, the patient suffered a possible allergic reaction to the Vitoss bone graft with superficial infection (Figure 5), The patient was admitted for incision and drainage (I&D) at that time, in which necrotic bone and tissue was debrided and all visible Vitoss was removed. Three week later, the wound was debrided again and then flooded with flowable Wound Matrix INTEGRA to fill in the deep craters of the wound and covered with INTEGRA skin mesh. The ulceration created by the I & D with debridement eventually healed with no other complications. Patient was then returned to wearing no shoe gear with any pain to the foot. Patient to date has reported no further complications (Figure 6).

DISCUSSION

In this present case study, surgical indications included failed conservative treatments as well as a rigid pes planus deformity with a vertical talus. The initial surgical intervention included a tendo-achilles lengthening (TAL), triple arthrodesis and medial column fusion. Since cystic changes caused poor bone quality adequate anatomical alignment, intraoperative and postoperative complications occurred.

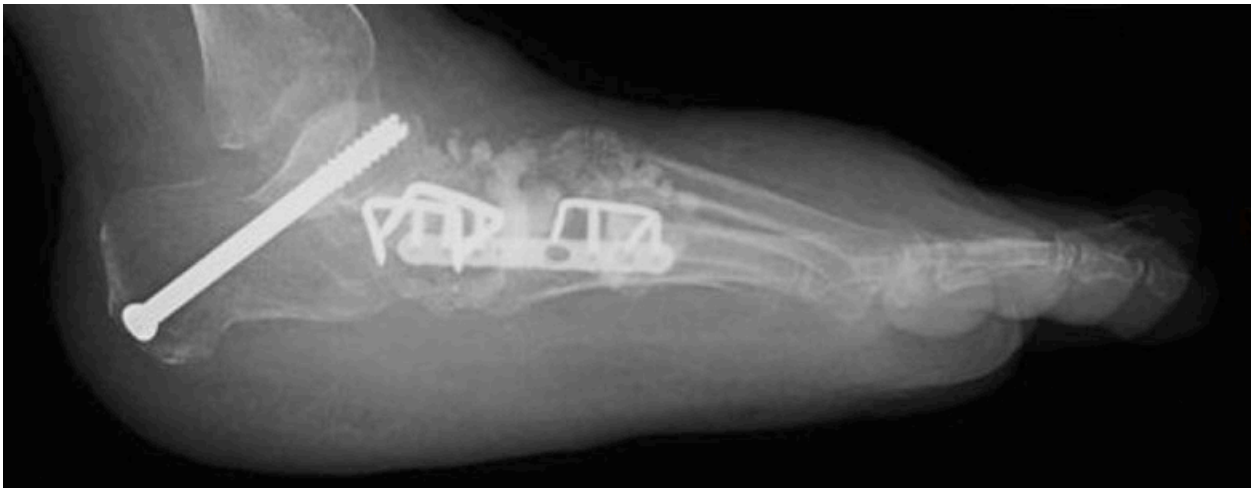

Figure 5: 13 weeks Post-operative lateral X-ray showing allergic reaction to Vitoss bone graft.

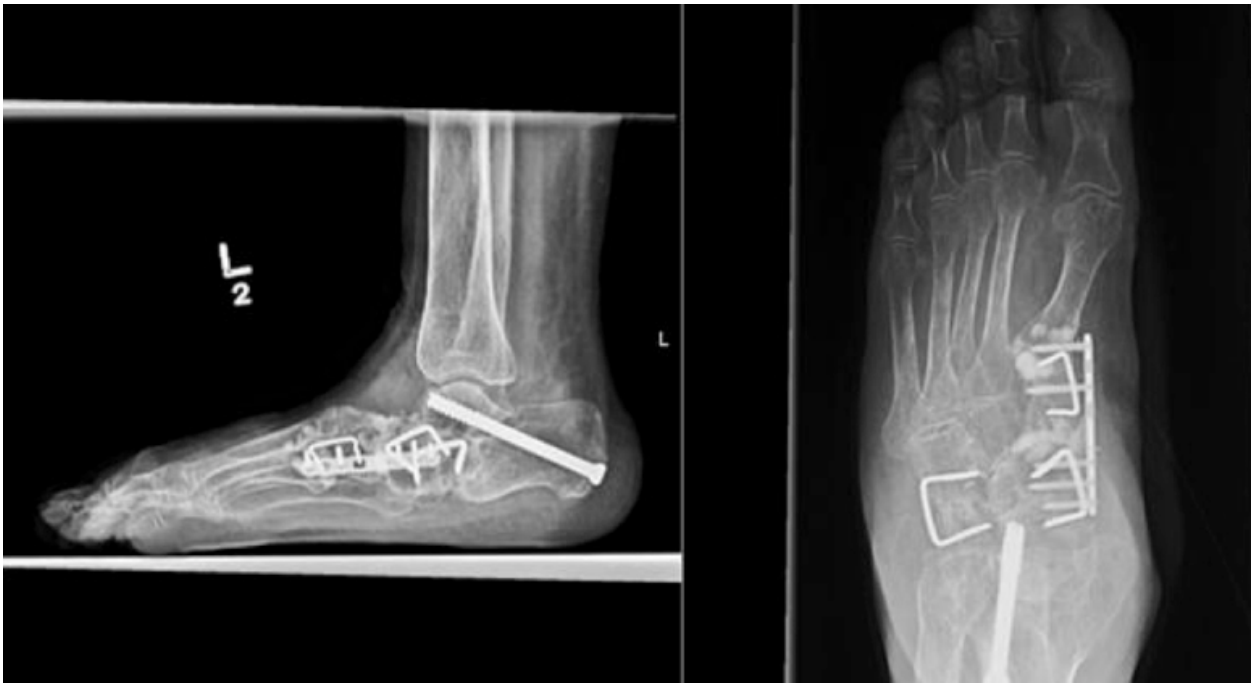

Figure 6: 8 months post-operative lateral and DP X-rays.

Poliomyelitis leads to a progressive paralysis of the anterior and posterior tibial muscles with resultant heel eversion by the unopposed action of the peroneal muscles. The talar head remains unsupported and moves into an equinus position. Green in 1945 proposed the insertion of bone grafts into the sinus tarsi to obtain an extra articular STJ arthrodesis in hopes of realigning the calcaneus relative to the talus.[6] Transfer of the peroneal muscles to the base of the second metatarsal assisted with dorsiflexion and in severe cases, the procedure would entail transfer of the longus tendon beneath the talus to increase support.[6] Grice in 1952 suggested a STJ arthrodesis be governed by the major requirements that the calcaneus is maintained in relation to the talar body, muscle imbalance must be corrected to

prevent reoccurrence via tendon transplantation, the deforming influence of the peroneal muscles should be negated and active inversion and dorsiflexion should be restored.[6] Gallien in 1989 reported excellent and satisfactory results following a combination of Grice and Green procedures in 84% of cases with valgus foot deformity.[8] Grice-Green and the variations on extra articular pes planovalgus reconstructions are typically performed on children and adolescents who are not skeletally mature in order to not affect normal bone growth.

Variations to the Grice-Green procedure have since been studied. Mann in 1978 found that to obtain the best results, bone stabilization should be used in combination with tendon transfer.[9] Faraj, in 1999, evaluated the use of full versus partial sub-fibular bone grafts as a subtalar joint arthrodesis on a patient population with a mean age of 10. All patients received a peroneal tendon transfer to the medial metatarsals and subtalar extra-articular arthrodesis. It was found that the combination of arthrodesis and tendon transfer gave better results than each of them alone.[7] Su et al suggested a slight valgus position of the heel is preferable as this is biomechanically sound, and the graft will be compressed when it is placed across the STJ.[10] Improper graft placement within the sinus tarsi, inadequate realignment of the calcaneus beneath the talus and failure to correct the sagittal plane equinus proved to result in poor outcomes. Peroneus longus and brevis tendon transfer was determined to be the cause of a resultant varus deformity, which was the chief complication reported on by Pollock in 1964. [11] Shortening of the tendo Achilles may be masked in patients with paralysis of foot dorsiflexors and inverters because of the medial displacement and subtalar subluxation. [12]

At the age of 44, years of weight bearing and microtrauma to misaligned joints caused the patient to suffer significant arthritic changes at the CCJ and STJ. Bone quality and unique pathologic bony relationships did not indicate bone grafting. Vitoss was placed to fill voids in the cystic bone differing from the originally described Grice-Green procedure. Further, the extra-articular arthrodesis procedure was originally created for skeletally immature individuals so as to avoid trauma to the growth plates and ensure normal development.

The overall success of triple arthrodeses is often assessed by achievement of stability with less pain. However, a triple arthrodesis is regarded as a salvage procedure. The destructive nature of the procedure inevitably induces arthritic changes in surrounding joints over time. Ahmad regards subsequent arthritic changes as a consequence of the procedure, rather than a complication.[13] Despite the inevitable arthritic changes, the triple arthrodesis procedure is often met with high patient satisfaction in people with rigid flat foot deformities. Much of this satisfaction is due to a redistribution in plantar pressures across the foot post-operatively. The triple arthrodesis provides immobilization in proper biomechanical alignment through the joints and contribute most to the rigid hindfoot valgus deformity.[14]

The current study suggests that a bone quality assessment be performed preoperatively in future cases of adults with a history of infantile poliomyelitis. Poliovirus causes flaccid paralysis of affected muscles, causing subsequent compensation through gait

manifestations, which lead to premature joint wear and tear. Muscle atrophy also leads to diminished blood flow to the affected areas and cause poor bone stock and osteopenia. Assessment of bone quality through the use of blood work, DEXA scans, or scintigraphy can help to more appropriately assess treatment options in patients with a history of infantile poliomyelitis.[15]

Complications included an allergic reaction to the Vitoss bone graft substitute and resultant incision and drainage procedures to remove necrotic tissue and any remaining cement. Bohner in his review of the design of ceramic based cements and putties for bone and graft substitution suggests the scientific aspects, such as physico-chemical and biological properties as well as industrial needs such as mixing, delivery, sterilization, and shelf-life all need to be considered in the allergic reaction of the body to these products.[16]

While this patient was compliant and had only minor postoperative complications, it is important to recognize that further complications may have occurred due to lack of surgical protocol in adult post-polio patients. Future research in this area should be targeted towards more inclusive preoperative planning with the use of bone scans, CT scans, and nerve conduction studies. Extensive follow up should also be performed due to the patients poor bone quality. The surgeon admitted the use of STJ bone block arthrodesis instead of lateral calcaneal slide osteotomy in order to recreate a better calcaneal inclination angle and Meary's angle especially in a patient with neurologic condition and poor bone stock. While adults with a history of polio are uncommon in today's society, their podiatric problems are often similar to those seen in other neuromuscular diseases. Therefore a treatment protocol should be put in place for the treatment of all pes planovalgus deformities as a result of neuromuscular deterioration.

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AUTHORS' CONTRIBUTIONS

Introduction- Loretta Cacace
Methods-Regina Fiacco, and Caroline Fruge
Discussion-Regina Fiacco, Loretta Cacace and Caroline Fruge
All authors were responsible for literature review and editing of the draft of this manuscript

STATEMENT OF COMPETING INTERESTS

The authors declare no competing interests in relation to this manuscript.

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Current Surgical Interventions in the Treatment of Congenital Convex Pes Valgus: A Literature Review

Yisheng Cao, BS and Mansi Patel, BA

Abstract

Introduction
Congenital convex pes valgus (vertical talus) is a rare and complex deformity that presents clinically as a severe form of congenital rigid flatfoot. While there have been many surgical interventions proposed in correcting this deformity, they all involve lengthening of tendons or tendon releases and open reduction of the talonavicular (TN) joint. The traditional treatments to treat congenital vertical talus (CVT) involving talus or navicular excisions, or two-incision reconstructive surgery involving tendon lengthening and talocalcaneal interosseous ligament release have led to complications such as recurrence and avascular necrosis. The purpose of this literature review is to compare the functional, anatomical, and radiological results of the following surgical methods in correcting congenital vertical talus (CVT): dorsal Seimon approach, posterior Cincinnati approach, and reverse-Ponseti casting following tenotomy of the Achilles tendon (Dobb's serial casting).

Study Design
Review of the Literature

Methods
The authors used PubMed to perform an English language literature search. Articles containing subjects over the age of 10, and articles older than 1980 were excluded. Inclusion criteria consisted of subjects below 10 years of age and terms "congenital vertical talus" OR "vertical talus surgical intervention." After retrieving a total of 63 articles, 9 articles were found to meet both the inclusion and exclusion criteria.

Results
All three surgical methods successfully reduced the TN joint and corrected the talocalcaneal (TC) and talo-first metatarsal angles in the anterior-posterior and lateral radiological views. Most patients did not require additional revision surgeries but several cases of avascular necrosis was observed with the Cincinnati approach. Both the Seimon incision and Dobbs method have shown lower rates of complications than the traditional Cincinnati approach. Deterioration of the TN reduction post surgery was associated with a sacral neurological disorder in addition to CVT. All three surgical methods are more efficient and provide better functional results than traditional surgical corrections.

Conclusion
The surgical treatment for CVT is continuously evolving as it aims to minimize the amount of dissection, thereby decreasing the risk of avascular necrosis as well as post operative pain and stiffness. While debate remains over the type of surgical approach used in treating CVT, particular attention should be paid to the TN joint capsule along with the dorsal and dorsolateral contracted tissues. Reducing and releasing these structures are the most important factors in determining the outcome and developmental successes from CVT surgical corrections.

Key Words
Vertical talus, Cincinnati incision, Seimon approach, Dobbs method, Reverse-ponseti

Level of Evidence: 4

INTRODUCTION

Congenital vertical talus (CVT), or congenital convex pes valgus, is an uncommon and most severe form of rigid flatfoot disorder. It is characterized by an irreducible dorsal dislocation of the navicular on the talar head and neck.[1] It was first described by Henken in 1914, and Lamy and Weissman produced the first English account of this condition in 1939.[2] Coleman classified two forms of CVT dependent on the condition of calcaneocuboid (CC) joint displacement.[3] Type 1 form has normal CC articulation whereas Type 2 form has CC subluxation or dislocation and is more resistant to treatment. CVT has an estimated incidence of 1 in 10,000, can be bilateral or unilateral, and affects boys more frequently than girls.[4] While the cause of this deformity remains unknown, several existing evidence suggest that a proportion of the identified cases are transmitted in an autosomal-dominant manner with incomplete penetrance.[1]

Etiology

Approximately 50% of identified cases are idiopathic whereas other cases occur in association with neuromuscular or genetic disorders. The etiology of CVT is multifactorial, and has been associated with CNS defects, muscular abnormalities, acquired deformities, and several genetic conditions. Patients with neuromuscular or neural tube defects have more rigid and less favorable functional deformities. Documented linked CNS defects include, but are not limited to, diastematomyelia, lipoma of the cauda equina, myelomeningocele, sacral agenesis, arthrogyposis, and neurofibromatosis.[1,5] In a form of muscular abnormality, CVT from the ischiocalcaneus band is a result of associated triceps surae contracture.[1] The ischiocalcaneus band is a rare fibrous muscle analogue originating from the ischium, spanning the popliteal fossa, and blending distally into the aeroneurosis of the triceps surae. Conjoined tibialis anterior and Achilles tendons is also highly associated with the deformity.[6] Acquired deformities include cerebral palsy, polio, spinal muscular atrophy, or an overcorrected clubfoot.[1] Many genetic syndromes characterize CVT as part of their clinical spectrum, such as but not limited to, Patau, Edwards, Freeman-Sheldon, Marfan, multiple ptergyium, Hurler, de Barsay, and Eagle-Barett syndromes.[1] Although different forms and degrees of CVT were identified, most surgeons continue to treat these cases as a single antomopahtologic entity.[6] Mutations in the HOXD10 gene and cartilage-derived morphogenetic protein-1 gene (CDMP-1) are associated with CVT in some familial cases.[7]

Relevant Anatomy

The pathological anatomy of CVT is a dislocated TN joint, where the navicular bone is transformed dorsally on the neck of the talus, and the talus itself lies in a plantar and medial position, almost vertically directed.[8] The navicular is displaced onto the dorsolateral aspect of the talar head and neck, leading to the navicular becoming wedge-shaped with a hypoplastic plantar segment. The talar head is observed to be flat dorsally with an expanded articular cartilage in order to accommodate the articular surface of the displaced navicular. Only the posterior one-third of the talar dome articulates within the ankle plafond since the calcaneus is plantar flexed and rotated posterolaterally.[1] The sustenaculum tali can become hypoplastic and lose its support of the talar head. The anterior

and middle subtalar facets are absent or replaced with fibrous tissues; the shape of the posterior facet can also be affected. In the more severe Type 2 CVT, the cuboid is laterally displaced and the plantar half of the cuboid becomes hypotrophic with large degree of dorsal subluxation occurring around the transverse tarsal articulation.[9]

Osseous deformation is associated with ligament and muscular alterations. The spring ligament, anterior fibers of the deltoid ligament, and medial fibers of the bifurcate ligament are stretched.[1] Contractures are found in the dorsal TN, calcaneofibular, interosseous TC ligaments and posterior capsules of the ankle and subtalar joints. The superior and inferior dorsal retinacula of the ankle are found to have merged and reduced into thick, shortened structure at the apex of the dorsal deformity.[9] The retinaculum becomes fibrotic and increases the mechanical advantage of the extensor tendons passing beneath it. The superior peroneal retinaculum is attenuated which results in subluxation of the peroneal tendons anterior to the fibula. All flexor and extensor muscles of the leg are contracted, with flexor muscle tendons subluxated anteriorly to act as dorsiflexors rather than normal plantarflexors. [8] The tibialis posterior is subluxated anteriorly, resulting in the tendon splaying out and becoming attenuated as it passes onto the plantar surface of the midfoot.[1] The peroneals are also anteriorly subluxated and bowstringed across the midfoot. The triceps surae inserts onto the superolateral aspect of the everted calcaneal tuberosity.

Clinical Evaluation

The surface features are the head of the talus produces a prominence on the medial side and the calcaneus produces a rocker bottom on the sole of the foot.[10] The forefoot is dorsiflexed, abducted, and everted on the midtarsal joint, and the hindfoot is fixed in an equinovalgus position. Presentation of CVT is associated with "Persian slipper foot", a lateral longitudinal column with abducted plantar contour, elongated and convex medial longitudinal column, and elevated and claw lateral toes.[6,11] Delayed intervention for CVT is common because CVT does not delay walking and is not apparent when the child first starts to walk.[6,11] The untreated foot will develop with a painful rocker-bottom deformity with gait, callosity, and multiple shoe wear problems. [12] Uncorrected CVT has been characterized to have a peg-head gait (an awkward gait with limited forefoot push off) with callus under a prominent talar head and the heel not in contact with the ground. In the unilateral presentation of CVT, the contralateral foot may have an equinovarus, calcaneovalgus, or metatarsus varus deformity.[6,11]

The radiological presentation of CVT in pediatrics is challenging because of limitations in visualizing ossification centers. A vertical talus lies parallel to the anatomic axis of the tibia and the calcaneus is in equinus angulation with a dorsiflexed and laterally translated forefoot.[1] Distinct soft tissue characteristics such as plantar surface convexity in addition to the bony deformity can be used to diagnose CVT.[5] Workup of CVT composes of increased TC angle from the anterior-posterior films, talo-horizontal and tibiotalar angles approaching 90^{o} and 180^{o} respectively in lateral films, and rigidly fixed hindfoot equinus in maximally dorsiflexed view, and irreducibility of the midfoot on the hindfoot in maximally plantarflexed view on dynamic films.[4] MRI

can be used to access the imbalance of extrinsic extensors and flexor muscles leading to the development of CVT.

The objectives for the treatment of CVT are to reduce the navicular and calcaneus to a normal anatomic relationship to the talus and maintain the reduction functionally on a weight-bearing surface.[5] Conservative treatments of manipulation and castings have traditionally produced poor success rates and require subsequent reconstructive surgery.[23] Traditional surgical interventions can be characterized into two main procedures: radical excision of the talus and/or navicular, or staged, two-incision reconstructive surgery involving extensor muscle and tendon-Achilles lengthening in addition to hindfoot and ankle capsulotomies.[14,15] While anatomical correction was achieved in these procedures, the functional successes were limited and there was a high incidence of long-term complications.

The Cincinnati Incision

A posterior horizontal incision exposes the posterior tibial neurovascular bundle, the sural nerve, and the Achilles tendon. The Achilles tendon is Z-lengthened, leaving the distal end attached medially to the calcaneus, and the posterior tibiotalar and subtalar joint capsules are divided.[9] To obtain complete subtalar release (CSTR), the TN joint capsule and spring ligament are incised, the posterior talofibular and calcaneofibular ligaments are divided, and the peroneus tendons are released laterally.[16] A retrograde Kirschner wire is passed through the talus and elevates the talus to reduce the TN joint. The wire is then advanced across the joint and out the dorsum of the forefoot.[16] The calcaneus is reduced and two additional K wires are passed from the plantar aspect of the heel through the calcaneotalar joint, holding the hindfoot in neutral position and the foot in 10-15^{o} in external rotation.[16] A long leg-cast is applied postoperatively with ankle in neutral and knee in 90^{o} flexion; the K-wires are removed 30 days after surgery and ankle-foot orthosis replaces the cast 50 days after surgery.[9]

The Dorsal Seimon Incision

A dorsal incision is made from under the medial malleolus to below the lateral malleolus with care given to save the dorsal veins and superficial peroneal nerve. The neurovascular bundle is preserved between the EHL and EDL, and Z-lengthening is performed on the tibialis anterior, EHL, EDL, peroneus tertius, longus and brevis.[4] The TN joint capsule is incised from the medial, dorsal and lateral sides, and the CC joint is also opened from the dorsal, lateral, and plantar sides to correct forefoot abduction and eversion deformities.[5] A smooth elevation is placed around the head of the talus to reduce the TN joint, along with manual pressure dorsomedially to the talar head with traction and forced plantar flexion of the forefoot.[4] A K-wire is inserted anterograde from the posterior side of the talus to reduce and fix the joint in a corrected position. Additional posterior vertical incision can also be made on the lateral aspect of the Achilles tendon for Z-lengthening to correct heel valgus.[5] The K-wire is removed 6 weeks post surgery; a knee cast is used for 3 months, and is later replaced by ankle-foot orthosis for 12 months.[5]

The Dobbs Method (Reverse-Ponseti)

The main mechanism behind the Dobbs method is manipulating the foot towards

gradually reduction of the TN joint followed by minimal surgery and Achilles tenotomy. Alaee described the manipulation, which consists of stretching the foot into plantarflexion, and inversion with one hand while counter pressure is applied with the thumb of the opposite hand to the medial aspect of the head of the talus.[17] After a few minutes of gentle manipulations, a long-leg plaster cast is applied to hold the foot in the desired amount of correction.[17] The cast is applied in two sections. The first section applied is the short-leg cast, which extends from the tip of the toes to just below the knee. Once the plaster has set, the cast is extended above the knee, with the knee in 90^{o} of flexion.[17] The position of the foot in the final cast used to achieve TN joint reduction should be in maximum plantarflexion and inversion, so to ensure adequate stretching of the contracted dorsolateral tendons and soft tissues.[17] A lateral foot radiograph should be taken in this cast to ensure that TN joint reduction is achieved. If TN joint is reduced, then surgery for percutaneous fixation of the TN joint with a K-wire is necessary.[17] Once TN joint is reduced and stabilized, a percutaneous tenotomy of the Achilles tendon is used to correct residual equinus deformity. [17] This is a complete release of the tendon done 1 cm proximal to the tendon insertion into the calcaneus.[17]

OBJECTIVES

This paper attempts to compare the anatomical and functional success, along with the development of adverse effects and complications, between the three more recently proposed surgical interventions in correcting CVT: posterior Cincinnati approach, dorsal Seimon approach, and reverse-Ponseti casting following tenotomy of the Achilles tendon (Dobbs' serial casting).

METHODS

Three independent online searches were performed using the Pubmed database. The search was done using the Boolean "and" and "or" operators. The first search included the terms "congenital vertical talus" OR "clubfoot" AND "dobbs method." This search provided 27 articles. The second search included the terms "congenital vertical talus" OR "clubfoot" AND "Cincinnati incision". This search provided 33 articles. The third search included the terms "Seimon method" OR "dorsal incision" AND "congenital vertical talus". This search provided 3 articles. Overall, 63 total articles were found. Search methods have been summarized in Figure 1. Exclusion criteria consisted of subjects over the age of 10 as well as articles older than 1980. Inclusion criteria consisted of subjects below 10 years of age and terms "congenital vertical talus" OR "vertical talus surgical intervention." After reading, evaluating and assessing the abstracts for their relevance to podiatry, 54 out of the 63 articles were excluded.

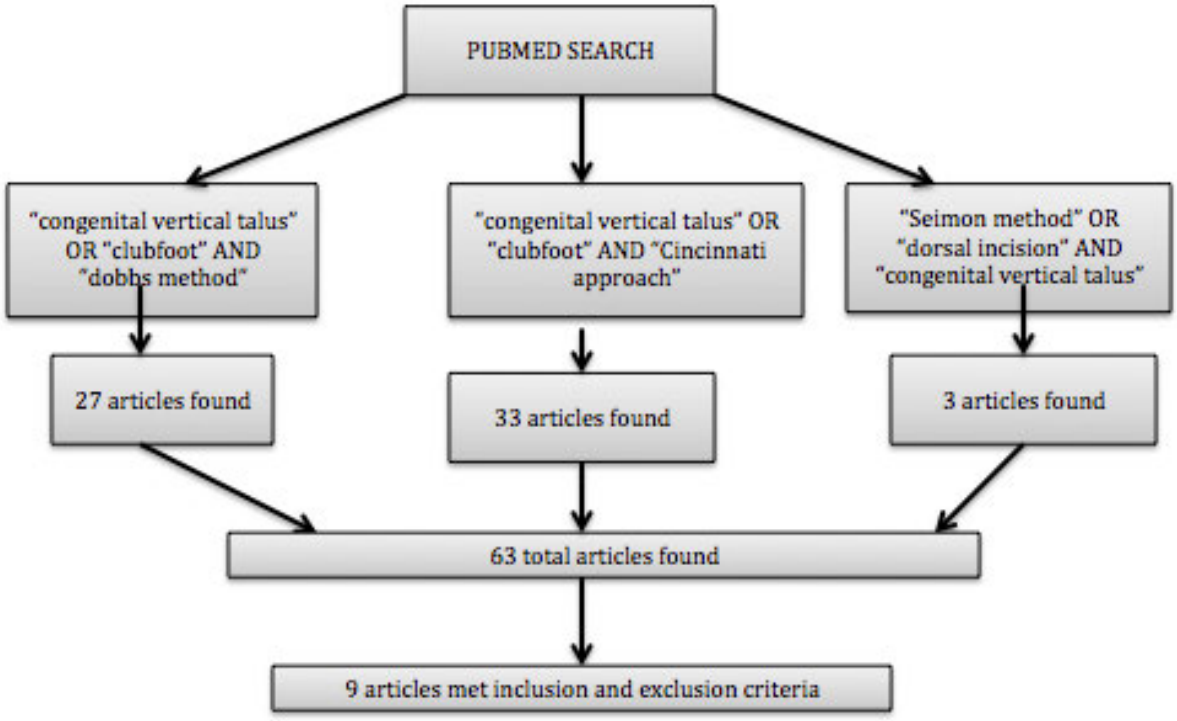

Figure 1: Acquisition of studies from the Pubmed Database

RESULTS

Study	Method	Number of Feet	Etiology (number)
Kodros[6]	Traditional Cincinnati	37	Idiopathic (10), Neuromuscular disorder (8), Malformations disorder (3)
Zorer[14]	Traditional Cincinnati	17	Idiopathic (8), Meningomyelocele (3), Cerebral palsy (4), Arthrogyposis (1), Tethered cord & hemivertebra (1)
Saini[3]	Semion + Posterior Incision	12	Idiopathic (2), Arthrogyposis (7), Neural tube defect (3)
Ramanoudjame[16]	Midtarsal release + Open Reduction	31	Idiopathic (15), Arthrogyposis (7), Spinal dysraphism (2), Others (7)
Mazzocca[2]	2 groups: Semion or Traditional Cincinnati	36 (Semion: 11, Cincinnati: 25)	Not mentioned
Aslani[22]	Dobbs Method	10	Idiopathic (5), Arthrogryposis & Larson syndrome (5)
Bhaskar[23]	Dobbs Method	4	Idiopathic (4)
Wright[24]	Dobbs Method	13	Idiopathic (7), Neuromuscular syndromes (6)
Dobbs[25]	Dobbs Method	15	Non-isolated CVT (15)

Table 1: Descriptive Results from each Article

Study	Functional Results	Anatomical Results	Radiological Results
Kodros[6]	Ankle dorsiflexion: 17° Ankle plantarflexion: 16° Decreased subtalar motion	N/A	Normal TC & talo-1st MT angles in AP & lateral views
Zorer[14]	Ankle dorsiflexion: 8.1° - Decreased 28.9% Ankle plantarflexion: 32.9° - Increased 59.5% 59.5% increase in lateral talar range 80.6% increase in TN & CC joints dorsal motion	Medial longitudinal arch formed in 12 of 17 feet Hindfoot: 8 neutral, 9 valgus Forefoot: 11 neutral, 6 abducted	Normal TC & talo-1st MT angles in AP & lateral views
Saini[3]	Ankle dorsiflexion: 10° Ankle plantarflexion: 10° Restricted subtalar motion & eversion of medial arch less than 10°	Medial longitudinal arch established No bony prominences or callosities	Normal TC & talo-1st MT angles in AP & lateral views No deterioration in all angles
Ramano udjame[16]	Subtalar movement reduced	Medial longitudinal arch flat in all feet	Decreased tibiotalar angle Positive calcaneal pitch angle Corrected talo-1st MT angle
Mazzocca[2]	N/A	N/A	No difference between groups on lateral TC and tibiocalcaneal angles No difference between groups on AP TC & talo-1st MT
Aslani[22]	N/A	N/A	TC angle: 31° (39° decrease) TAMBA: 15° (45° decrease)
Bhaskar[23]	N/A	N/A	TC angle: 30° (40° decrease) TAMBA: 10° (50° decrease)
Wright[24]	N/A	N/A	TC angle: 23° (11° decrease) TAMBA: 14° (26° decrease)
Dobbs[25]	N/A	N/A	TC angle: 35° TAMBA: 10°

Table 2: Functional, Anatomical and Radiologic Results

Study	Method	Follow-Up Complications
Kodros[6]	Traditional Cincinnati	1 superficial pin-site infection 6 weeks post surgery 10 feet repeated surgery: tendon-lengthening, equinovarus deformity, heel valgus
Zorer[14]	Traditional Cincinnati	TN joint reduction deteriorates over time 4 feet with persistence hindfoot valgus & cannot attain medial longitudinal arch
Saini[3]	Semion + Posterior Incision	None reported
Ramanoudjame[16]	Midtarsal release + Open Reduction	Pes planovalgus & inadequate reduction in 5 feet Tricipital insufficiency in 3 feet
Mazzocca[2]	2 groups: Semion or Traditional Cincinnati	Talar osteonecrosis in 12 feet (Cincinnati) 1 pin migration & 1 calcaneal fracture (Cincinnati) 1 superficial pin-tract infection (Semion)
Aslani[22]	Dobbs Method	None reported
Bhaskar[23]	Dobbs Method	None reported
Wright[24]	Dobbs Method	Recurrence noted in 5 children (10 feet)
Dobbs[25]	Dobbs Method	Recurrence noted in 3 children (5 feet)

Table 3: Follow-Up Complications from each Article

DISCUSSION

CVT is a complex foot deformity with multiple surgical interventions proposed. Surgical correction becomes increasingly difficult with increasing age of the child due to contracture of the joint capsule and periarticular structures. Several studies have suggested that the different surgical techniques do not differ in producing significantly better results when assessing TN reduction post surgery.[5,8,19] Nonetheless, notable differences exist in maintaining the reduction and limiting other complications during the follow-up phase of the surgical intervention.

The Cincinnati Incision

The Cincinnati procedure is a popular surgical correction for congenital talipes equinovarus although it was originally designed for treating CVT.[20] Kodros and Zorer have since contributed the largest sample size studies concerning CVT with solely Cincinnati intervention. According to Kodros, this Cincinnati approach provides clear exposure of the deformity to allow a complete correction of the plantarflexed vertical talus, reduction of the TN dislocation, and the realignment of the equinovalgus deformity of the calcaneus.[9] This procedure also allows for a complete release and reduction of the talocalcaenonavicular joint.[16] In both studies, there was decreased ankle dorsiflexion and increased ankle plantarflexion to achieve normal total range of motion. Both studies also reported improvements in the TC and talo-first metatarsal angles in both AP and lateral views to within normal range. There is also support for excellent wound healing and good cosmesis by both studies as initially proposed for this procedure.

Maintaining the reduction with biplanar K-wire fixation and releasing the adjacent CC joint are important aspects to the effectiveness of the Cincinnati intervention in CVT treatment.[9] Zorer did not observe TN reduction deterioration because of the short follow-up period of 42.9 months, and most revision surgeries are performed after 5 years with increasing rates.[21] As it is believed that deterioration occurs due to the plastic deformation of the TN joint, ankle-foot orthosis and orthopaedic boots are advised for at least a year post-operation.[16] Another cause of recurrent deformity after surgical correction is an underlying neurological problem.[9,16] Kodros reported three cases with sacral neurological deformity where unopposed plantarflexion by the peroneus longus with transferred tibialis anterior resulted in a gradual development of a cavus deformity.[9] Zorer subsequently did not transfer the tibialis anterior tendon after lengthening. A limitation of the Cincinnati procedure as highlighted by Zorer is the difficulty in reaching the dorsal extensor structures, which leads to increased potential in damaging the vascular structures surrounding the talus resulting in avascular necrosis.[16]

The Dorsal Seimon Incision

Alternatively, the Seimon approach provides a direct exposure to the dorsolateral dislocated TN joint and the secondary contracted extensor tendon structures. Both Saini and Mazzocca reported good and fair results using the Seimon approach with recovery of normal functional range in ankle dorsiflexion and plantarflexion, and

improvement in TC and talo-first metatarsal angles in anterior-posterior and lateral views.[4,5] Mazzocca also reported an improvement of the TAMBA score with both the Seimon and Cincinnati approach, a measurement of the amount of dorsal dislocation of the navicular over the talus.[4] Seimon first reported success in this approach by lengthening the contracted dorsal tendons and capsulotomy of the dorsal TN ligament without releasing the CC joint.[10] Stricker also achieved similar success with the Seimon approach by evaluating 20 cases (17 good and 3 fair outcomes) less than 27 months old.[22] Some patients did experience stiffness in ankle and subtalar motions and mild residual forefoot abduction with midfoot sagging at the TN joint post surgery.

Saini reported that the dorsal TN joint capsule must be incised in order to reduce the joint.[5] Extending the dorsal incision laterally will also allow CC joint release and lengthening of the peroneus muscle tendons. Achilles lengthening is advised by Seimon and also performed by Saini with a small vertical posterior incision. Although Saini released the posterior ankle and subtalar capsules, Mazzocca reported that percutaneous heel cord lengthening without open lengthening and posterior capsulotomy is a satisfactory correction of the hindfoot.[4] It remains a debate whether the posterior joint capsules need to be released to completely reduce the TN joint in CVT. Ramanoudjame suggested that the lengthening of the Achilles tendon should not be routinely performed due to tricipital insufficiency during growth, and the posterior tibiotalar joint should only be opened when performing an anterograde K-wire fixation of the TN joint.[18] Open reduction of the TN joint and lengthening of the extensor tendons can produce good radiology and functional results, and the lengthening of the Achilles tendon is indicated if equinus remains after reduction.[18] This procedure, however, did produce pes planovalgus and deterioration of the reduction in the follow-up period. An approach to reducing these complications is distal osteotomy of the calcaneus and dorsal reorientation of the CC joint to displace the cuboid plantarwards.[18] Pes planovalgus is also avoided by lengthening the lateral column.

Previous comparative literature review of the Cincinnati and Seimon approach revealed that CVT operated by the Cincinnati approach required a greater number of surgeries to correct the residual deformities such as TN subluxation as compared to the Seimon approach. While both procedures are effective in TN joint reduction without significant deterioration, the incidences of avascular necrosis are higher in the Cincinnati approach, as mentioned by Mazzocca, where 48% of the cases treated with the Cincinnati approach observed necrosis as opposed to none by the Seimon group. Another study also observed necrosis in one-third of their cases with the Cincinnati approach.[23] The lesser incidence of avascular necrosis of the talus from the Seimon approach is attributed to a smaller dissection required to access the contracted dorsal tendons and capsule as opposed to approaching them posteriorly in the Cincinnati approach.[5] The smaller Seimon approach reduces the potential disruption of the interosseous vascular communications adjacent to the capsule and ligamentous attachments around the talus. Overall, the dorsal Seimon approach is a simpler procedure requiring less operative time and produces better clinical scores with fewer complications three years after surgery.

The Dobbs method (reverse-Ponseti)

Several studies describe the Dobbs method as being most successful in TN joint reduction and the angles associated with it. Aslani showed that the Dobbs method could be applied to the treatment of CVT caused by both congenital and idiopathic disorders.[24] Patients were evaluated both clinically and radiographically in an average follow-up period of 2 years after treatment. After 2 years of treatment, several improvements were seen. First, all patients had plantigrade and flexible feet with good radiographic corrections and showed no recurrence of deformity.[24] Second, mean TC and talar axis metatarsal angles before and after treatment significantly improved (Table 2). Patients also wore ordinary shoes with no discomfort.[24] Most importantly, after 18-36 months, all patients were pain free and had flexible legs. [24] Despite the success in TN joint reduction for all patients, there were limitations to their study. Specifically, due to the short follow-up time, the long-term outcomes were unknown. [24] Additionally, the small sample volume, heterogeneity cohort, and lack of comparative cohort were other limitations to their study.[24]

Bhaskar managed to do a unique treatment with cast application performed in two stages. The first one shows a below the knee cast applied in an abducted forefoot which is gently plantarflexed and inverted with one hand while the other hand is used to manipulate the talus.[23] The second stage shows a cast that is extended above the knee. This procedure is repeated at a 7-10 interval and usually 4 or 5 casts are required until the plantarflexed talus is in line with the 1st ray.[25] The average follow-up period was 8.5 months.[25] At the end of treatment, all feet moved easily and were plantigrade while still using an ankle-foot orthosis.[25] Both the mean TC angle and TAMBA improved after casting (Table 2). The only limitations to this study are a single author experience and a short follow-up.[25]

Similarly to Aslani, Wright conducted a study with children of both congenital and idiopathic etiology. Treatment begins with weekly serial manipulations and casting. The foot is stretched in plantarflexion and inversion while counter pressure is applied to the prominent medial aspect of the head of the talus.[25] A plaster cast is applied below and above knee in two sections to maintain the correction. Results in Table 2 showed that the technique is effective for initial correction of both idiopathic and teratological groups as seen in the angle reductions. However, the difference between the 2 groups did not reach statistical significance, although this may reflect the relatively small sample size seen in this rare disorder.[26] Analysis of the children with teratological CVT showed that all eventually required a mini-open capsulotomy as a secondary procedure to achieve reduction of the TN joint.[26] Complications occurred in 6 out of 9 feet in the teratological group and 4 out of 12 feet in the idiopathic group.[26]

Dobbs completed a retrospective study on 15 patients, which was reviewed at a minimum of 2 years following treatment.[27] At the time of presentation, the severity of the vertical talus deformity was assessed radiographically as either Type I or Type II.[28] In contrast to the other studies, radiographic data obtained from this study was compared with age-matched normative values. All angles were significantly smaller ($p < 0.0001$) indicating TN joint reduction.[25] Initially, correction was achieved in all cases and the mean number of casts required was 5.[27] According to the

Adelaar scoring system, 4 patients had an excellent result, 10 had a good result, and 1 had a fair result.[28] Unfortunately, three patients in this series experienced a relapse after initial successful correction and they all had Coleman type II deformity in initial presentation.[25] The treatments for these patients require reduction of both the TN and CC joints.[26]

Limitations

Two limitations are consistently found in current literature available for the surgical treatment of CVT: small sample subjects and short post-operative follow-up durations. The small sample size, in addition to the inconsistencies of the etiology of each CVT case makes it difficult to form standardize surgical intervention for subsequent cases. Nonetheless, since CVT is a rare deformity, it will take many years to present a study with a large sample of CVT feet. Prospective studies that compare different surgical procedures in controlled settings are hard to obtain due to the limited number of trained surgeons capable of performing multiple techniques with equal expertise. The available retrospective comparison studies provided by Mazzocca and Saini provide a good framework for the single-incision approach. Finally, it should be kept in mind that clinically significant deformities may take up to 5 years after the initial TN reduction surgery to develop, and hence future papers should attempt to include longer follow-up results when possible. In addition, there are also limited longitudinal studies available that characterize the development process into adulthood after having received a surgical intervention for CVT during childhood.

CONCLUSION

The surgical treatment for CVT is continuously evolving as it aims to minimize the amount of dissection, thereby decreasing the risk of avascular necrosis as well as post operative pain and stiffness. Currently, the three methods as stated by this literature review prove to be most successful. Both the Seimon incision and Dobbs method have shown lower rates of complications than the traditional Cincinnati approach. The occurrence of AVN of the talus is significant with the Cincinnati approach and should be mentioned as a negative for this approach. While it is evident that controversy exists over the type of surgical approaches used to treat CVT, particular attention should be paid to the TN joint capsule along with the dorsal and dorsolateral contracted tissues. Reducing and releasing these structures are the most important factors in determining the outcome and developmental success of CVT.

AUTHOR'S CONTRIBUTIONS

YC and MP equally contributed towards the design of the study and evaluated the available articles. YC researched on the Cincinnati and Semion approaches. MP researched on the Dobbs method. YC completed the revisions. All authors drafted, read and approved this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Common Etiology, Pathology, and Effective Treatments for Medial Tibial Stress Syndrome: A Systematic Review

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Abstract

Introduction
The purpose of this study is to review the literature on Medial Tibial Stress Syndrome (MTSS) in order to better understand the etiology, pathology, and treatment options for this common lower extremity injury.

Study design
Systematic Review of the Literature

Methods
A literature search was conducted via PubMed and Google Scholar databases with search terms 'Medial Tibial Stress Syndrome', 'MTSS', and 'Shin Splints'. The PubMed database search returned 124 results. Of the results, 14 articles were selected based on the abstract summary, and applying inclusion/ exclusion criteria, 8 articles were selected for further review. Google Scholar database search returned 24,700 results. Of the results, 30 articles were selected based on the abstract summary, and applying inclusion/exclusion criteria 11 articles were selected for further review. In total, 19 articles were selected for final review.

Results
The authors found that the pathology of MTSS includes pain along the medial aspect of the tibia with posteromedial muscle tenderness. Many factors are shown to be associated with MTSS, including an increased navicular drop, increased body mass index, decreased bone density, minimal running experience, and improper training. Treatment options include reduction in physical activity, non-steroidal anti-inflammatory drugs, shock absorbing insoles, and posterior fasciotomy surgery.

Conclusion
The objective of this paper was to explore the origin and treatment of MTSS, however the significance of certain risk factors and treatment options were inconsistent and varied between studies. This proves that further research needs to be conducted to better understand this common pathology.

Key words
Medial Tibial Stress Syndrome, MTSS

Level of Evidence: 4 (Class IV)

INTRODUCTION

Medial Tibial Stress Syndrome (MTSS), better known as 'Shin Splints', is one of the most common lower extremity injuries in runners and athletes of high impact sports, such as sprinters and football players.[1] It has been cited to have an incidence of 4 to 35% in the military personnel and athlete population.[2] In a study conducted on non-professional athletes, it was found that as many as 15% of male runners and 22% of female runners develop medial shin pain.[2,3] Patients often seek their podiatrist for treatment of MTSS, receiving custom foot orthoses, palliative care, and surgical intervention.[1] The diagnosis for MTSS is usually made on a physical examination alone, although x-rays and MRIs are often used to exclude other serious conditions. The occurrence of MTSS is well documented, but its etiology remains unclear.

MTSS is a distinct condition from other common running related injuries, such as compartment syndromes, stress fractures, popliteal artery entrapment, and lower extremity neuropathy. These conditions are often considered in the differential diagnoses, and can also manifest concurrently with MTSS.[4] MTSS is defined as pain and/or posteromedial muscle tenderness along the medial aspect of the tibia, especially where the soleus muscle has its fascial attachment.[5] Since the first articles describing shin splints were published, the oldest of which date back to the 1950's, many different mechanisms of pathology and differential diagnoses have been proposed for MTSS.[5] Although there is a considerable list of potential causes and comorbidities associated with MTSS, the influence of each factor remains uncertain. Our objective is to compile a literature review of case studies and meta-analyses of risk factors and treatments for MTSS. Our focus will be directed at proposed risk factors for MTSS such as increased navicular drop, high body mass index, gender, orthotic use, strength imbalance of lower extremity muscles, and subtalar pronation. Various conservative treatments as well as surgical correction will be evaluated for their effectiveness in the treatment of MTSS.

METHODS

Both authors performed literature searches using PubMed and Google Scholar databases. Search terms included 'Medial Tibial Stress Syndrome', 'MTSS', and 'Shin Splints' on each database. The inclusion criteria included articles published between 2000 and 2014, and articles that discussed etiologies or treatment options for MTSS. Exclusion criteria included articles in which the main topic was not MTSS, articles not written in the English language, and articles not available in full text. The search employed the Boolean operators "or" and "and" for the terms "Medial Tibial Stress Syndrome" AND "Risk factors" OR "Pathology" OR "Treatment". The PubMed database search returned 124 results. Of the results, 14 articles were selected based on the abstract summary, and applying inclusion/exclusion criteria, 7 articles were selected for further review. Google Scholar database search returned 24,700 results. Of the results, 30 articles were selected based on the abstract summary, and applying inclusion/exclusion criteria, 11 articles were selected for further review. In total, 18 articles were selected for review.

RESULTS

PATHOLOGY

Many signs are associated with the pathology of MTSS, such as myofascial strain, periosteal inflammation, tendinopathy, absence of myofascial attachment, and bone stress reactions.[6] MTSS is most likely a combination of various responses that occur after repetitive loading and strain on the tibia, including tendinopathy, breakdown and remodeling imbalance, periostitis and other stress reactions.[4,7] One of the most striking physiological changes that occurs in individuals with MTSS is increased anterior compartment pressure post-exercise, as compared to before exercise.[8] Furthermore, changes in bone remodeling and a decrease in bone density have been associated with MTSS.[5]

ETIOLOGY

Navicular drop

One of the etiologies associated with MTSS is a navicular drop. In a prospective study of 66 patients by Raissi et al., those with MTSS symptoms were determined to have a significant increase in navicular drop.[3] In this study, navicular drop is defined as the drop in the navicular tuberosity level from bilateral to unilateral stance on the affected leg. Another investigation of a navicular drop in 2012 on 77 cross country high school runners showed that runners with a navicular drop of greater than 10mm were about seven times more likely to complain of exercise related medial leg pain.[9]

Inversion/eversion strength imbalance

Several studies also investigated the kinematics of running and how alignment and anatomy play into the development of MTSS (shin splints), though many findings showed poor associations, as seen with intercondylar femoral distance (P = N.S) and and left/right Q angle (P = N.S). [1,3,11] A study in 2011 by Yuskel et al. proposed that an imbalance of strength between the inverter and everter muscles may play a role in the etiology of shin splints.[10] This is because greater eversion strength can lead to excessive pronation of the foot during midstance and an overloading of the soleus muscle. They found that the average eversion strength at 30 degrees/sec and 120 degrees/sec angular velocity was higher in the group of patients with MTSS ($p < 0.05$), but the strength of inversion was similar among both groups. It was suggested that the imbalanced ratio of inverter to everter muscles in the patients was responsible for changes in soleal loading, which led to shin splints. A review by Galbraith et al., which also investigated kinematics, suggested weakness of the triceps surae as a risk factor in developing shin splints (an opposite finding). This weakness, either due to inherent lack of muscle development or tiredness after repetitive use, leads to altered running mechanics and an increased strain on the tibia.[4]

Body mass index indications

It is commonly believed that many lower extremity injuries can be at least partially attributed to an increased body mass index (BMI). In a study involving 105 high school students, increased BMI was shown to be significantly associated with an increased risk for MTSS symptoms.[1] In this study, there was

no statistical significance found in MTSS injuries between boys and girls, and no difference in navicular drop in association with MTSS. The method of navicular drop measurement (sitting to unilateral standing navicular height) was different than those of Raissi et al (bilateral to unilateral navicular height), possibly contributing to the discrepancy.[3]

Orthotic use

A meta-analysis study by Newman et al. did find an overall statistical significance in prior orthotic use and increased incidence of MTSS injury (403 subjects: RR 2.31, 95% CI P<0.0001).[6] The study suggests a possible link between prior orthotic wear for an unspecified amount of time and MTSS development, something that should be explored in greater detail in future studies.

MTSS risk factors in runners

Newman et al. found that individuals with fewer years of running experience were at higher risk of developing symptoms of MTSS.[6] In a study of 125 high school cross country runners, there was an association, however not statistically significant, between fewer years of running experience and increased incidence of MTSS symptoms.[9] Other implications for runners in developing shin splints include an abrupt increase in intensity, duration, and length of running or training.[4] Injury rates increase significantly in runners who log in more than 40 miles weekly.[7] It has been demonstrated that in patients with prior leg or foot injuries, MTSS symptoms were twice as likely to occur.[3] Furthermore, it has been shown that a previous history of exercise related leg pain put the athlete at 12 times a higher chance of recurrence, which suggested that some people may be predisposed to developing the condition due to genetic, anatomic, or exercise related factors.[9]

Gender

It has been proven that females are at a greater risk for developing shin splints, possibly due to kinematic and environmental influences.[4,6] A study by Burne et al. looked at 167 individuals in the Australian Defense Force Academy, and found significant differences in the prevalence of MTSS in male versus female (30.6% in women and 9.8% in men).[11] Another study by Loudon et al. also found that females have disproportionate rates of running injuries and medial shin pain.[12] This study investigated kinematic differences in running between gender, and found the sole significant difference in males and females suffering from MTSS was that the females had a higher degree of pelvic tilt than males while running. However, in a control group of athletes without medial shin pain, no differences in the kinematics of the control group were found. It has also been found that women are at a 1.5-3.5 times higher risk of developing stress fractures of the tibia as a sequelae to MTSS, which could be due to a lower baseline mineral density.[4, 6]

Bone density

Since MTSS is likely a combination of various stress responses to repetitive loading including periostitis, bone changes are likely to be evident with the condition.[4, 7] A study on male soccer players with MTSS found that the average tibial bone density was 15% lower than in a group of non-athletic control subjects, and 23% lower than in a group of

athletic subjects, which may suggest that decreased bone density is either a cause or sequelae of MTSS.[5]

TREATMENT OPTIONS

Graded running program

While abstaining completely from athletic activities is a commonly prescribed treatment option, and has been shown to be effective, it is not an ideal treatment for most athletes due to lack of compliance. A study on 74 athletes with MTSS performed by Moen et al. examined different treatment options by assigning the athletes to a recovery program of either a graded running program, a graded running program with exercises, or a graded running program while wearing a compression stocking.[14] The recovery of the athletes was determined by the time it took them to complete a running program and also their satisfaction with the outcome of the treatment. Even though most of the athletes did experience improvement in their condition, there were no statistically significant differences between each of the three different groups. A scaled-back training program, possibly combined with other low impact exercises like swimming, pool running and biking has been supported by many other scientists and physicians as well.[14] Current commonly prescribed treatment regimens include NSAIDs to reduce pain and inflammation, physical therapy and stretching exercises. However, it is clear that the most important variable in the treatment of MTSS is allowing adequate time for healing, as it has been shown that resting is equal in effectiveness to ice, NSAIDs, physical therapy and activity modification.[15]

Shock absorbing insoles

A study by Craig et al. reviewed an insole option of conservative care regarding MTSS correction. Shock absorbing insoles are defined as an unspecified shock dissipating material that is uniformly placed in shoes to reduce the pressures of body weight and ground reaction forces, while insoles that control navicular drop were modified with a protruding navicular flap, preventing a large drop in the navicular bone and thus limiting excessive pronation in gait. The best outcomes were found in patients who wore shock absorbing insoles in their shoes as well as insoles which control navicular drop, but the results were not statistically significant.[16] The results may be due to the shock absorbing nature of the insoles, which contribute to less muscle exertion and the sequelae of inflammation and compartment syndromes. Different insole materials and amount of shock absorptivity in relation to MTSS alleviation was not discussed, and this promising treatment option warrants further research.

Shock wave therapy

A study of 14 patients diagnosed with MTSS and 11 control patients determined that in patients with MTSS as compared to the control group, there was lower midfoot kinematics, but increased surface electromyographic (SEMG) signals in the tibialis anterior muscle.[17] Future electrical stimulation studies may further elucidate the physiological changes that accompany MTSS symptoms. Extracorporal shock wave therapy is currently being explored as a possible course of prevention for lower extremity injuries, and as a therapy to speed up the

recovery of symptoms associated with MTSS.[7,15]

Surgical correction studies

Surgery is an alternative option for chronic MTSS pain. A study of 78 patients with MTSS explored more invasive procedures, specifically surgical correction posterior fasciotomy, for pain symptoms associated with the common lower extremity injury.[13] Patients who did not experience relief in symptoms or pain perception based on the visual analog scale after at least 12 months of various conservative treatments were candidates for surgery. Posterior fasciotomy procedure makes incisions in the fascia to relieve pressure that may be associated with MTSS. Of the 46 patients followed thirty months post-operatively, 69% experienced a significant reduction in pain (as determined with the visual analog pain scale), while 9% had poor outcomes. The case series displayed generally favorable results in pain reduction, however only 41% of post-op patients returned to their peak physical activity before symptoms of MTSS occurred. Although surgical intervention can provide symptomatic relief, it is usually reserved for patients who have not shown improvement after conservative methods, as most athletes do improve without surgery.[4] The possibility for a decline in future physical activity post-operatively must be considered and balanced when investigating the pros and cons of invasive methods.

DISCUSSION

Navicular drop

While it has been shown that navicular drop is correlated with MTSS symptoms, not all of the studies investigating arch height in relation to MTSS symptoms found the same results.[3, 6] Certain studies reported no relation between MTSS symptoms and medial longitudinal arch height or angle in neither weight bearing nor non weight bearing measurements.[6, 10] It is possible that the discrepancies among studies lie in the measurement technique of navicular drop, or the sample size of the study. A measurement of navicular drop greater than 10 mm could be a useful clinical tool as a cutoff point in determining a patient's risk of developing MTSS, but further studies should be conducted regarding the differences among navicular drop, pes planus, and congenital and acquired flat footedness in relation to developing MTSS. It is also possible that acquired pes planus is at a higher risk for developing shin splints than congenital pes planus, as progressive hyperpronation may lead to the development of shin splints and a navicular drop. The study by Raissi in 2009 supports this idea, because it noted a difference between the right and left navicular drop in patients with MTSS, suggesting that the drop was worsening over time and was not congenital.

BMI indications

Several studies have investigated how BMI plays a role in developing MTSS, and also how it can contribute to a longer recovery time.[6, 15] Other studies noted that there was not a significant difference between the BMI between a group of patients with MTSS and a

control group.[9] The clear takeaway is that there is much conflicting and inconclusive data regarding BMI, and that more research on this topic should be performed. Though it is true that a higher BMI could contribute to higher amounts of loading, athletes can also have relatively higher BMIs than sedentary individuals due to higher amounts of muscle mass. Further studies that take into account of the fitness level and fat to muscle ratio of the patients should be conducted.

Gender

Another common finding among studies was female gender as a risk factor for developing shin splints.[4, 6] This could be due to several factors, some of which may be modifiable, including inadequate nutrition and a lower bone density, but inherent genetic differences between sexes predispose females to stress fractures and differences in anatomy that more often lead to running injuries. This is exemplified through the fact that females who developed shin splints had higher degrees of pelvic tilt than males, whereas females who did not develop shin pain did not exhibit this pelvic tilt. Thus, the higher rates of shin splints in females could be a result of kinematic differences in running alignment between genders, with females being more likely to tilt their pelvis while running. In that case, the problem could possibly be corrected by educating the patient, training properly with a running coach, and being aware of alignment while running (the methods of treating pelvic tilt were not described). However, a higher degree of pelvic tilt in women could also be a congenital difference in anatomy and therefore not modifiable. Since a lower baseline mineral bone density also contributed to post-MTSS stress fractures, women are inherently more susceptible. The outcome of MTSS could be slightly changed with proper nutrition and injury education, though women will most likely always have lower bone densities compared to their male counterparts and remain at a higher risk of developing stress fractures.

Risk factors for runners

Several other risk factors that can be controlled by the athlete should be noted by doctors and trainers so that they can best educate their patients about proper training to avoid injury. These risk factors include total mileage per week, increase in duration and intensity of a training program from week to week, running shoes and orthotics, alignment and kinematic during running, and the patient's prior history with foot or leg injuries. Although it has also been shown that an abrupt increase in intensity, duration, and length of running or training increases the likelihood of developing shin splints, further studies should be done to determine what level of increase is safe and training programs should be developed for athletes based on the available data.[4] Since there is an increased risk of developing medial shin pain in a runner with fewer years of experience, studies should be conducted to determine the maximum safe increase in intensity and duration of training from week to week for a new runner. Shock absorbing insoles and orthotics may useful for MTSS injuries as they can reduce the force of impact and control navicular drop. Well fitting, dry sneakers that are changed often (experts suggesting anywhere from about every 250 to 600 miles) are imperative for optimal running comfort and safety, though not directly linked to preventing MTSS.[4,16]

Running is a complex movement of open and closed-chain kinetics that involves several muscle groups and the placing of repetitive forces on all joints of the lower extremity, which eventually get passed through the foot. The importance of proper kinematics and strength balance in avoiding running injuries has been discussed by several studies. An imbalance of relatively weak inverter muscles or overactive everter muscles may lead to overpronation and excessive strain on the tibia. Furthermore, an exaggerated pelvic tilt (whether anatomic or due to prior injury) also has been shown to increase the risk of developing MTSS symptoms.[12] These studies prove the importance of making athletes aware of the certain modifiable movements and positions that can put them at a higher risk for shin splints. Educating the patient about early detection, adequate nutrition, muscle conditioning, and proper footwear may help prevent related stress fractures.

Treatments

Although several studies have been conducted on the effectiveness of various treatments of MTSS, no single treatment has proven to be most effective. Commonly prescribed and investigated treatments include NSAIDS, proper conditioning, physical therapy for stretching and strengthening of the calf musculature, rigid neoprene orthotics to correct foot hyperpronation, shock absorbing insoles, activity modification and rest.[15] Many experts agree that activity reduction and modification is the best not only due to the fact that the athlete is not likely to comply with stopping their exercise routine altogether, but also because a scaled back program has been shown to be an equally effective treatment as rest in treating MTSS.[4, 18] However, as the athlete looks toward the future, it is important to optimize the kinematics of running so that proper alignment and maximum shock absorption can be obtained, and the risk of re-injury can be reduced.

CONCLUSIONS

Lower extremity injury symptoms range from a minor inconvenience to debilitating, crippling pain, and MTSS has been associated with both sides of the spectrum. Complications that arise from MTSS may interfere with not only the athletic endeavors but also the daily routines of patients. Several studies show that navicular drop, BMI, and bone density correlate with MTSS symptoms, while activity reduction was shown to reduce symptoms.[1,3,8] It is important to note the complexity and frequent occurrence of MTSS injuries, as well as the scientific and clinical work taken upon the podiatric community in analyzing the injury in order for us to appreciate the intricacy of MTSS in its entirety. As more evidence based research is conducted regarding the origin and treatment of MTSS, doctors, professional athletes and recreational runners alike will be able to better understand the injury and be provided a comprehensive and conclusive treatment plan.

AUTHOR'S CONTRIBUTIONS

Both authors contributed to the design of the paper, and performed literature searches and inclusion/ exclusion criteria. MR contributed to the abstract, introduction, conclusion and edited the discussion of the paper. DD contributed to the methods, results and discussion of the paper. Both authors contributed equally in the writing of this report and reviewed the final version for submission.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Injection Treatments for Plantar Fasciitis with the use of Corticosteroid, Autologous Platelet-Rich Plasma, Dextrose, or Botulinum toxin type A: A Literature Review

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Abstract

Introduction
A literature review was conducted to evaluate the evidence available for plantar fasciitis injection therapy modalities, specifically corticosteroid, autologous platelet-rich plasma (PRP), dextrose (DP), botulinum toxin type A (BTX-A). The purpose of this study is to assess the current literature for effectiveness of injection treatment options to resolve plantar fasciitis pain.

Study Design
Qualitative Systematic Review of the Literature

Methods
A literature search was performed using PubMed and Medline databases. Inclusion criteria: all articles are either prospective, observational follow-up studies, randomized controlled trials, or randomized single and double-blind studies consisting of a history of plantar fasciitis pain for at least three months where conservative therapies have failed. Exclusion criteria: diagnosis of inflammatory arthritis, prior surgery or trauma to the heel region.

Results
Five articles were obtained from the PubMed and Medline databases that met the criteria.

Conclusion
Local corticosteroid injection is the preferred method for plantar fasciitis. PRP, DP and BTX-A should be considered for the treatment of chronic plantar fasciitis to obtain patient improvement prior to surgical options. Future studies should include injections of PRP, DP, and BTX-A with variable quantities to test for efficacy at the lowest dose.

Key Words
Plantar fasciitis, platelet rich, platelet rich plasma, growth factor, dextrose, Botox, botulinum toxin A, cortisone injection, steroid.

Level of Evidence: 4

INTRODUCTION

Plantar fasciitis is the most common cause of heel pain, observed in up to 10% of the general population and seen most amongst sedentary individuals, athletes and those participating in running sports.[1,2] Heel pain due to plantar fasciitis is described in the literature as having a multifactorial etiology and still remains to be an unknown definite clinical entity.[3] Common risk factors for plantar fasciitis can be precipitated by a change in an individual's activity or individual's biomechanical foot types. Diagnosis of plantar fasciitis is established solely by history, elicitation of pain at the medial calcaneal tubercle or exclusion to other causes of heel pain.[2] A physician can confirm the diagnosis of plantar fasciitis by measuring the thickness of the inferior calcaneal border of the plantar fascia having greater than or equal to 4mm via ultrasound imaging[4].

The initial treatment options for patients presenting with plantar fasciitis may include simple measures such as application of ice and heel cups, patient-directed therapies, orthosis, activity modification, and a stretching/strengthening exercise program.[4] Patients that persist with heel pain, who failed to respond to these simple measures, have treatment options that include the use of non-steroidal anti-inflammatory medications, deep-tissue massage therapy, posterior night splints, ultrasound, physical therapy, iontophoresis, and phonophoresis.[4,5] These treatment options typically are effective for 90% of the cases within a timeframe of weeks to a few months, leaving 10% of the patients failing to respond, requiring more aggressive procedures such as injection therapy, extracorporeal shock wave therapy, and in some cases, surgical release of the plantar fascia.[4,5]

Although most patients respond to conservative treatment options, some patients require further treatments such as local injections. Different pharmacodynamic theories exist in terms of the injection's mechanism of action. Four injection modalities will be reviewed, specifically corticosteroid, autologous platelet-rich plasma, dextrose, and botulinum toxin type A.

The most commonly given injection for plantar fasciitis is a corticosteroid injection.[4] The steroid reduces the body's inflammatory response therefore decreasing the amount of pain. However, the steroids are not always successful, and multiple injections are occasionally required due to the short-lived relief.

Recently, different injections, such as the autologous PRP injection have been employed to resolve chronic plantar fasciitis. Local autologous PRP injections are aimed to deliver high concentrations of the patient's own platelets to the plantar fascia. The platelets become activated in the body and will secrete a wide variety of cytokines and growth factors, which act as chemo-attractants for reparative cells at the site of plantar fascia injury.[4,6] These cytokines and growth factors heal the micro-injury in the plantar fascia resulting in pain relief.

Having similar pharmacodynamics as autologous PRP is the use of hyperosmolar DP injection. The dextrose injection, in theory, may potentially have a biologic effect, increasing platelet-derived growth factor expression at the site of injection. This increase in growth factors results in the up

regulation of multiple mitogenic factors to signal mechanisms for repair of the tissue injury.[4]

The injection of BTX-A into the muscle results in a brief loss of muscle volume due to intrinsic muscle atrophy of adductor hallucis and flexor digitorum brevis. Thus, a possible relief of pressure on the neurovascular structures near the enlarged plantar fascia is achieved. BTX-A has been shown to inhibit substance P from dorsal root ganglia and block the release of glutamate from synaptosomes, therefore reducing pain stimuli perceived by the patient.[2,7] Furthermore, BTX-A decreases the local inflammatory response after administration. Less inflammation at the site of the plantar fascia results in less pain.

The purpose of this study is to review the current literature on plantar heel injections for treatment of chronic plantar fasciitis. This study aims to compare the efficacy of four injection procedures: corticosteroid, autologous PRP, DP and BTX-A.

METHODS

The authors conducted a review of literature retrieved from PubMed and MEDLINE databases. Utilizing the MeSH advanced search builder, the keywords "plantar fasciitis injection" yielded 167 articles. The Boolean operator "AND" was used to incorporate the term "plasma", "PRP", "platelet rich", "dextrose", "botulinum toxin type A", and "cortisone injection", which narrowed the results to 84 articles. After the authors reviewed each article, employing the inclusion and exclusion criteria, only five articles remained. The studies acquired and reviewed by the authors were not limited to publications solely in the United States, however language limits were set to English only. Restrictions were applied to the search for articles published between the years of 2011 to 2014. The inclusion criteria for the publications were all prospective, observational follow-up studies, randomized controlled trials, or randomized single and double-blinded studies consisting of a history of plantar fasciitis pain for at least three months where conservative therapies have failed. The authors excluded any diagnosis of inflammatory arthritis, prior surgery or trauma to the heel region.

RESULTS

The majority of publications for plantar fasciitis injections as a treatment do not compare a single type of injection to a placebo. Most of the randomized controlled studies compare a form of injection to corticosteroid. The lack of standardized patient assessment due to different scaling systems used in various studies make it difficult to compare one study to another. The authors compared the efficacy of treatment of each study in terms of statistically significant $p=0.05$ or less, to draw conclusions of injection success.

Five articles met the inclusion criteria. The results were further evaluated for average age, number of patients in the study, duration of pain from plantar fasciitis and statistically significant treatment option in each study. (Table 1)

	Corticosteroid vs. Placebo	PRP vs. DP	PRP vs. Corticosteroid	BTX-A vs. Corticosteroid	BTX-A vs. Placebo
Authors	Ball et al.	Eunkuk et al.	Raymond R. Monto	Ismael et al.	Babcock et al.
Study Design	Randomized controlled trial	Single-blinded, randomized controlled study	Prospective randomized comparative series	Randomized controlled study	Double-blinded, placebo-controlled study
Total sample size	65 patients	21 patients	40 patients	56 patients	27 patients
Mean age	49 years	37 years	55.5 years	53.9 years	44 years
Sex	29 males 36 females	11 males 10 females	17 males 23 females	19 males 37 females	9 males 18 females
Study Duration	12 months	2.8 years	1 year	6 months	2 months
Outcome Measures	Visual analog scale at baseline follow-up 6 and 12 weeks after injection	Foot Functional Index collected before first injection, at 2 weeks (before the 2nd injection), 2 months and 6 months follow up	American Orthopedic Foot and Ankle Society (AOFAS) measured pre-treatment, 3, 6, 12, and 24 months following injection treatment	Foot Health Status Questionnaire at baseline, 1 month, and 6 months after treatment	Pain Visual Analog Scale, Maryland Foot Score, Pain Relief Visual Analog Scale, all measured at baseline, 3 weeks and 8 weeks post-injection
Statistical Analysis	Analysis of covariance revealed significant differences in mean VAS scores between the corticosteroid and placebo groups at 6 weeks (p=0.03) and 12 weeks (p=0.009)	PRP group showed better outcomes compared with DP group at all re-evaluation intervals. However, there were no significant differences between groups at all follow-ups (P= 0.295 at 2 weeks, p= 882 at 10 weeks, p= 0.603 at 28 weeks).	The difference between the post-treatment AOFAS scoring results of the cortisone and PRP groups was statistically significant (P=0.001) at 3-, 6-, 12-, and 24-month follow up evaluations.	Patients in both treatment groups presented a significant improvement in all items at one month post-injection and the difference between groups did not reach statistical significance. At 6 months, the authors observed a clear and significant difference in favor of BTX-A in the results (p<0.001 BTX-A vs. CS).	Compared with placebo injections, the BTX-A group improved in all measures and there was statistically significant changes in the treatment group (P< 0.005 at 3 weeks and 8 weeks post-injection)

Table 1. Summary of studies and statistical outcomes. PRP, Platelet rich plasma; CS, corticosteroid; BTX-A,

DISCUSSION

Corticosteroid Injection vs. Placebo

Ball et al. conducted a randomized controlled trial recruiting 65 patients with inferior heel pain. The inclusion criteria of the study were heel pain over the medial tubercle of the calcaneus failing to respond to eight weeks of conservative therapy. This study compared corticosteroid injection using a mixture of 0.5ml of methylprednisolone acetate/0.5ml of 0.9% saline versus the placebo of 1ml of 0.9% saline. There was a statistically significant difference between the two study groups using a VAS pain scale at six and twelve weeks (p=0.03 and p=0.009, respectively). The clinical trial shows benefits up to twelve weeks but further studies need to be conducted for long-term benefit.[8, 9,10]

Platelet-Rich Plasma vs. Dextrose Prolotherapy

A single-blinded, controlled study by Eunkuk et al. had a sample size of twenty-one patients treated with either PRP or DP. The patients

recruited in the trial had unilateral foot symptoms for a minimum of six months. All the patients had failed previous therapy of non-steroidal anti-inflammatory drugs, stretching exercises, physical therapy, a night splint, arch supports, corticosteroid injection and extracorporeal shock wave therapy. The PRP injection is a mixture of 0.05mL of the patient's own platelet concentrate and 2mL of supernatant plasma, while the DP injection consisted of 1.5mL of 20% dextrose/0.5mL of 0.5% lidocaine[4]. The study concluded no statistical significance between either injection groups. The authors of the study reported both injections demonstrated improvement in pain and function. Autologous platelet-rich plasma and dextrose have similar theorized mechanisms of action, but future studies can incorporate different amount of concentrated PRP.[4]

Platelet-Rich Plasma vs. Corticosteroid Injection

Raymound Monto performed a level 1, prospective randomized comparative series study comparing PRP efficacy versus corticosteroid injection. The study consisted of forty patients with unilateral chronic plantar fasciitis that did not respond to four months of standardized traditional non-operative treatment. The patients were either given a single ultrasound-guided injection of 3 cc PRP or 40 mg DepoMedrol cortisone. An American Orthopedic Foot and Ankle Society hindfoot scoring was completed for all patients immediately prior to PRP or cortisone injection at time 0, 3, 6,12 and 24 months following injection treatment. The post-treatment AOFAS scores were clinically significant with a P=0.001 at all follow-up evaluations. The study concluded that PRP was more effective and durable than cortisone injection for chronic recalcitrant cases of plantar fasciitis.[6]

Botulinum Toxin A vs. Placebo

Babcock et al. assessed the use of botulinum toxin type A versus saline for the treatment of bilateral plantar fasciitis on twenty-seven patients. Each affected foot was randomized to group A or group B. A total of 70 units of the botulinum toxin A was divided into two injection sites of one foot. The first injection was administered in the tender area of the medial aspect of the heel, close to the calcaneal tuberosity (40 units) and the second injection in the middle of the foot plantarly (30 units). The placebo group received the same volume of normal saline in the same areas of the foot. The patients were examined before the injection, at three weeks, and at eight weeks. The results yielded a comparison of the two groups using pain visual analog scale ($P<0.005$), Maryland foot score ($P=0.001$), pain relief visual analog scale ($P<0.0005$), and pressure algometry response ($P=0.003$). The authors of this study concluded that Botulinum toxin A injected for plantar fasciitis was statistically significant in pain relief and overall foot function at both three and eight weeks after treatment when compared to placebo.[2,11]

Botulinum Toxin vs. Corticosteroid Injection

The study conducted by Ismael et al., which used the same method described by Babcock et al., assessed the use of botulinum toxin type A versus corticosteroids on twenty-eight patients in each treatment group. The patients were evaluated using the Foot Health Questionnaire. The patients were examined one month and six months after the injections. At one month there was no statistical

significance between the two study groups for pain relief (P=0.069). When followed up at six months, patients treated with the botulinum toxin type A continued to improve, whereas the corticosteroid group lost part of the improvement achieved at one month. The patients in the two groups were evaluated for pain, function, footwear and self-perceived foot health. The results are as follows: BTX-A versus corticosteroids respectively, pain 19.10/-6.84 (P = 0.001), function 16.00/-8.80 (P<0.001), footwear 13.48/-7.95 (P=0.004), self-perceived foot health 25.44/-5.41 (P<0.001).[7]

P-Value Significance Outcomes

When comparing the five randomized controlled studies, it is difficult to draw conclusions due to different grading scales used in each study. The authors only drew conclusions on statistical significance. After assessing the literature, the use of corticosteroid proves to be better than no treatment. When corticosteroid was compared to PRP, PRP shows to be a statistically better treatment option. When corticosteroid was compared to BTX-A, BTX-A was superior in a long-term assessment. The results of the study were impressive for BTX-A because of reproducibility, in two different studies. No conclusion can be drawn for corticosteroid versus DP, since no study compared the two treatment options but when compared to PRP, DP shows to be statistically similar treatment option.

Limitations to the Study

The term plantar fasciitis is presumed synonymous with inflammation of plantar fascia due to the suffix "-itis". According to Harvey Lemont, "Plantar fasciitis is almost always used to describe a painful heel with inflammation of the plantar fascia at its origin, as opposed to pain originating along the course of the fascia."[2] Lemont advocates the term fasciitis should be used to describe a disease state of inflammation and the term faciosis should be used to describe the disorder associated with the degenerative changes that is evident in the plantar fascia. Despite the terminology that is often misused, different treatment options may address differing etiological factors. The studies suggested that all patients had chronic plantar fasciitis due to failed conservative treatment option or a given time frame, but no study proved an inflammatory process aside from pain. The studies failed to mention edema, heat, swelling or histological leukocyte accumulation.[2,12,13] Future studies should mention clinical observation due to different mechanisms of action of such injections. Studies should include injections with variable amounts to test for efficacy at the lowest dose. In the future, a randomized control study comparing all of the different injection options using the same pain scale should be conducted.

CONCLUSION

Patients suffering from plantar fasciitis after failed conservative treatment options should also be presented with the options of corticosteroid injection, autologous PRP, DP and BTX-A injection. There are published clinical trials showing the effectiveness of these injections, such that if one form of injection fails, another form of injection therapy may be effective treatment option rather than surgery. Eunkuk et al.'s study proves that patients still can have significant

pain relief even after failed corticosteroid therapy. This review suggests that Botulinum toxin type A injection had the greatest reproducible improvement in pain based on patient evaluation. In two separate studies, BTX-A injections with the same formula and location injection site concluded positive patient satisfaction. BTX-A helps to alleviate multiple causes of pain from enlarged plantar fascia. It is still unknown the exact causes of why patients have plantar fasciitis and it is difficult to address the exact cause of pain that a patient is experiencing. A patient may have enlarged plantar fascia that is compressing neurovascular structures or have pain from inflammation. By its mechanism of action, BTX-A seems to address the symptoms patients are experiencing. Studies in the future should also address the efficacy of variable amounts of injection type of formula, as patients may require more or less for sufficient relief of their symptoms.

AUTHOR'S CONTRIBUTIONS

The authors, A.J., K.J, and A.B. equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Interleukin-1β, Interleukin-6 and Interleukin-18 as Novel Contributors to the Development of Foot Ulcers in Diabetic Patients: A Systematic Review

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Abstract

Introduction
The purpose of this article is to further comprehend the roles of three pro-inflammatory cytokines in the development of diabetic foot ulcers (DFU): Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and Interleukin-18 (IL-18). These cytokines are known to have pro-inflammatory roles, but the mechanism that mediates their increased serum concentration and the incidence of DFU has yet to be studied in depth.

Study Design
Qualitative systematic review of the literature

Methods
An online database search was done using PubMed with the MeSH terms "Interleukin" and "Diabetic Foot ulcer". Inclusion criteria included: diabetic foot infection (DFI), IL-1, IL-6, and IL-18. Exclusion criteria were: interleukin–8 (IL–8), osteoarthropathy (acute Charcot foot), and non-human subjects.

Results
The search yielded 42 articles and 5 articles from 2005–2014 satisfied the criteria and were selected for a qualitative review.

Conclusions
Increased levels of IL-1β, IL-6 and IL-18 were shown to be associated with DFUs. The study of these cytokines may influence newer approaches in chronic foot ulcer treatments because of their pro/anti-inflammatory regulatory activity.

Key Words
Diabetic foot ulcer (DFU), Interleukin-1β, 6, 18 (IL-1β, 6, 18)

Level of Evidence : 4

INTRODUCTION

For many decades, the comorbidity of foot ulcers in diabetic patients has been held as a predicament for many podiatrists. Diabetic patients are more susceptible (about 12-25% lifetime risk) to develop chronic ulcers on their distal appendages, specifically on their feet, and the treatments are often insufficient.[1] Living with diabetic foot ulcer (DFU) is costly, thus affecting one's quality of life and potentially leading to distal extremity surgeries and amputations.[1]

To understand how to treat a foot ulcer, one must understand the underlying physiological mechanisms of an ulceration. Diabetic neuropathy, ischemia or both are the main contributing factors, and trauma or other forms of mechanical stresses are the secondary contributing factors of DFU.[1]

Diabetes mellitus type II or non-insulin dependent diabetes mellitus (NIDDM) is a result of a two-fold pathological construct where the target tissues (muscles, liver, adipose) become resistant to the effects of insulin and consequently do not allow the uptake of glucose leading to hyperglycemia.[2] As a result of this insulin intolerance, β-cells of pancreas cannot keep up with the demands of the body and their capacity to secrete insulin over time decreases.[2,3] NIDDM also has a large genetic component of which certain genes were seen to be heavily associated with either insulin resistance and the failure of β-cells to produce insulin. Such genes like the obesity genes may be associated with impaired insulin tolerance being that it codes for the expression of factors associated with glucose metabolism by adipose tissue.[4] A genetic component that may influence β-cell malfunction is the TCF7L2 (transcription factor 7-like 2) gene which considered by Florez et.al to be the strongest known genetic risk factor for NIDDM.[5] This failure of the β-cells to compensate in NIDDM patients can be attributed to both inflammatory and immunological factors and these factors possibly can answer why several vital organs become resistance to the effects of diabetes and induce β-cell failure.[3] For NIDDM patients who suffer from the comorbidity of foot ulcers, the contributing immunological and inflammatory factors may perhaps postulate a mechanism that can initiate not only DFUs but also diabetes itself. Several studies have demonstrated possible mediators that suggest a relationship between the higher risk rates of developing foot ulcers in diabetic versus non-diabetic patients. Patients, specifically diagnosed with NIDDM, are statistically shown to have a strong association with an increase in serum concentration of the following cytokines: Interleukin-1β (IL-1β), Interleukin-6 (IL-6) and Interleukin-18 (IL-18).[6,7,8]

Recent studies of cytokines IL-1β, IL-6 and IL-18 have demonstrated that there is a clear association between an increase in their serum concentration and the presence of DFUs in diabetic patients.[6,7,9] These cytokines have been observed to have pro-inflammatory activity, however, their relationships with DFUs are unknown. The most novel of the three is IL-18 (IFN-γ inducing factor), a member of the IL-1 cytokine superfamily along with IL-1β.[6] The study by Esposito et al. was the first to quantify cytokine levels in non-diabetics, demonstrating that diabetic patients without DFUs had a higher serum concentration of IL-18.[7,8] It was shown to be higher in diabetic patients with DFUs by Sabuncu et al.[6] Similarly, cytokine IL-1β

shows pro-inflammatory activity when released by monocytes.[9] IL-1β are known to activate endothelial cells to express ligands and selectins for chemokine secretion and induce fever by acting on the hypothalamus.[10] IL-1β levels, when altered, are seen to be associated with a depressed immune response in NIDDM, which further suggest that any type of disturbance in the immune system can lead to wound infections and hinder the healing process.[11] IL-6 is also a pro-inflammatory cytokine and is an independent risk factor of NIDDM.[6,12] It is well comprehended that IL-6 stimulates differentiation of naïve T-cells into effector cells of cell mediated immunity and like C-reactive protein, it upregulates hepatic synthesis of acute-phase proteins after an infection.[10] This review will analyze the quantification of these cytokines present in human subjects with DFUs. The objective is to further expand our comprehension on how these three pro-inflammatory cytokines play a role in the balance between the pro/anti-inflammatory processes and potentially serve as markers for future treatments.

METHODS

The online database search was performed using PubMed. The Boolean operator "AND" was applied to MeSH terms "Interleukin" AND "Diabetic Foot Ulcer". The search yielded 42 articles and all abstracts were examined for inclusion and exclusion criteria. Inclusion criteria were: diabetic foot infection, IL-1, IL-6, IL-18. Exclusion criteria were: IL-8, osteoarthropathy (acute Charcot foot), and non-human subjects.

RESULTS

The search yielded 42 articles, and 5 of those articles from 2005–2014 satisfied the criteria and were selected for a qualitative review.

Sabuncu et al. measured the biochemical levels in healthy patients and diabetic patients both with and without foot ulcers.[6] There were 21 patients in the control group, 20 patients in diabetics with foot ulcers group and 21 patients in diabetics without foot ulcers group. IL-18 levels were analyzed in all groups after a 12-hour fast with an enzyme-linked immunosorbent assay kit (ELISA). The results showed that within the experimental groups, IL-18 levels were significantly higher in diabetic patients with foot ulcers (498.12 pg/mL) in contrast to diabetic patients without foot ulcers (421.06 pg/mL). Moreover, diabetic patients without foot ulcers showed higher levels of IL-18 as compared to the control group (379.73 pg/mL). In addition to IL-18, the diabetics with foot ulcers group showed highest level of high-sensitivity C-reactive protein (hsCRP) and erythrocyte sedimentation rate (ESR).

Oncul et al. examined phagocytic activity index (PAI), and intracellular killing activity (IKA) of polymorphonuclear leukocytes (PMNL) and IL-1β levels.[9] PMNLs, in addition to monocytes, contribute significantly to the inflammation, releasing cytokines and carrying out phagocytosis (measured via PAI). Moreover, IKA of PMNL can also expect to increase during inflammation. Therefore, in theory, PAI and IKA can be reduced or be impaired during DFUs. The experiment initially divided 28 healthy patients (control group) from 38 diabetic patients with foot ulcers. After some recovery, the diabetic patients with foot ulcers

were retrospectively categorized into healing group (HG) and non-healing group (NHG) based upon the recovery. Overall, there were 28 patients in the control group, 23 patients in the healing group and 15 patients in the non-healing group. The mean IL-1β level was higher in diabetic groups (4.5 pg/mL ± 4.5), including HG and NHG compare to the control group (2.8 pg/mL ± 3.8). Within the diabetic patients, HG showed highest level (8.02 pg/mL ± 3.08) of IL-1β before the treatment. Two week after the treatment, level decreased to 2.67 pg/mL ± 1.21 and remained constant until the fourth week. NHG also showed high level (5.96 pg/mL ± 2.98) of IL-1β before the treatment, but increased to 6.46 pg/mL ± 3.56 and 6.96 pg/mL ± 3.47 in the second and fourth weeks, respectively, after the treatment.

Kheiralla et al. measured IL-1β level in addition to complement C3 levels.[11] There were three groups: group I consisted of 20 diabetic patients without foot ulcers and without other complications such as hypertension, ischemic heart disease, peripheral vascular disease, cerebrovascular, neuropathy and diabetic retinopathy. Group II consisted of 50 diabetic patients with foot ulcers and some above-mentioned complications and group III or the control group consisted of 10 healthy patients. Kheiralla et al. used Assay Max Human complement C3 and IL-1β ELISA Kits to measure complement C3 and IL-1β in sera, respectively. Group II had significantly older patients (57.48 years) compared to group I (46.2 years) and had longer disease duration. Group II contained 68% males, and few had complications: 72% hypertension, 42% ischemic heart disease, 14% peripheral vascular disease and 10% neuropathy. Results showed significantly higher concentrations of complement C3 in group II (18.48 ng/mL ± 8.64) as compared to group I (13.49 ng/mL ± 8.04) and group III (12.63 ng/mL ±7.12). In addition, a much higher concentration of IL-1β (10.68 pg/mL ± 6.59) was measured in group II as compared to group I (7.16pg/mL ± 4.4) and group III (6.2 pg/mL ± 4.59).

Zubair et al. measured the level of plasma IL-6 and plasma hsCRP by immunoenzymatic enzyme linked immmunosorbent assay method.[12] Study consisted of two groups: group A with 162 diabetic patients with foot ulcers and group B with 162 diabetic patients without foot ulcers. Results showed that group A had significantly higher levels of plasma IL-6 (32.5 ng/mL) and plasma hsCRP (12.6 mg/mL) as compared to group B 6.7 ng/mL and 8.4 mg/mL for plasma IL-6 and plasma hsCRP, respectively.

Karakas et al. studied 27 patients with DFUs and 6 out of 27 patients eventually had

	Diabetic with foot ulcers* (n=20)	Diabetic with foot ulcers (n=21)	Non-diabetic without foot ulcers (n=21)
IL-18 (pg/mL)	498.12	421.06	379.73

Figure 1: Sabuncu et al.
*Highest level of hsCRP and ESR in diabetic with foot ulcers

amputations.[13] Therefore, Karakas et al. compared the levels of C-reactive protein and serum IL-6 between 21 diabetic ulcer patients and 6 diabetic ulcer patients with amputations. Patients with amputations showed higher levels of serum IL-6 (20.8 pg/mL) compared to patients without amputations (i.e. 9.7 pg/mL). C-reactive protein levels were 25.6 mg/L for the patients without amputations and 23.8mg/dL for the patients with amputations.

DISCUSSION

The study conducted by Sabuncu et al. showed that there is a direct correlation between IL-18 and DFUs.[6] Moreover, mean serum concentration of IL-18 in patients with DFUs (498.12 pg/ml ± 62.06) was much higher than in patients with diabetes without ulcers (421.06 pg/ml ± 41.28) and in healthy control groups (379.73 pg/ml ± 30.46). Sabuncu et al. argued that IL-18, one of the

	Diabetic: Healing group (n=23)	Diabetic: Non-Healing group (n=15)	Non-Diabetic with Foot Ulcers (n=28)
IL-1β (pg/mL) Before Treatment	8.02	5.96	Mean = 2.8
IL-1β (pg/mL) 2 Weeks After Treatment	2.67	6.46	Mean = 2.8
IL-1β (pg/mL) 4 Weeks After Treatment	2.95	6.96	Mean = 2.8

Figure 2: Oncul et al.

	Diabetic Without Foot Ulcers (n=20)	Diabetic with Foot Ulcers (n=50)	Non-Diabetic Without Foot Ulcers (n=10)
IL-1β (pg/mL)	7.16	10.68	6.2

Figure 3: Kheiralla et al.

	Diabetic with Foot Ulcers* (n=162)	Diabetic Without Foot Ulcers (n=162)
Plasma IL-6 (ng/mL)	32.5	6.2

Figure 4: Zubair et al.
* Higher level of sCRP (12.6 mg/dL)

	DFU with Amputation (n=6)	DFU Without Amputation (n=21)
Serum IL-6 (pg/mL)	20.8	9.7

Figure 5: Karakas et al.

pro-inflammatory cytokines, is involved in the recruitment of immune cells to the site of wound repair by signal amplification and stimulating release of monocytes and neutrophil chemoattractant proteins.[6] In addition, increased levels of IL-18 are associated with surgical wounds and sepsis in general. Reddy supports this statement by suggesting that IL-18 increases in number in septic patients and is instrumental in eliciting adaptive immune response.[14] It should be noted that DFUs can potentially lead to sepsis.

In another study, the mean concentration of IL-1β, which is a member of IL-1 family, was observed to be higher in diabetic patients (4.5 pg/mL ± 4.5) than in the control group (2.8 pg/mL ± 3.8).[9] The highest concentrations were seen in patients with healing diabetic foot infections (8.02 pg/mL ± 3.08) prior to treatment, and then reduced in the second week (2.67 pg/mL ± 1.21). On the other hand, the mean concentration of IL-1β in the non-healing group was high (5.96 pg/mL ± 2.98) prior to treatment, and then increased in the second week (6.46 pg/mL ± 3.56). These results suggest that there is an increased expression of IL-1 family proteins during wound healing process. Inflammatory stimuli trigger the release of early response cytokines such as IL-1 from local macrophages and mast cells. Furthermore, Kheiralla et al. suggest that increased levels of IL-1β might be associated with weakened immune response, which slows the wound healing process and leads to repeated infections.[11] Repeated infections contribute to the development of recurrent foot ulcers. The study of Kheiralla et al. demonstrated that out of 60% diabetic patients with foot infections who had abnormal levels of IL-1β, 12% had reduced levels, while 48% had increased levels. The decreased IL-1 levels are linked to reduced cytokine release by macrophages and impaired function of neutrophils. Thus, the decreased levels of IL-1β contribute to the immunosuppression of the diabetic patients.

The results of another study performed by Zubair et al. showed that IL-6 could contribute to the development of DFUs.[12] The mean plasma concentration of IL-6 was 32.5 ng/ml in patients with DFUs and 6.7 ng/ml in diabetic patients without the foot ulcers. These results indicate that inflammatory markers such as cytokines play a crucial role in the vascular and foot complications associated with diabetes. About one-quarter of systemically circulating IL-6 is derived from subcutaneous adipose tissue and may modify adipocyte glucose and lipid metabolism. Karakas et al. conducted a similar study evaluating the effects of IL-6 on lower extremity amputations in patients with DFUs.[13] The mean plasma concentrations of IL-6 in DFUs with and without amputations were 20.8 pg/ml and 9.7 pg/ml, respectively. Analysis of the correlation yielded an important correlation between the IL-6 concentration and the erythrocyte sedimentation rate (ESR) ($r=0.497$, $p=0.008$).

The severity of infection can be assessed by analyzing the levels of inflammatory markers such as ESR and C-reactive protein.[1] A significant increase in ESR (>70 mm/h) is indicative of bone infection, but there is low sensitivity associated with this finding.

CONCLUSION

Increased levels of IL-1β, IL-6 and IL-18 are associated with DFUs. IL-18 is involved in the proliferation and delivery of immune cells via cell signaling to the site of wound repair. Thus, the regulation of IL-18 release in a timely manner is important in hastening the wound healing process. IL-1β contributes to the weakening of the immune system, which in turn delays the healing of the wound and causes repeated foot infections. IL-1β is also linked to dysregulation and impairment of polymorphonuclear leukocytes such as neutrophils. Therefore, IL-1β is considered as one of the contributing factors causing recurrent DFUs. Finally, IL-6 was found to be an important independent risk determinant contributing to vascular and foot complications in diabetic patients. Thus, the above-mentioned interleukins may be regarded as contributing factors linked to the development of DFUs. Since both pro- and anti-inflammatory processes are important in different stages of the wound healing process, the dysregulation of the immune system, in terms of cytokine release, can lead to the development of chronic, nonhealing wounds such as those seen in DFUs. Therefore, more research is needed to determine the effect of inhibition of certain interleukins at particular stages of wound healing process. Moreover, further research should focus on exactly how IL-1β depresses the immune system and which particular cells of the innate and adaptive immune system it downregulates.

AUTHOR'S CONTRIBUTIONS

Three authors contributed equally to the production of this article. All conceived the topic, performed initial literature reviews, evaluated abstracts, authored introduction, results, discussion and conclusions. All authors drafted, read, reviewed and agreed upon the final manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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A Qualitative Review of the Efficacy of Plant-Based Topical Antifungals for the Treatment of Tinea Pedis

Rebecca Herman, BA, Erin Kunz, BS, and Yu Ting Saw, BS

Abstract

Introduction
Conventional topical antifungal treatments for tinea pedis may pose a risk for drug-drug interactions and infection reoccurrence. Some plant-based topical antifungals can provide safer, less expensive and more effective treatment. A review of the current available literature was performed to explore the safety and efficacy of plant-based alternatives: oil of bitter orange, tea tree oil, ozonized sunflower oil, Solanum chrysotrichum, traditional Chinese herbal extracts, and ajoene extracts.

Study Design
Qualitative Systematic Review.

Methods
Literature searches were conducted using the Cochrane and Pubmed databases. Exclusion criteria eliminated articles with fungal infections that were not tinea pedis, or articles that only studied the treatment of traditional or currently prescribed oral and topical antifungals. Articles that were non-English or published prior to 1990 were also excluded. Alternative treatments that were not plant-based were excluded from review. Inclusion criteria consisted of: tinea pedis infections, herbal remedies, natural or plant derived treatments, and alternative treatments.

Results
Seven articles were found using the Cochrane and Pubmed Database searches that met the inclusion and exclusion criteria.

Conclusion
The plant-based therapies for tinea pedis all show varying degrees of benefit and could be presented to patients as alternatives to the classically prescribed terbinafine, miconazole nitrate, tolnaftate, and ketaconazole. Tea tree oil was proven to contain anti-mycologic properties by reducing tinea pedis symptomatology, although tolnaftate provided a significantly more effective mycological cure. Bitter Orange oil produced mycological cure in a shorter period of time compared to imidazole, but with mild side effects. Patients who used Ozonized sunflower oil were not observed to have reoccurrence of mycologic infection, as they did when utilizing ketaconazole. Treatment with *Solanum chrysotrichum* produced a higher rate of complete cure compared to treatment with a miconazole nitrate cream. When the efficacy of garlic extracts was compared to terbinafine, participants in both groups were found to be mycologically cured. Lastly, in a Chinese herbal extract study, three of the most potent antifungal herbal extracts, Fructus psoraleae, Rhizoma curcumae longae, and Folium eucalypti globuli were combined and compared to terbinafine. There was a statistically significant decrease in fungal load with the herbal extract treatment.

Key Words: Tinea pedis, Athlete's Foot, Oil of Bitter Orange, Tea Tree Oil, Ozonized Sunflower Oil, Ajoene, Solanum chrystotrichum, Chinese Herbs

Level of Evidence: 4

INTRODUCTION

Tinea pedis, or athlete's foot, is the most common superficial fungal dermatophyte infection seen on the foot in developed countries.[1] At any time, tinea pedis affects approximately 10% of the population.[2] Its appearance is characterized by skin reactions such as redness, scaling, edema, and itchiness on the surface of the foot.[3] Organisms causing the contagious infection are classified as the dermatophytes (Trichophyton rubrum, Epidermophyton floccosum, and Microsporum canis).[3]

Topical antifungal agents commonly prescribed to treat tinea pedis are terbinafine[4,5], miconazole nitrate[6], imidazole[7], tolnaftate[8] and ketaconazole.[3] However, these topical antifungal medicines do not always produce a complete mycological cure even when the patients are compliant.[3] Patients with tinea pedis often suffer relapses, which may in turn cause them to suffer repeated side effects each time they are treated with these medications.[3] Consequently, patients may become frustrated with traditional therapies and choose to seek alternative treatment options.[9]

Patients most at risk for fungal infections are diabetics as well as those individuals that wear form fitting boots for long periods of time (e.g. combat soldiers, law enforcement officers, etc).[3] Additionally, African Americans have a higher genetic predisposition for tinea pedis infections.[3] The combination of drugs taken for other diseases as well as antifungal medications can potentially cause serious adverse effects due to drug-drug interactions or lead to other negative consequences for the patients such as allergic reactions.[1] The increase in the aging population in developed countries needing medications, as well as the abundance of medications available to treat chronic diseases, has led to the need to find effective alternative treatments to manage tinea pedis.

This review seeks to compare the quality, efficacy, and safety of alternative plant-based medicines to conventional topical antifungal agents. These plant-based treatments are oil of bitter orange[7], tea tree oil[2,8], ozonized sunflower oil[3], S. *chrysotrichum*[6], traditional Chinese herbal extracts[4], and ajoene extracts.[5] Each study shows that some plant-based medicine not only helps reduce symptoms of the infection, but also may surpass the conventional treatment in successfully treating tinea pedis infections. Additionally, they provide a low-cost alternative to the topical antifungal treatments.[3]

The effectiveness of the plant extract for the treatment of tinea pedis infections is based upon clinical improvement, mycological cure, completeness of cure, and the time to achieve these cures. A mycological cure is defined as achieving a culture negative for fungi causing the tinea pedis. Clinical improvement is observable reduction in symptomatology (red, dry, itchy, burning skin). A complete cure is a mycological cure with a clinical cure. Time of treatment is often measured in weeks.

METHODS

Three searches of the primary literature were conducted using the Cochrane database. All searches used the Boolean operator "and."

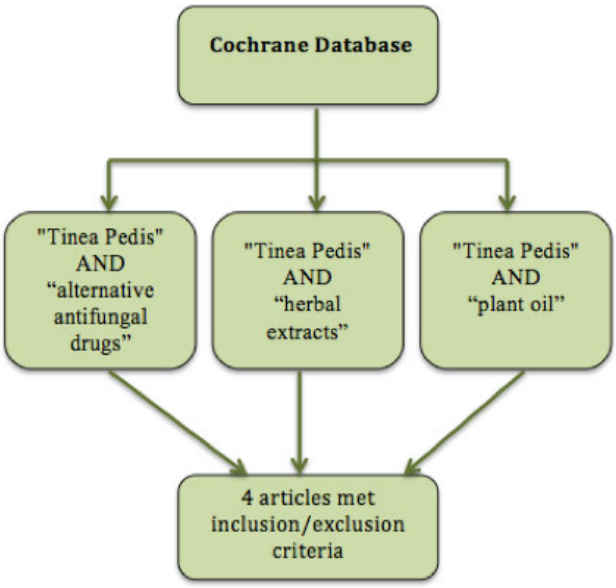

Figure 1: Summary of search results from Cochrane Database

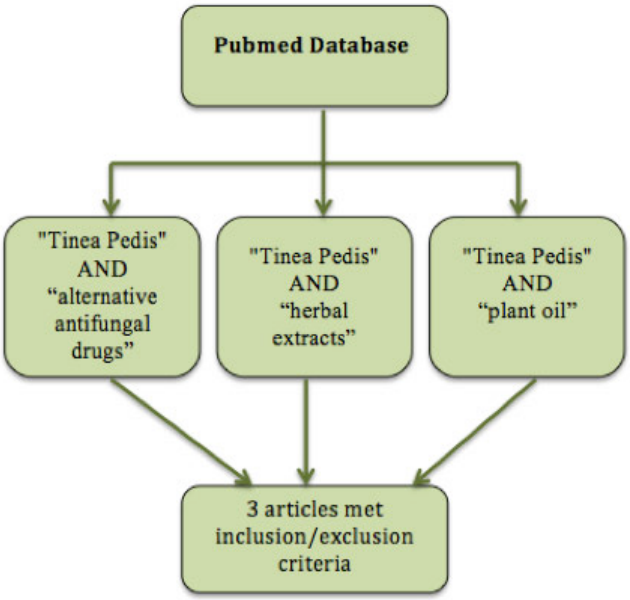

Figure 2: Summary of results from Pubmed Database

The first search was for "tinea pedis" AND "alternative treatment." This search yielded 6 articles. Only 1 article fit the inclusion/ exclusion criteria. The second search used the terms "tinea pedis" AND "plant oil". This search yielded 5 results, 3 of which fit the inclusion and exclusion criteria. A third search, which used the terms "Tinea Pedis" AND "herbal extracts," resulted in one article, which did not fit the review criteria. In total, the Cochrane database presented with 12 articles from the 3 searches, of which 4 fit the inclusion/exclusion criteria. See figure 1 for a summary of the searches conducted with the Cochrane Database.

Three searches of primary literature were executed using the PubMed database. All searches used the Boolean operator "and." The first search was "Alternative antifungal drugs" AND "tinea pedis." This search yielded 18 articles; of which only 1 fit the inclusion/exclusion criteria. The second search was "tinea pedis" AND "Herbal Extracts". The search yielded 5 articles; of which only 1 fit the inclusion/exclusion criteria. The third search employed the terms "tinea pedis" AND "Plant Oil". The search yielded 5 articles; of which 1 fit the inclusion/ exclusion criteria. In total, 28 articles were found using the PubMed database, of which 3 fit the inclusion/exclusion criteria. See figure 2 for a summary of the searches through the PubMed Database.

Exclusion criteria consisted of articles with fungal infections that were not Tinea pedis, or articles that only studied the treatment of traditional or currently prescribed oral and topical antifungals. Articles must have compared a plant-based treatment to a currently prescribed topical antifungal. Articles that focused on non-plant based treatments, written in languages other than English, or were published prior to 1990 were excluded from the review. Inclusion criteria consisted of: Tinea pedis infections, herbal remedies, natural or plant derived treatments,

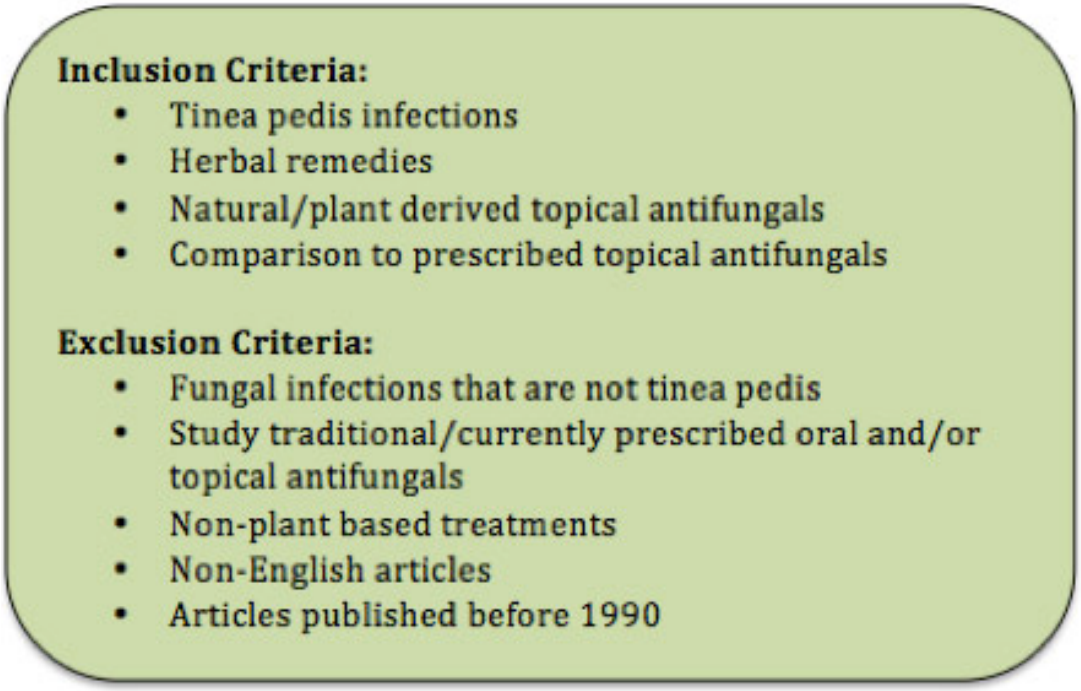

Figure 3: Summary of inclusion and exclusion criteria

alternative treatments, and the term "Tinea Pedis." See figure 3 for a summary of the inclusion and exclusion criteria.

RESULTS

The total number of articles found using both the PubMed and Cochrane Databases was 56 articles. After evaluating the papers for proper inclusionary and exclusionary properties, approximately 14% met criteria, resulting in 7 articles that were chosen from both the Cochrane and PubMed databases.

TREATMENTS

I. Oil of bitter Orange[7]

Background: Oil of bitter orange is obtained from the peel of bitter orange, *Citrus aurantium*. It contains d-limonene, citral, decylaldehyde, methyl anthranilate, linalool, and terpineol.[7]

Methods: Ramadan et al. performed an in vivo study of 60 patients with tinea pedis. The 60 patients were divided into 3 groups, each treated with varying concentrations/solutions of a topical oil of bitter orange (OBO). The treatments were: 25% emulsion of OBO, 20% OBO in alcohol, and pure OBO.[7] The oil of bitter orange was compared to previously acquired data on the topical antifungal imidazole. Clinical cure was defined as having no more signs or symptoms. Mycological cure was defined has having no "fungal elements" on microscopy and in culture.[7]

Results: Results show that with a 25% emulsion of OBO, all patients (100%) achieved mycological cure with 80% achieving the cure within 1-2 weeks. The second group treated with a 20% OBO in alcohol showed 50% of the group achieving mycological cure within 1-2 week, 30% within 3-4, and 20% within 5-6 week. The 3rd group was treated with pure OBO. Some experienced skin irritation with that OBO concentration. 25% of that group dropped out of the study, 60% achieved mycological cure within 1-2 weeks, and 7% in weeks 2-3. The oil of bitter orange was compared to the topical antifungal imidazole. 80% of the imidazole group achieved mycological cure after 4 weeks of treatment.[7] See Figure 4 for a summary of results.

	25% emulsion OBO	20% OBO in alcohol	Imidazole
1-2 weeks	80%	50%	N/A
3-4 weeks	N/A	30%	N/A
5-6 weeks	N/A	20%	80% (after 4 weeks)

Figure 4: Summary of results from Ramadan study on oil of bitter orange[7]

Limitations: Topical application of the treatment medications varied considerably in times per day between the treatment groups. The length of treatments in days however was the same. This was done to reflect the concentration or solution of the antifungal given. There was too much variation between each group. An additional study should be performed to compare the different concentrations of OBO that would be the most effective. The authors also never explained their inclusion/exclusion criteria for patient selection, nor their reasoning for comparing the OBO to imidazole. A blinded, randomized study would be best for comparing treatments.[7]

II. Tea Tree Oil (Melaleucae alternifolia)[11,2,8,10]

Background: Tea tree oil comes from the Australian plant *Melaleucae alternifolia.*[8] Tea tree oil contains over 60 terpenoids that interact with biomembrane and membrane proteins, suggesting antibacterial and antifungal properties.[10] It is a common ingredient in lotions and creams.[2] There is a lack of randomized clinical trials exploring the medical benefits of tea tree oil for tinea pedis. Two studies are reviewed – one comparing tea tree oil cream to a topical tolnaftate and a sorbolene cream placebo (Study 1),[8] the other comparing different concentrations of tea tree oil with a sorbolene cream placebo (Study 2).[2]

Study 1: Tong and colleagues compared the efficacy of a 10% tea tree oil cream to 1% tolnaftate and a sorbolene cream placebo by conducting a randomized, double-blind trial in Sydney. The trial consisted of 104 people (79 males, 25 females, ages 19-65) placed randomly into one of the three treatment groups. Creams were applied twice a day for 4 weeks, with cream applied after washing and drying feet. Patients were excluded if they had a negative mycology culture or had been taking any systemic antifungals. Efficacy was based on the combination of

signs and symptoms and on re-culture. Signs and symptoms (clinical efficacy) were scored on a scale of 0 to 4 (0 being absent and 4 being the most severe) to qualify scaling, inflammation, itching and burning of the skin. Efficacy of treatment was based on the combination of clinical and mycological responses which were classified as follows: 1) mycological cure (negative culture) and improvement in symptoms; 2) mycological cure and no improvement in symptoms; 3) no mycological cure and improvement in symptoms; and 4) no mycological cure and no improvement of symptoms. An effective treatment or "complete cure" was defined as mycological cure with clinical improvement.[8]

Results: No patients were lost to followup. One patient in the tolnaftate group experienced erythema of the skin. Duration of infection in the tolnaftate group was about 4 weeks longer than in the tea tree oil and placebo groups. Tong and colleagues found that tolnaftate was significantly more effective at producing a mycological cure than both the placebo group and tea tree oil group. No statistical significance was found between the placebo group and tea tree oil group for mycological cure. Clinical efficacy was statistically higher in both the tolnaftate and tea tree oil groups compared to the placebo group. The proportion of patients that showed a "complete cure" in the tolnaftate group was not significantly higher than that of patients in the tea tree oil group, but it was significantly higher than that of the placebo group. The difference between tea tree oil and placebo groups was not statistically significant.[8] See Figure 5 for a summary of results.

Study 2: Satchell et al. based their assumptions and experimental design on the Tong et al. study. Satchell and colleague conducted a randomized, controlled, double-blinded study in Sydney to determine the efficacy and safety of 25% and 50% tea tree oil in the treatment of interdigital tinea pedis. One hundred and fifty-eight patients with tinea pedis were randomly placed into one of three groups - treatment with 25% tea tree oil, 50% tea tree oil, or with a sorbolene cream placebo treatment. Patients applied the solution twice daily to affected areas for 4 weeks.[2]

Results: A reduced symptomatology (red, scaly, itchy skin) was seen in 68% of the patients treated with 50% tea tree oil, and in 72% of the patients treated with 25% tea tree oil. Of the placebo group, 39% of the patients showed reduced symptoms. Mycological cure was assessed by culture of skin scrapings after 4 weeks of treatment. The mycological cure rate was 64% in the 50% tea tree oil group, 55% in the 25% tea tree oil group, and 31% in the placebo group. Four (3.8%) patients applying tea tree oil experienced mild to severe dermatitis. The skin reaction improved when the medication was discontinued.[2] See Figure 5 for a summary of results.

Discussion: The Tong et al. study shows that tea tree oil, in combination with washing feet, could be an effective complementary treatment to the more commonly used topical antifungals or possibly even systemic antifungals. Tolnaftate treatment was most effective at achieving a mycological cure, but tea tree oil treatment showed a similar effect on symptoms like itchy, inflamed, scaly, burning skin as tolnaftate treatment. 21% of those in the placebo group attained mycological cure, suggesting washing and practicing good hygiene can play a part in

	10% TTO	25% TTO	50% TTO	Tolnaftate	Sorbolene
Mycological Cure	30%[11]	55%[10]	64%[10]	85%[11]	31%[10] 21%[11]

Figure 5: Summary of results from Tong[8] and Satchell[2] studies on Tea Tree Oil (TTO)

attaining a cure. Tong et al. explains that tea tree oil is difficult to use in a cream form, and obtaining a higher concentration of the oil is needed to see more effects.[8] Satchell and colleagues' study answers the question – exploring the safety of tea tree oil solutions with higher concentrations, and did support that dermatitis can result with use.[2]

Limitations: Tong and colleagues' study was performed in 1992, and is therefore potentially outdated. Tolnaftate is a common over-the-counter topical treatment for tinea pedis in Australia, but is considered more effective for infections such as tinea corporis.[10] A new study should be conducted to compare tea tree oil with more modern topical treatments for tinea pedis. Ernst and Huntley point out that Tong and colleagues never explain their blinding protocol. The smell of tea tree oil, which is found in many lotions and cosmetic, should be mimicked in the two other creams tested to ensure blinding. They also suggest the study should be conducted over a longer period of time to see more effects of tea tree oil.[11] Tong and colleagues found that washing feet also aided in the treatment of tinea pedis.[8] A study should be conducted to observe the effects of good hygiene for tinea pedis infections.

III. Ozonized sunflower oil[3]

Background: Ozonized sunflower oil or Oleozon is the product of a reaction between ozone and sunflower oil. Oleozon, composed of aldehydes and carboxylic acids with hydroperoxides contains antimicrobial and antifungal properties.[3] A clinical study comparing the use of Oleozon to ketaconazole, a topical antifungal cream, to treat tinea pedis was conducted.[3]

Study: Menendez et al. conducted a controlled randomized phase III assay study comparing Oleozon to ketoconazole. 200 patients (87% male, 62% white) were recruited and split into 2 groups of 100 patients each. The trial took care to split the experimental and control group evenly by race, longevity of disease, and age. Care was taken to ensure that patients of African descent, who have an increased predisposition to fungal infections, were equally represented in both groups. Most of the participants were young male soldiers. The experimental group patients were instructed to apply topical Oleozon twice a day for 6 weeks. The control group patients were instructed to apply 2% ketoconazole cream, twice daily for 6 weeks. Patient exclusion criteria included advanced stage cancer, decompensated diabetes mellitus, severe septic state, hepatopathy, nephropathy, pregnancy, any hypersensitivity to the medications, or utilization of any corticoids, cytostatics, antibiotics, or immunosuppressive drugs. Efficacy was determined based on cure of symptoms (clinical efficacy) and mycological cultures. Clinical cure was determined based on the eradication of the physical appearance of lesions and checked weekly. Mycological cure was based on negative mycological cultures and checked at the end of the six-

	At end of Study	At end of Study	6 months post study
	Complete Cure	Not Cured	Recurrence Rate
2% Ketoconazole	81%	19%	4%
Oleozon	75%	25%	0%

Figure 6: Summary of Menedez et al. study on efficacy of Oleozon in treating tinea pedis.[3]

week study. In order for a patient to have complete cure, both criteria had to be met upon completion of the treatment. The fungi investigated in the study were *Trichophyton rubrum* (59%), *Trichophyton mentagophytes* (10%), *Epidermophyton floccosum* (8%), and *Candida albicans* (14%).[3]

Results: No adverse effects or infections were reported in the study. No patients were lost to follow-up. There were no statistically significant differences between the two treatment options, Oleozon and ketoconazole, in curing the 4 fungal species tested. The study determined that both Oleozon and ketoconazole are effective treatments for tinea pedis. Patients treated with Oleozon obtained a negative mycological culture 6 months post treatment. However, patients treated with ketoconazole experienced a 4% recurrence.[3] See Figure 6 for summary of results.

Discussion: The study showed that Oleozon could be an effective low cost alternative medication to treat tinea pedis. The lack of reoccurrence for patients treated with Oleozon after long-term follow up is very promising compared to ketoconazole.[3]

Limitation: Most of the participants were young male soldiers (mean age 28 years) who are required to wear boots. Additionally, the study was single blind. A new study should be carried out as a randomized double blind study with participants engaged in a diverse range of foot activities along with different shoes.[3]

IV. Solanum chrysotrichum (Schldl.)[6]

Background: *Solanum chrysotrichum* is within a category of several species known as 'sosa. In tropical climates such as Mexico, the plant is commonly used to treat various skin infections. The particular species, *Solanum chrysotrichum* (Schldl.) has been found to be particularly effective for treatment of tinea pedis. The study included two components, an ethnobotanical and a clinical study. The ethnobotanical study was conducted in Chiapas, Mexico, a rural town, in which local health professionals collected information from patients using the sosa plants including the diseases, frequency, method of administration, side effects, as well as the type of sosa used. This confirmed the identity of the plants. The clinical trial located in Morelos, Mexico, carried out the study on a group of selected participants.[6]

Methods: Lozoya et al. performed a double-blinded clinical study of 28 participants diagnosed with tinea pedis at the IMSS General Hospital No. 1 in Cuernavaca City, in Morelos, Mexico. One group of 14 people applied 2% miconazole nitrate cream as a control, whereas the experimental group of 14 applied 5% of the methanolic extract of S. *chrysotrichum* Schldl. leaves. Participants

were evaluated on a weekly basis by health professionals at the hospital.[6]

Results: The plants were taken from Chiapas, Mexico, to the New York Botanical Gardens for confirmatory identification. *Solanum chrysotrichum* Schldl. was verified as the most common sosa used. Additionally, the plants were found to be particularly effective in curing tinea pedis. Within the control miconazole nitrate treatment group, after 4 weeks, some signs and symptoms disappeared, but 0% of patients treated with miconazole nitrate were cured. The experimental group treated with *S. chrysotrichum* Schldl. had a 42.8% complete cure rate, and the remainder 57.2% experienced considerable improvement in symptoms.[6] Refer to Figure 7 for a summary of results.

Limitations: The study was conducted in 1991 comparing the plant extract to 2% miconazole nitrate cream. It should be conducted again comparing the plant extract to a more updated common fungal medication. Additionally, the 2% miconazole nitrate cream was used to test efficacy against 5% methanolic extract of S. *chrysotrichum* Schldl.[6] A study should be conducted that compares various concentrations of S. *chrysotrichum* to various concentrations of the miconazole cream.

V. Chinese herbal extracts[4]

Background: Based on 83 Traditional Chinese Medicines (TCM), and herbal species with antifungal activity in the Pharmacopoeia, 11 were previously found to be efficacious against the *Trichophyton* strains: Bulbus allii, Fructus galangae, Semen cassiae, Herba cichorii, Rhizoma curcumae longae, Semen juglandis, Herba portulacae, Cortex pseudolaricis, Fructus psoraleae, Fructus chebulae, and Folium eucalypti globuli.[4]

Study: A prospective epidemiological study was conducted in Hong Kong from December 2006 to December 2008. Of the 11 TCM species with antifungal activity, aqueous and ethanol extracts were made. *In vitro* antifungal tests were used to evaluate the efficacies of the antifungal species by measuring the minimum inhibitory concentration (MIC). Based on the measured MICs, the most potent antifungal species were identified. To measure the efficacy of these herbal extracts *in vivo,* experimental guinea pigs were used and given tinea pedis for seven consecutive days. On the seventh day, guinea pigs in the control group received aqueous cream to treat tinea pedis, whereas the three separate experimental groups received individual topical application of FP, RCL, and FEG. The experiment was then extended by comparing the same control group with 2 other experimental groups: one which was treated with terbinafine (Lamisil), and another which used a 1:1:1 combination topical cream of the most potent antifungal species.

Results: Among the 11 TCM herbal extracts known to have anti-Trichophyton properties, three agents, Fructus psoraleae (FP), Rhizoma curcumae longae (RCL), and Folium eucalypti globuli (FEG), were demonstrated *in vitro* to be the most potent. Although these herbal species did not seem efficacious when applied individually, when used in combination as a herbal formula cream with equal parts of each herbal species (1:1:1), synergism was observed, refer to Figure 8. There was a significant decrease ($P<0.01$) in

	Complete Cure	Recurrence Rate
2% miconazole nitrate	0%	100%
5% methanolic extract	42.8%	57.2%

Figure 7: Summary of Lozoya et al. study of efficacy of *S. Chryostrichum* Schldl. in treating tinea pedis.[6]

Treatment	Fungal Burden
Herbal Combination	0*
Terbinafine Cream	2.5 ±1.8*
Aqueous Cream (Control Group)	8.0 ± 2.9

Figure 8: Fungal burden measured on guinea pigs with tinea pedis after the application of herbal combination of Fructus psoraieae, Rhizoma curcumae longae and Folium eucalypti globuli (1:1:1), terbinafine Cream, and Aqueous Cream (control group)[4]
*P<0.01 compared to Control Group

fungal burden, or amount of fungus found at the sites of application, with treatment of the herbal combination compared to the control group that received aqueous cream. However, the herbal combination was much less potent than terbinafine.[4]

Discussion: Among the 11 TCM species with antifungal activity, FP, RCL, FEG were found to be the most potent at inhibiting growth of dermatophytes *in vitro*. When the herbal extracts were made into a topical herbal formula (1:1:1) and applied to the guinea pig model, its significant reduction in amount of fungus found at the site of application proved promising when compared to the aqueous cream, but paled in comparison to terbinafine (Lamisil). The inability to measure up to terbinafine's effectiveness may have been due to the herbal formula's lack of epidermal penetration, rendering the herbal cream with only superficial dermatophyte-killing abilities. In conclusion, the combination cream could be used as an alternative on patients who may have developed a resistance to terbinafine (Lamisil).[4]

Limitations: Safety issues of the herbal formula have also never been addressed previously, hence they may pose possible concerns for allergic or hypersensitivity reactions. Furthermore, FP has shown to be associated with liver injury, and could be the basis of further investigation.[4]

VI. Ajoene[5]

Background: Ajoene, an organosulfur compound from garlic extracts, has been previously demonstrated, both *in vitro* and *in vivo*, to have anti-mycotic properties. Furthermore, a previous study demonstrated 79% effectiveness in short-term treatment of

	0.6% Ajoene	1.0% Ajoene	1.0% Terbinafine
30 Days	60%	100%	88%
60 Days	72%	100%	95%

Figure 9: Percentage of mycologic cure at 30 and 60 days follow-up of treatment groups receiving 0.6% Ajoene, 1.0% Ajoene, and 1.0% terbinafine[5]

tinea pedis, while showing high tolerability by patients.[5]

Study: A double-blind comparative study was conducted between Ajoene and terbinafine in treating tinea pedis. Seventy soldiers with mycologic diagnosis of tinea pedis interdigitalis were randomly distributed into three treatment groups: 0.6% ajoene, 1% ajoene, or 1% terbinafine. They were examined the day they began the study, then at 30 days, and then at 60 days, where pruritus, erythema, desquamation, fissure, vesiculation, and maceration were all evaluated. They were then quantifiably measured on a scale of 0 = absent, 1 = light, 2 = moderate, 3 = intense. The patients' skin scrapings were then cultured in 20% KOH. If their signs and symptoms were mycologically cured and exhibited symptoms of less than or equal to 2, they were considered to be "effectively treated", whereas if upon examination and mycologic cultures, were both negative, they were considered mycologically cured.[5]

Results: At thirty days, 60% of patients in the 0.6% ajoene group, 100% of patients in the 1% ajoene group, and 88% of patients in the 1% terbinafine group had achieved mycologic cure, refer to Figure 9. Sixty days after ending the treatment, 72%, 100%, and 95% of patients from the same respective groups were found to also be mycologically cured, refer to Figure 9. No statistically significant effects were observed during the study.[5]

Discussion: This study shows that both forms of treatment are equally effective when used topically. Because many agents used topically must be used for a longer period of time, ajoene can currently be considered preliminarily, a potent fungicidal agent.[5]

Limitations: A limitation of this study is the high number of withdrawals. Of the seventy soldiers who were enrolled in the study, 23 were unable to complete follow up due to relocation, returning to civilian life, or the inability to follow through during the study period. This largely diminished the sample size, and may affect the validity of the results. Terbinafine has only been used in short-term treatment of tinea pedis, therefore ajoene could also be used in experimentation in the short-term. Further studies are needed to determine its efficacy in the long-term treatment of tinea pedis.[5]

CONCLUSION

Limitations: Many of the studies reviewed were published between 1990 and 2000. More updated randomized controlled trials studying the effectiveness of plant extracts and studies comparing the efficacy of plant extracts to more modern topical antifungals could provide additional insight into the best current treatment for tinea pedis. With more advances in medical treatment and the introduction of new antifungal agents, plant extracts can provide fewer drug-drug interactions. This is especially important in elderly patients, the immunocompromised patient, and the diabetic patient,with whom drug-drug interactions are a risk. Studies should be conducted observing these agents over longer periods of time and at differing concentrations to see if there are any more adverse effects. Mistrust in plant-based treatments, and the lack of FDA approval, can hinder the study and development of such treatments. More studies can help overcome this.

Furthermore, all the articles reviewed used different criteria to measure efficacy in the treatment of tinea pedis, making it challenging to compare how efficacious each one may be against the classically prescribed anti-mycologic treatment. A standardized system of assessment spanning various treatment methods may yield a more reliable study by simply quantifying data for inferential statistical analyses.

Discussion: The plant-based therapies for tinea pedis all show varying degrees of benefit and could be presented to patients as alternative therapies to the classically prescribed terbinafine[4,5], miconazole nitrate[6], imidazole[7], tolnaftate[2,8], and ketaconazole.[3] Tea tree oil was proven to reduce tinea pedis symptomatology such as red and itchy skin and contained anti-mycologic properties.[2,8] However, tolnaftate proved to have significantly more effective mycological cure.[2,8] Bitter Orange oil, at varying concentrations, produced mycological cure in a shorter period of time compared to imidazole.[7] However it did produce mild side effects of skin irritation.[7] Additionally, patients who used Oleozon were not observed to have reoccurrence of mycologic infection, as compared to ketaconazole utilization.[3] When Solanum chrysotrichum, a plant with anti-mycologic properties were used, 42.8% of the participants saw a complete cure, as compared to miconazole nitrate cream.[6] When the efficacy of ajoene extracts were compared to terbinafine, participants in both groups were found to be mycologically cured.[5] Lastly, when a combination of FP, RCL and FEG were used to treat tinea pedis, the previously predicted synergistic effect was not observed; and although the mixture still contained anti-mycological properties, its potency failed in comparison to terbinafine.[4] See figure 4 for a summary of the results gathered from each reviewed paper.

Overall, plant-based therapies for tinea pedis can provide a less expensive, effective, and safer option to treating tinea pedis.

AUTHOR'S CONTRIBUTIONS

Three authors contributed equally to the production of this article. All conceived the topic, performed initial literature reviews, evaluated abstracts, authored introduction, results, discussion and conclusions. All authors drafted, read, reviewed and agreed upon the final manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Oral B12 Treatment of Diabetic Peripheral Neuropathy: A Systematic Review

Aaron Bradley, BS, Gireesh Reddy, BS, and Danielle Boyle, BS

Abstract

Introduction
Diabetic peripheral neuropathy (DPN) can lead to debilitating gangrenous limb destruction and ultimately limb amputation if patients do not undergo proper treatment. Local intravenous (IV) treatment of vitamin B12 has been shown to reverse DPN by increasing axon density. Additionally, oral B12 supplementation has been shown to have the same effects as IV B12, but with better patient compliance. Therefore, a literature review was conducted to assess and evaluate the efficacy of oral vitamin B12 based on current clinical use and the high quantity of research articles within the literature.

Study Design
Qualitative Systematic Review of the Literature

Methods
An english language literature review was conducted using the PubMed and Cochran databases. Studies which contained HIV positive subjects, non-English articles, immunocompromised subjects, and patients who were prescribed immunosuppressants were excluded from this review. Review articles that were published prior to 2000 were also excluded to ensure all data was relevant. Inclusionary criteria consisted of: adults and children, HIV negative subjects, immunocompetent patients, and terms “Oral B12” OR “Diabetic Peripheral Neuropathy.”

Results
Ultimately, 6 articles were obtained through the PubMed and Cochran database that met the criteria for the study. General conclusions can be made from the studies. Oral B12 supplementation increased serum oral B12 level, decreased MMA levels and decreased homocysteine levels. Symptoms and signs of DPN decreased based on several endpoints.

Conclusion
Based on the studies that were used for this observational qualitative study without statistical meta-analysis, one can conclude that oral B12 is a promising low risk treatment for DPN. Due to the lack of data in the literature, oral B12 has yet to become a conventional treatment modality for DPN. Additionally, a major limitation of this systematic review was the use of inconsistent endpoints by the studies to evaluate their subjects. Future studies need to use a standardized system of endpoints to allow for proper extrapolation in the literature. As a final point, after analyzing all of the studies used in this review, oral B12 supplementation showed a major decrease in the neuropathological symptoms of DPN.

Level of Evidence: 4

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a painful and debilitating neurodegenerative disease that affects at least fifty percent of patients with Diabetes Mellitus.[1,2] According to an epidemiological cohort study, seven million diabetic patients are diagnosed with DPN each year in the United States alone.[3] Additionally, foot ulcers, which often go unnoticed in a diabetic with DPN, are the major cause of morbidity among patients with diabetes and may lead to gangrenous limb destruction. In fact, every ten minutes an amputation occurs in the United States; 87% of which are related to neuropathy. Furthermore, the mortality rate after such amputations is approximately 50% within 5-10 years of limb loss.[4] The high incidence of severe pain and limb loss among DPN patients not only results in decreased quality of life, but also places a significant economic burden on our nation's healthcare system. In 2012 alone, 245 billion dollars were spent on diabetic treatment.[5,6]

Chronic hyperglycemia and vitamin B12 deficiency play a significant role in the development of DPN by increasing the production of vascular superoxides. The increased vascular superoxides inactivate nitric oxide production in endothelial cells causing vascular degeneration.[7-9] Hyperglycemia also interferes with the nerves' ability to transmit signals by causing a decrease in axonal myelin density, which ultimately inhibits proper saltatory conduction.[2,10]

Vitamin B12 analogues include methylcobalamin (MeCbl), cobalamin, cyanocobalamin (CNCbl), hydroxocobalamin (OHCbl), and adenosylcobalamin (AdoCbl). Vitamin B12 has numerous roles in the metabolism of fatty acid synthesis, DNA synthesis**,** and intrinsic to the proper functions of the Krebs cycle.[11] It is important to note that the active analogue of vitamin B12, MeCbl, is used in humans as a co-enzyme to synthesize methionine from homocysteine. Recent studies have shown that diabetic patients with low B12 and subsequent high homocysteine plasma levels have enhanced effects of DPN.[11]

While there are many factors leading to the development of DPN, vitamin B12 deficiency holds a strong link and plays a pivotal role in the progression of DPN complications. Its importance necessitates a review of the literature for vitamin B12 supplementation treatment and its effects on DPN. The promising effects of MeCbl treatment include the promotion of axonal regeneration and improved nerve conduction in patients with DPN.[12,13] The purpose of this manuscript is to systematically review the literature and analyze the therapeutic effects of oral vitamin B12 supplementation in DPN.

METHODS

Two searches of the primary literature were performed using the Pubmed database. The initial search employed the Boolean operators "and" and "or" for the terms "Treatment efficacy of Diabetic Peripheral Neuropathy with oral supplements" AND "Vitamin B12" OR "Methylcobalamin." The first search yielded 327 articles. The second search employed the Boolean operators "and" and "or" for the terms "Peripheral Neuropathy Treatment" AND "Vitamin B12." The second search yielded 346 articles. The total number

of articles found using the above mentioned Pubmed search was 673 articles. Exclusion criteria consisted of articles with intravenous distribution of vitamin B12, use of vitamin B12 for anticonvulsant therapy, pernicious anemia, Parkinsons, Type 1 diabetes, HIV +, Animal studies, Case Reports, non-English articles, and articles published prior to 2000. Additionally, the following inclusion criteria were applied: HIV-, DPN, vitamin B12 supplement, medical food, RCT, Type II diabetes, measurement including Vibration perception threshold, Monofilament, Doppler tests, and Pain survey. After careful evaluation of the papers using the inclusion and exclusion criteria mentioned above, 99.26% of the articles were excluded from

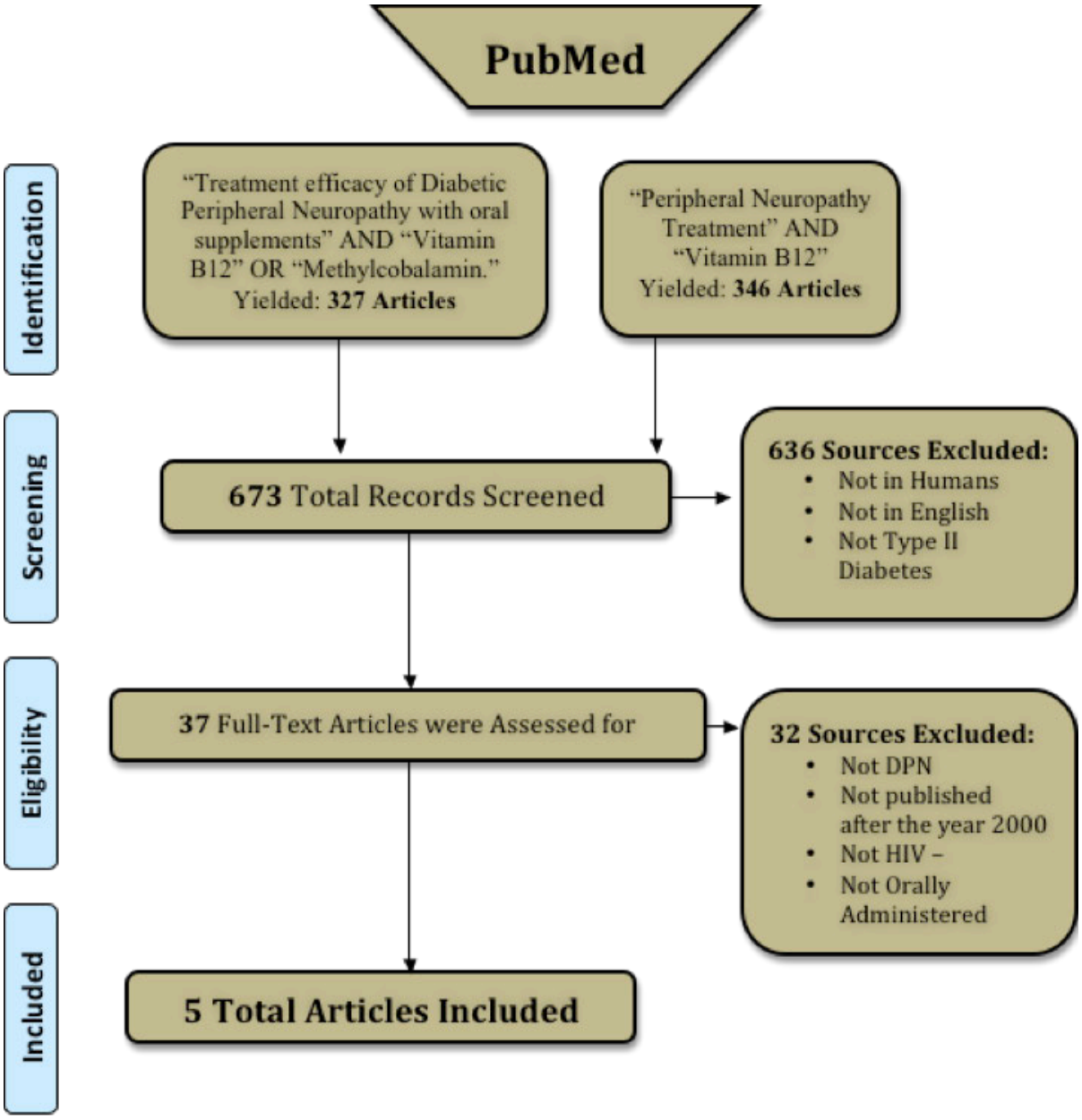

Figure 1. PubMed acquisition of studies based on inclusion and exclusion criteria.

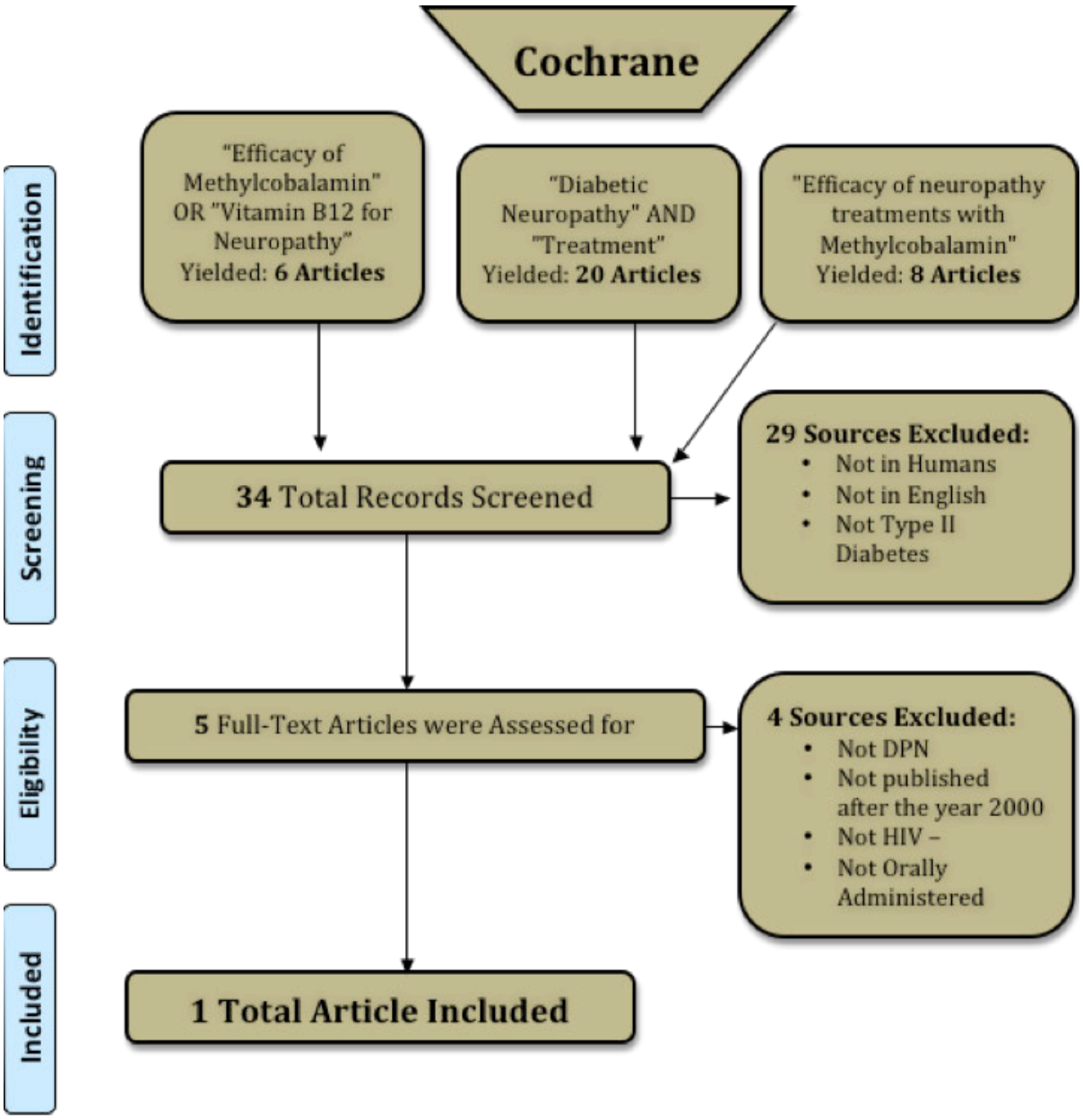

Figure 2. Cochrane acquisition of studies based on inclusion and exclusion criteria.

review, resulting in 5 final articles selected from the PubMed database.

Additionally, three searches of the primary literature were also performed using the Cochrane database. The initial search employed the Boolean operators “and” for the terms "Diabetic Neuropathy" AND ”Treatment.” The first search yielded 20 articles. The second search employed the Boolean operators "or" for the terms “Efficacy of Methylcobalamin" OR ”Vitamin B12 for Neuropathy.” The second search yielded 6 articles. The third search employed the Boolean operators “or” for the terms "Efficacy of neuropathy treatments with methylcobalamin" OR “Vitamin B12.” The third search yielded 8 articles. The Cochrane

database search yielded 34 total articles. After applying the same exclusion and inclusion criteria mentioned for the Pubmed search, 98% of the articles were excluded from review, resulting in 1 final article chosen from the Cochrane database.

From the Pubmed and Cochrane searches, a total of 6 articles met the criteria for this qualitative systematic review. For these 6 selected papers, a search through the bibliographies and other relevant studies mentioned in the papers was conducted. Only one study mentioned in the Cochrane review met the inclusion and exclusion criteria. A total of 6 studies were thus selected for review of the full paper.

To maintain consistency for proper extrapolation with this literature review, all data gathered had to be compared using a systematic, clinically significant analysis. Data gathered from the articles consisted of: sample size (N) of the studies, tools used to measure DPN, design of the study, length of the study, results, and outcome measurements. To employ clinically significant data, we calculated the mean scores of the baseline and outcome measurements to evaluate and compare the treatment efficacies for DPN.

RESULTS

Biosynthetic forms of B12

A total of six separate studies were selected for this systematic review. In four of the studies, methylcobalamin form of B12 was used while the other two studies used cobalamin or cyanocobalamin. Of the four studies that used methylcobalamin, three used methylcobalamin in the dosage of 2mg in

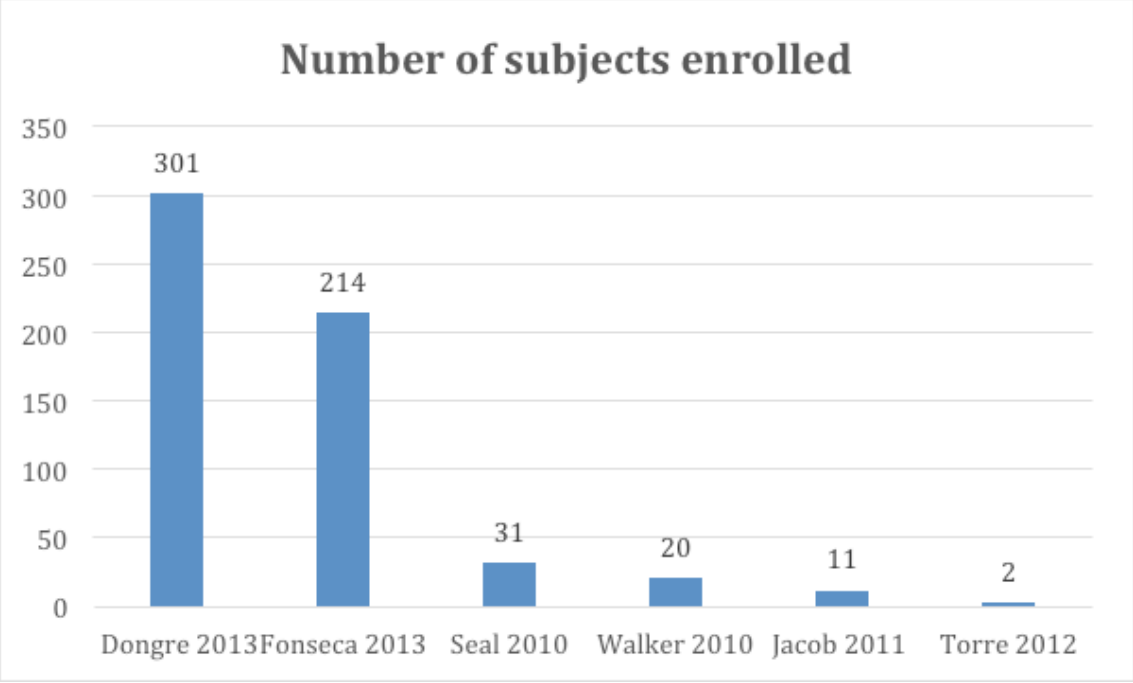

Figure 3

combination with L-methylfolate, and pyridoxal 5 phosphate.

Duration of the studies and number of subject enrolled

The study by Fonseca et al.[14] was the only randomized double blind study that fit the inclusion and exclusion criteria for this systematic review. The total number of subjects enrolled across all 6 studies were 579, with 52% of subjects enrolled in the study by Dongre et al.[15] and 37% in the study by Fonseca et al.[14] The duration of the studies varied greatly and ranged from 2 weeks in the study by Dongre et al.[15] to 52 weeks in the study by Walker et al.[16] The mean duration of the studies was 20 weeks. The wide range in the number of subjects enrolled, duration of the studies and forms of B12 used made it difficult to quantitatively compare data across all 6 studies.

Duration of Type II Diabetes

Type II Diabetes was part of the inclusion criteria for all the studies selected, however, only 4 studies mentioned the number of years the subjects were diagnosed with Type II Diabetes. In the study by Fonseca et al.[14], 11.5 years was the mean number of years the subjects were diagnosed with type II diabetes. The study by Walker et al.[16] had the lowest diabetes duration of 6 months. Additionally, in the study by Walker et al.[16], only subjects that were already on a stable level of neuropathic pain medication, such as pregabalin, were enrolled. This information was not provided in other studies included in this systematic review.

Serum B12 levels

Serum levels of B12 were used by the studies to measure the absorption of orally administered vitamin B12. In the study by Fonseca et al.[14], baseline level of serum B12 was 443 pmol/L and increased significantly (P=<0.0001) to 2308 pmol/L at 16 weeks. At the 24 week point, the serum B12 levels remained at a significantly increased level of 2242 pmol/L. In the study by Torre et al.[17], the B12 baseline level of 53 ng/L increased to 346 ng/L at 12 weeks. Lastly, in the study by Seal et al.[18], the subjects taking 10 mcg and 50 mcg of B12, the baseline levels were 140 pmol/L and 162.9 pmol/L respectively. After 4 weeks, the serum B12 levels increased in both groups by an average of 45 pmol/L. On the whole, oral administration of B12 seems to increase serum levels of B12.

Methyl Malonic Acid and Homocysteine levels

In addition to serum B12 levels, methyl malonic acid (MMA) and homocysteine levels were also measured to track the absorption of oral B12. In the study by Fonseca et al.[14], at both 16 and 24 weeks, the MMA levels significantly (p=0.0008) decreased. In the study by Torre et al.[17], the MMA baseline level of 117 mcg decreased to 10 mcg. In addition to MMA levels, homocysteine levels were also studied by Fonseca et al.[14], and significantly decreased by 2.7±3.0 μmol/L. In Torre et al.[17], homocysteine decreased by 10.1 mcg pmol/L in the 10mcg group and by 43 mcgpmol/L in the 50mcg group. An aggregation of data from these studies clearly demonstrates that oral administration of oral B12 increased serum B12 levels and decreased MMA and homocysteine levels.

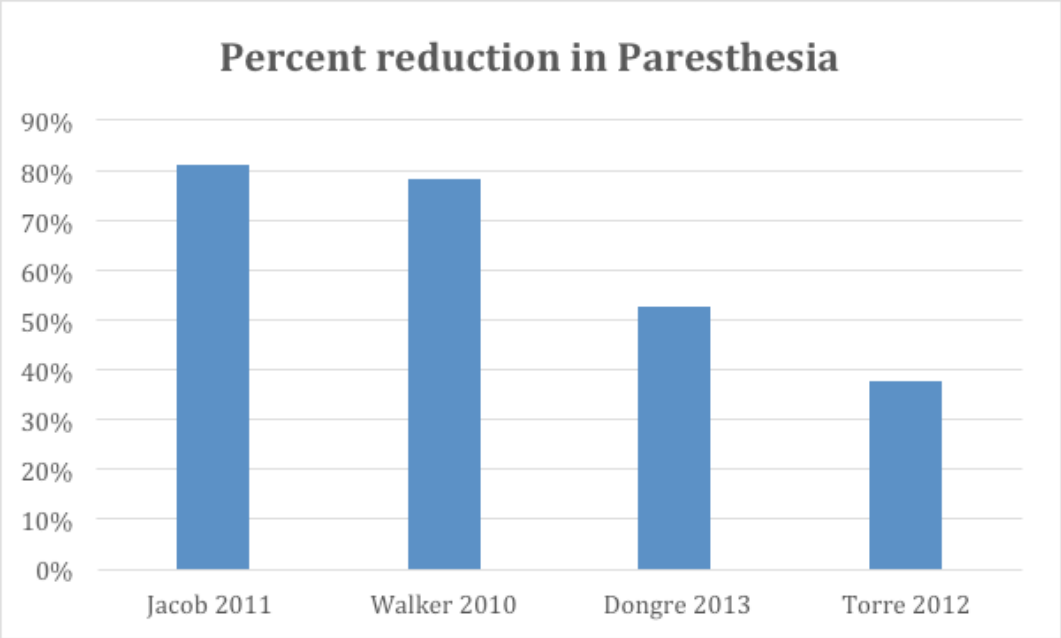

Figure 4

Clinical evaluation of DPN signs and symptoms

To analyze the manifestations of diabetic peripheral neuropathy, several different endpoints, including subjective surveys and objective tests were used in the studies selected for this review. These endpoints, including the visual analogue scale, somatosensory symptoms, vibration perception threshold, and neuropathy total symptom score-6 (NTSS-6) , have high specificity and sensitivity for DPN.

In the study by Dongre et al.[15], the baseline paresthesia, numbness and tingling was reported by the subjects to be at 55.10%. After 7 days of 1500 mcg B12 immediate release treatment, paresthesia was reported to decrease to 39% and further decreased to 26.1% at 14 days. In the study by Walker et al.[16], subjects reported a 78% decrease in numbness and paresthesia. Similarly, Jacobs et al.[19] found an 81% reduction in paresthesia while Torre et al.[17] found a reduction from a baseline of 8/10 to 5/10 post treatment.

In the study by Dongre et al.[15], hyperesthesia, burning sensation, muscle weakness and sleep disturbances were also recorded. Hyperesthesia decreased from a baseline of 48.20% to 22.4% in 14 days. Burning sensation decreased from a baseline of 63.20% to 24.8% in 14 days. Both muscle weakness and sleep disturbances were reported to have decreased substantially.

The study by Fonseca et al.[14] used the neuropathy total symptom score-6 to evaluate neuropathy symptoms of numbness and/or insensitivity,prickling and/or tingling sensation, burning sensation, aching pain and/or tightness, sharp, shooting, lancinating pain, and allodynia and/or hyperalgesia. At both 16 and 24 weeks, there was a significant (p=.013 and p=.033 respectively) improvement in NTSS-6 score. The improvement in NTSS-6 suggests that oral B12 supplementation is decreasing the symptoms of DPN. In a skin

punch biopsy used to measure epidermal nerve fiber density, 73% saw an increase in nerve density according to Jacobs et al. study. The baseline level of 1.56 fibers/mm increased to 3.07 fibers/mm. Although a skin punch biopsy is an extremely quantitative method to measure the manifestations of oral B12, this test was not performed by other studies included in this systematic review.

DISCUSSION

Oral B12 Safety

After performing the observational qualitative study, there were only 6 articles that met the inclusion and exclusion criteria. This minimal finding in the literature was a major limitation, which proves that oral B12 is still in its early stages. Safety of B12 is warranted, given there are no reported upper limit and no adverse side effects associated with excess B12 from food or supplements.[20] In the study conducted by Dongre et al.[15] sedation, dizziness, drowsiness, nausea and giddiness was found in less than 5% of the subjects. Furthermore, the RCT conducted by Fonseca et al.[14] found adverse effects in less than 2% of the subjects, with the same ratio of adverse effects in subjects placed on the placebo. Additionally, orally administered B12 is convenient and cost effective as the patient can take the medicine at home and does not need to come into the office for administration of the medication, as would be the case for intramuscular injections (IM).

Biochemical forms of oral Vitamin B12

Vitamin B12, also known as cobalamin, is the generic descriptor for corrinoid compounds containing a colbalt centered corrin ring. Vitamin B12 (cobalamin) is an essential co-factor which can be found in vivo in various forms including cyano-, methyl-, deoxyadenosyl- and hydroxyl- cobalamin.[21] Literature has shown that the biochemical form methylcobalamin is the most essential form needed to aid in the healing of the microvascular destruction, and less likely to be degraded in the ileum.[7-9] Four of the studies in this review used the methylcobalamin form of B12 while the other two studies used cobalamin or cyanocobalamin. Additionally, findings in the literature stating that the methylcobalamin form of B12 is the active form of cobalamin and absorptive studies confirmed its effectiveness compared to other B12 forms.[7-9] Our data concludes that all 3 forms of B12 had therapeutic effects for treating DPN.[6,7,15,16, 25] The problem is that all six of the studies used in this review had different end-points to evaluate the efficacy of the oral B12. This finding allows for future studies to be conducted to differentiate the validity of using particular biochemical forms of oral vitamin B12.

Absorption and Metabolism of oral B12

Malabsorption is the predominant cause of B12 deficiency in humans.[22] Naturally occurring B12 in food is bound to protein and must be released for absorption. Gastric acid is essential for the release of this dietary B12 from. Thus, incorporating animal products into one's diet does not ensure the absorption and assimilation of vitamin B12 throughout the body. In contrast, the synthetic B12 found in oral supplements is not bound to protein and therefore, does not rely on the breakdown in the stomach. Serum levels of vitamin B12 in the study by Fonseca et al.[14] increased

approximately 5 times the baseline levels. In the study by Torre et al.[17], the vitamin B12 levels increased approximately 7 times the base level. Supplemental B12 can undergo passive absorption via simple diffusion throughout the small intestine.[6,7,22] These studies prove that the oral B12 is getting absorbed and assimilated into the blood.

Serum B12, Homocysteine and MMA

The current protocol for the evaluation of vitamin B12 status is its concentration in the serum, though concerns have been raised about the use of serum vitamin B12 measurements alone.[21] Low serum vitamin B12 levels is a sensitive indicator of vitamin B12 deficiency and assess the quantity of B12 available, but do not adequately evaluate the functional abilities of the B12 found in the serum.[24] Therefore, evaluating the homocysteine and MMA levels provide additional information about the functional capability of the B12 to perform the necessary functions in the body. After administering the oral B12 supplement in studies conducted by Fonseca et al.[14] and Torre et al.[17], serum levels of B12 increased significantly, while serum levels of Homocysteine and MMA both decreased significantly. These serum levels illustrate that the oral supplement was absorbed and able to be functionally active and useful in the two primary biological pathways that require B12.

Understanding the biological functions of B12

Vitamin B12 is an essential cofactor involved in two primary enzymatic pathways in the human body. The first reaction, depicted in Figure 5 number 1, which occurs in the cytoplasm, is the re-methylation of Homocysteine to Methionine by Methionine Synthase, which is essential for the synthesis of purines and pyrimidines.[21] In this reaction, methionine synthase requires vitamin B12 in the methyl-cobalamin form.Without methyl-cobalamin, levels of Homocysteine increase, which has been associated with vascular damage. Homocysteine levels were studied by Fonseca et al.[14], and were found to decrease by 2.7±3.0 μmol/L. In Torre et al.[17], homocysteine decreased by 10.1mcg pmol/L in the 10mcg group and by 43 mcgpmol/L in the 50mcg group. These decreases in homocysteine levels suggests that the oral B12 is being absorbed and is working to halt the microvascular damage occurring in DPN.[21-22]

The second reaction, illustrated in Figure 5 number 2, is the conversion of L-methylmalonyl coA to Succinyl coA by methylmalonyl coA Mutase. This reaction, which occurs in the mitochondria, is dependent on the availability of vitamin B12 in the adenosylcobalamin form. Without adenosylcobalamin, L-methylmalonyl coA accumulates and is hydrolyzed to form coA and Methylmalonic Acid (MMA). MMA is a myelin destabilizer and accumulation of MMA has been found to be associated with the neurodegeneration seen in vitamin B12 deficiency.[23] Thus in B12 deficiency, one would expect to see ↑Homocysteine and ↑ MMA in the blood. In the study by Fonseca et al.[14], at both 16 and 24 weeks, the MMA levels significantly ($p=0.0008$) decreased. In the study by Torre et al.[17], the MMA baseline level of 117 mcg decreased to 10 mcg. This shows that the oral B12 supplement was absorbed and was being properly integrated into the biological pathway in which it was needed.

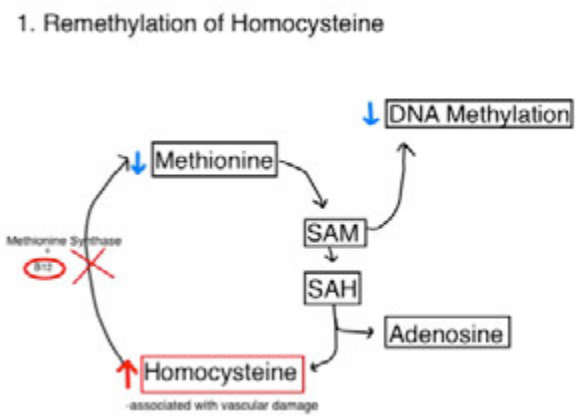

Figure 5- The vitamin B12 dependent reactions of the body. 1. Remethylation of Homocysteine and 2. The conversion of L-methylmalonyl coA to Succinylcholine coA.

Potential Benefits of Methylcobalamin for the treatment of DPN

The underlying pathophysiological cause of DPN is vascular degeneration[7-9] and decreased nerve conduction.[25-28] Diabetic hyperglycemia causes damage to capillary endothelial cells which supply blood to the nerves. Specifically, hyperglycemia increases the production of vascular superoxide, which inactivates the nitric oxide production in endothelial cells, leading to vascular degeneration.[7-9] Hyperglycemia not only damages capillary supply to nerves but also interferes with the nerves' ability to transmit signals by causing a decrease in axonal myelin density, which ultimately inhibits proper saltatory conduction.[19] These neurodegenerative changes were clinically measured and quantified using various endpoints such as hyperesthesia, burning sensation, and muscle weakness. In the study by Dongre et al.[15] hyperesthesia decreased from a baseline of 48.20% to 22.4% in 14 days. Burning sensation decreased from a baseline of 63.20% to 24.8% in 14 days. In addition, muscle weakness was reported to decrease significantly. [15] These clinical findings exemplify the function of B12 as a cofactor to neutralize oxidative-stress byproducts, such as superoxide and peroxynitrite, and promote myelination of nerves.[14,29-31]

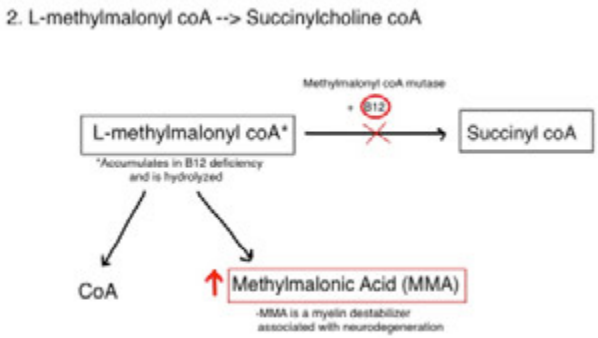

Figure 6- The vitamin B12 dependent reactions of the body. 1. Remethylation of Homocysteine and 2. The conversion of L-methylmalonyl coA to Succinylcholine coA.

Lack of Gold standard for Endpoints in Pain Measurement

When comparing the various studies, there was inconsistency in the measurement of the pain associated with the subject's DPN. Although all of the endpoints used, including Visual Analog Scale (VAS), Somatosensory Symptoms, Vibration Perception Threshold (VPT), and Neuropathy Total Symptom Score-6 (NTSS-6) have high specificity and sensitivity, this variability in end-point selection lacks a homogeneity between the evaluation of oral B12. For instance, the skin punch biopsy that measures epidermal nerve fiber density (ENFD) was only performed in the study by Jacobs et al. The other studies selected for this systematic review did not

perform this objective test to measure the manifestations of B12 treatment. Having different end points made it difficult to objectively compare the results of the studies. There needs to be an established gold standard for the measurement and diagnosis of peripheral neuropathy.

A major difficulty the researchers in our studies encountered was subject compliance for invasive end point measurements. The studies that were used in this review found that the use of pain scale surveys and complete blood counts (CBC) had minimal issues with patient compliance. In this review 3 out of 6 studies used a pain scale survey and had a lower number of subjects that dropped out of their studies. Also, having multiple studies with the same end point allows for the research to be analyzed and extrapolated for clinical use. Although, pain scale surveys can lack validity and reliability because of the involvement of subject emotions, the studies in this review have proven that pain scale surveys are critical to use as a valid end point and should be implemented in future studies when measuring the effects of B12.

CONCLUSION

Based on the studies that we found for this observational qualitative study, one can conclude that oral B12 is a promising low risk treatment for DPN. Though the literature has shown that there is major potential for effective DPN treatment using oral B12, the research is still in its elementary stages. Due to the lack of research studies and variability in study end point, comparing and analyzing the data between the studies was difficult. One of the major patterns that was found during this study was that orally coupled B-vitamin therapy had better results as opposed to monotherapy. Also, the studies that used pain scale surveys had the best results for reduced paresthesia as opposed to VPT end points, which did not show any change when using oral B12. In fact, the nerve density study can prove that oral B12 is an effective treatment for DPN. This study validates the theory that B12 increases nerve fibers using objective measuring end points. Consequently, more studies need to be performed to show that oral B12 is a credible source to increase nerve fiber density because there is only one in the literature.

Future studies should have homogeneity between end points when evaluating their subjects to allow for B12 to become a reliable treatment method. For oral B12 to become a standard medication for neuropathy treatment, there needs to be a plethora of consistent data in the literature. Although, oral B12 has minimal adverse effects and the research is promising yet minimal, practitioners still need to take proper precautions prior to administering oral B12 to patients with DPN.

AUTHOR'S CONTRIBUTIONS

Three authors contributed equally to the production of this article. All conceived the topic, performed initial literature reviews, evaluated abstracts, authored introduction, results, discussion and conclusions. All authors drafted, read, reviewed and agreed upon the final manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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The Masquelet Technique used in the Reconstruction of an Osteomyelitic Talonavicular Joint: A Case Report

Muntasir Khaled BA and Mudasser Javed, BS

Abstract

Introduction
Osteomyelitis is an infection of the bone. Infections may reach the bone through a variety of sources. Common avenues include the blood stream, a nearby infection, or direct contact to the bone. Staphylococcus aureus is the most common type of bacteria that causes osteomyelitis. Risk factors for patients developing osteomyelitis include diabetes, hemodialysis, poor vascular supply, and intravenous drug users. A surgical plan was developed using the Masquelet technique, which consists of removal of necrotic bone, application of an antibiotic bone spacer with a six to eight week delay under intravenous antibiotics and wound care prior to final application of fixation and a bone graft.

Study Design
Case Report

Methods and Results
A 51 year old male presented to the emergency room with a fluid filled abscess on the dorsal medial aspect of his right foot. Clinical presentation along with x-rays revealed osteomyelitis of the talonavicular joint. Surgical intervention was performed to incise and drain the abscess, debride bone, and place an antibiotic bone spacer implant. An external fixation device was applied. The second stage of the surgery was performed eight weeks later and included removal of the antibiotic spacer and external fixation device. An allograft bone graft was placed in the defect and stabilized with internal fixation.

Level of Evidence: 4

INTRODUCTION

Osteomyelitis is an infection of a bone or bone marrow. Infections reach the bone through a variety of mechanisms; they can go through the blood stream, spread from a nearby infection, or from direct contamination of bone to the outside environment. When the bone becomes infected, leukocytes are able to release enzymes that lyse the bone. Pus may enter the bone and impair the bone's vascular supply, and cause that area to become necrotic. These necrotic areas are what defines whether the infection is acute or chronic. Chronic osteomyelitis occurs when there is a presence of bacteria inside the bone cells, which may spread to nearby cells. When bacteria are in the bone cells, they may become resistant to antibiotics, which makes chronic osteomyelitis difficult to control.[1-4]

Osteomyelitis may affect people of all ages. In children, this disease often affects the long bones of the upper and lower extremities, while in adults, it may occur in the spine, the hips, or the feet. Symptoms of this disease are similar to the symptoms that may occur with any infection and include, but are not limited to, fever, pain, swelling, warmth, and redness to the area. In order for osteomyelitis to occur, a person's bone must become weak in some way. Some of the methods that make the bone susceptible to infection may include: a recent injury, uncontrolled diabetes, sickle cell disease, dialysis machines, or illicit drug use.

Bone infection has statistically been treated with bone debridement, leading to a segmental defect once bone is taken out which is particularly challenging for doctors to take care of.

Masquelet et al. described a procedure combining induced membranes and cancellous autografts. Bone grafting is often delayed after primary fixation to allow soft tissue healing, decrease the risk of re-infection, and prevent graft resorption. In infected wounds, antibiotic impregnated cement beads or spacers are often used for local antibiotic administration to the soft tissue bed. Additionally, the advantages of inserting a spacer include maintaining a well-defined void to allow placement of a graft, providing structural support, offloading the implant, and inducing the formation of a biological membrane. Masquelet proposed that this membrane prevents graft resorption and improves vascularity and corticalization. It has been described that, after the initial placement of the antibiotic impregnated spacer, an interval of four to five weeks is necessary for the development of a suitable membrane. The spacer also maintains the defect and inhibits fibrous ingrowth.[9]

Papineau also reported a similar technique in 1973, as an alternative to amputation for infected bones. It was used to strengthen defects by applying open cancellous bone grafts after removing necrotic bone and soft tissue.[10]

We describe the use of these innovative techniques with cortical bone autograft to achieve an anatomic and functional reconstruction of the talonavicular joint in a 51-year-old male.

Case: Methods and Results:

A 51 year old male, presented to the emergency department with a chief complaint

of right foot pain and swelling. The patient stated that he had chronic right foot pain for more than a year. He recently noticed swelling the over past few days, which lead to the emergency department visit. On examination, the dorsalis pedis and posterior tibial pulses were both palpable, no cyanosis was present, there was warmth to the medial aspect of the right foot, and there was significant edema present on the medial aspect of the talonavicular joint. Noted was a fluctuant mass medial to the talonavicular joint consistent with an abscess. The patient complained of very severe pain on palpation to the mass as well any ranges of motion of the foot. A neurological exam revealed protective sensation intact. Dermatological exam revealed normotrophic scars along the calcaneocuboid, talonavicular, and laterally to the subtalar joint. Skin quality was very thin and atrophic particularly to the medial side because of previous surgeries. A detailed history was obtained, and the patient admitted to tobacco use and occasional alcohol consumption. He also stated he was the caretaker for his autistic child. His past medical history included diabetes type II and gout. He reported that he had a myocardial infarction within the past two years. His past surgical history included a right subtaral joint fusion in 2012 secondary to post traumatic arthritis from an old calcaneal fracture three years prior to the surgery. After subtalar joint fusion he was lost to follow up and was seeing a private podiatrist. He was seen a year later after he had the calcaneocuboid joint fusion and talonavicular joint fusion, complicated by wound dehiscence to the talonavicular joint site, requiring hyperbaric oxygen therapy, hardware removal, and possible septic joint per chart review. Poor compliance, poor wound healing capabilities and past smoking history are all possible reasons for poor healing in general.

Radiographs were ordered for the patient's right foot and they revealed a nonunion of the talonavicular joint and calcaneocuboid joint with likely osteomyelitis to the talonavicular joint at the area of the soft tissue abscess, which was confirmed with culture intra-operatively (MSSA). The decision was made to perform a bedside incision and drainage of the abscess after acquiring consent from the patient because of the pain, skin tenting of fluctuant mass, and concern for the abscess. The patient was injected with 24 cc's of 1% lidocaine. A blade incision was made and 50 cc's of purulence were aspirated out. The area was then flushed with sterile saline, packing gauze applied, with a clean dry dressing. The patient was instructed to stay non-weightbearing to the right lower extremity and IV Unasyn (1.5g q6hr) was given. The patient was also instructed to obtain medical clearance and MRI's, which were both necessary to continue with surgery.

The procedure was performed one week after the initial emergency room visit to optimize the patient for surgery. In the first stage of the surgery, one screw was removed from the subtalar joint to make sure it did not interfere with the current procedure. An incision and drainage procedure was then conducted to remove the excess fluid present in the abscess, along with debridement of necrotic tissue and bone, under conscious sedation and local anesthesia over the talonavicular joint. The surgical plan consisted of performing the Masquelet technique with removal of necrotic bone, application of an antibiotic spacer into the defect with an a six to eight week delay under intravenous antibiotics and wound care prior to the final application of fixation and

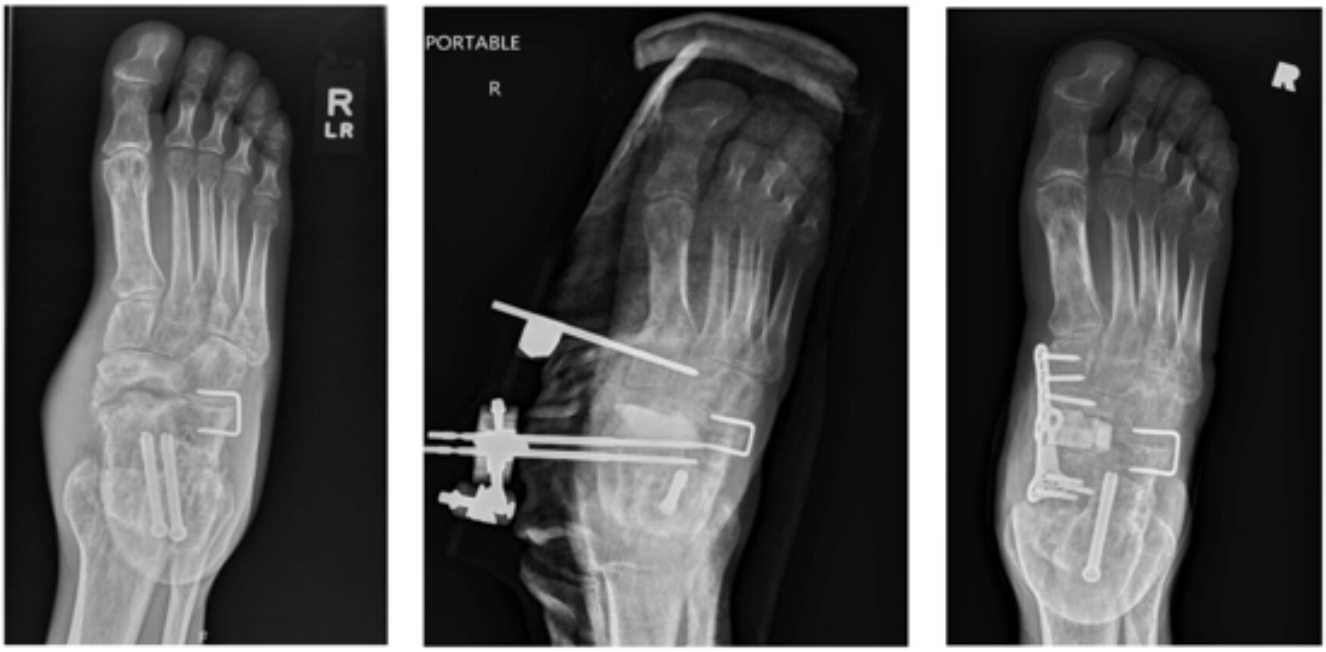

Figure1: (left image) initial ED visit, (middle image) radiograph after step 1 of the procedure, (right image) s/p 14 weeks step 2 of the procedure.

bone graft. A Stryker Hoffman external fixator was put in to maintain the void of the bone removed and to preserve the medial column during the first stage. (Figure 1) The patient was followed up every week for eight weeks with serial radiographs to monitor maintenance of medial column length and spacer integrity.

The patient previously had two surgeries in this area. The first was a talonavicular joint fusion and second was hardware removal from the talonavicular joint a few years later. These previous surgeries lead to poor skin quality in the area, requiring the patient to have a wound vacuum at the site for eight weeks. This would be monitored by a visiting nurse every day, in between the patient's weekly clinic visits.

The second stage of the surgery was done eight weeks after the first stage and included removal of the antibiotic cement spacer and the external fixation device. A tricortical bone allograft replaced the antibiotic spacer and fixation was achieved via a medial column plate. The patient followed up at the clinic every week for dressing changes and radiographic evaluations. After the second surgery, an ulcer wound formed in the area where the incision was made at the dorsal aspect of the talonavicular joint. Seven weeks after the surgery, he was instructed to receive hyperbaric oxygen chamber treatments to accelerate the recovery process. The patient is presently 14 weeks post-operative and is still following up in the clinic on a weekly basis.
At the current time, the patient is still non-weight bearing and ambulating with crutches.

DISCUSSION

The patient presented to the emergency department with severe foot pain and

swelling. Imaging modalities showed very poor bone quality; also seen was intact hardware at the subtalar joint with no evidence of attenuation. There were evident cortical erosions to the navicular in addition to joint destruction of the talonavicular joint. Along with the radiographs, an MRI was ordered, regardless of the fact that there was hardware that might obliterate the evaluation of the midfoot joints, but deemed necessary due to the extent of the abscess found as well as to evaluate for bone infection extending to the forefoot. Cultures were taken during the incision and drainage for anaerobic, aerobic, and pathology specimens in order to confirm the diagnosis of osteomyelitis. He was admitted on the suspicion of osteomyelitis. The surgeon chose to proceed by performing surgery using the Masquelet and Papineau techniques in order to eliminate the infection. Clinical, experimental, and fundamental studies have shown the interest of a foreign body-induced membrane to promote the consolidation of a conventional cancellous bone autograft for reconstruction of bone defects. The Masquelet technique is a procedure of combining two steps that allows the reconstruction of bone defects. In the first stage, a cement spacer is inserted into the defective area and this forms a pseudo-synovial membrane. After insertion of the spacer, four to five weeks is needed for development and maturation of a biologically active membrane suitable for grafting.[9] The spacer also maintains the defect and inhibits fibrous in-growth. The membrane may play the role of in situ delivery system for growth factors (VEGF, TGFbeta1, BMP-2).[11] The induced membrane from the antibiotic spacer provides for adequate scaffolding for osteoconduction, an adequate vascularization in the defect; and also creates a positive environment in which osteogenic cells and substances are retained.[12] Prior to the bone graft being applied, one must remove the necrotic bone and soft tissue, avascular periosteum, and scarred subcutaneous tissue and muscle. This is absolutely necessary for the success of further treatment. In the second stage of the surgery, which occurred two months after the first and incorporated the Papineau technique, the defect is reconstructed by autologous cancellous bone graft. Bone bridging may be achieved along with secondary soft tissue coverage in which granulation tissue forms over the graft. Following this, a skin graft may be applied in order to close the skin in that area.[10]

Makridis et al. have described the effective implementation of the Masquelet technique in reconstruction of the first metatarsal. They discussed its use in a comminuted grade 3B open fracture of a 53 year old male. There was osseous healing and no signs of infection, osteolysis, or hardware failure at 14 months, and no pain with return to normal daily activities at eighteen months. This along with our case study shows the effectiveness in the reconstruction of extensive bone defects in the foot.[17]

The technique we presented offers advantages and disadvantages. The use of an intramedullary device for initial reconstruction allows earlier weight bearing. This is particularly important in patients who are non compliant and tend to render the reconstruction inadequate. The patient can return to normal daily activities earlier. There are possible complications from the procedure such as infection, implant failure, malunion, and nonunion. The main disadvantage is that it is a two-step procedure that can involve multiple hospitalizations along with unnecessary exposure to increased anesthesia.

Other potential disadvantages are limitation on the amount of osseous grafts available, pain, hematoma, and infection.[5]

If surgical treatment is not deemed necessary, non-surgical treatment modalities may be used to treat osteomyelitis. Serial bone biopsies and serial x-rays are needed to monitor the bone quality. If osteomyelitis is suspected, x-rays need to be taken and reviewed; however, bony changes may take several weeks to appear on plain radiographs. Bone biopsies may also be taken in order to help observe the bone quality. A culture of bone may be acquired percutaneously in order to identify the pathogen responsible for causing the osteomyelitis. The main non-surgical option is treating the patient with IV or oral antibiotics. Studies comparing surgical management and non-surgical management have reported similar outcomes between the two groups. Antibiotics that treat against gram positive organisms and ones that treat gram negative organisms and obligate anaerobes have been shown to be equally effective.[13-16]

Although questions remain regarding the role of the antibiotic spacer, its use for reconstruction of bone defects after resection of necrotic bone and tissue offers an effective alternative to amputation. The procedure is technically simple, yet very effective. We believe the technique merits further investigation to better define its use compared with other methods of reconstruction.

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AUTHORS' CONTRIBUTIONS

MJ and MK worked together to gather and analyze the case information, conduct a search of the literature, draft, and edit the manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare no competing interests in relation to this manuscript.

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PI DELTA

* Denotes Pi Delta Member

Quantification and Reduction of Shear Force in Diabetic Patients as a Preventative Measure of Ulcerations in the Lower Extremity

J. Adrian Wright, AM and Jessica Fink, BS

Abstract

Introduction
Individuals with diabetes are at a higher risk of ulceration secondary to neurovascular compromise. Current literature supports the need for methods to quantify shear forces as a means of predicting ulcerations. Until recently, the ability to independently quantify shear force was difficult due to lack of measuring devices. It is the goal of this study to review the current literature for quantitative assessment methods of shear force and the effects of viscoelastic insoles in reduction of these forces.

Study Design
Literature Review

Methods
Utilizing the MeSH advanced search building tool within the PubMed interface, an initial search of the literature was performed for "shear force" with the Boolean operator "and" employed to include the terms "foot ulceration" which yielded 13 articles. An additional search utilizing the same protocol was performed on Google Scholar yielding 116 articles and the Cochrane database, yielding 3 articles. Inclusion criteria: articles must be written in English, must be preformed on diabetic patient populations, and must be studies that measure the outcomes of repetitive stress on the plantar surface of the foot. Clinical studies were excluded if patients were not diagnosed with Diabetes Mellitus Type II or if the study failed to make a distinction between repetitive vertical forces and shear forces.

Results
In a novel attempt to independently assess shear force, Wang et al. developed a fiberoptic sensor utilizing the bend loss technique to determine the amount of shear force affecting a particular area. Zang et al. discovered that pressure and shear force are both directly related to decreased blood perfusion of a particular tissue. In two studies by Lavery et al, patients' receiving shear reducing insoles were found to be at lower risk for developing ulcerations than those who received insoles that only reduced vertical pressure. Additionally, of the shear reducing insoles available, Lavery et al. determined Glideforce reduced shear by the greatest amount (43%).

Conclusions
At this time, there is no well-accepted measurement of stress. Reducing pressures on the soles of the feet with therapeutic footwear and shear reducing insoles is pivotal in the prevention of foot ulcerations. In addition, diabetic patients should be screened for loss of protective sensation and treated appropriately.

Key Words
Shear Force, Ulceration, Diabetes Mellitus

Level of Evidence: 4

INTRODUCTION

With the rapidly growing population of diabetic patients in the United States, attention has turned towards the optimal management of these individuals. Medicine has quickly progressed to a model that focuses on cost reduction. The most effective way to reduce cost is prevention. This is evident by the large incentive models established by insurance companies for individuals and providers to make certain attempts at screening patient populations at risk of certain diseases or co-morbidities.

Diabetic patients are at high risk for peripheral vascular disease. These insults on the microvasculature lead to severe and sometimes life-threatening complications (kidney failure, loss of eye sight, gangrenous ulcerations, etc).[1-4] Unfortunately, the consequences of uncontrolled diabetes are not confined to the vascular system, but also affect the nervous system. The relationship between nerve damage and microvascular compromise may be primary or secondary.[5,6] Numerous studies have supported a relationship between uncontrolled diabetes mellitus and the development of peripheral neuropathy resulting in the loss of protective sensation and proprioception.[7] Aside from the painful effects of small nerve fiber involvement, individuals with compromised protective sensation are at increased risk of severe injury and infection.[8] Because these individuals may become completely insensate, repetitive trauma may go unnoticed resulting in hyperkeratotic lesions and ulcerations.

Due to the diminished vascular perfusion in diabetic patients, and an attenuated immune response, it is crucial that these patients avoid any form of open lesions, as this may quickly result in a complicated infected ulcer with notably delayed healing.[1] The perfect storm of hypoperfusion, lack of efficient immune coverage, and delayed healing, may present the ideal opportunity for an organism to cause life-threatening circumstances that may result in amputation.[9] Naturally, one way to prevent these life-threatening situations is to prevent the initial ulcer formation. Numerous research projects have attempted to propose solutions to prevent morbidity and mortality which range from assessing the intricate aberrant molecular pathways involved in the pathogenesis of uncontrolled diabetes mellitus, to modifying the external forces involved in the initial formation of ulcerations.

Neuropathy, peripheral vascular disease, foot deformity, limited joint mobility, footwear, fatigue and body weight are all factors that can contribute to elevated foot pressures, resulting in diabetic foot ulcerations. Plantar foot pressures, when elevated, require less repetitive stress to initiate soft tissue breakdown.[10] Mechanical forces such as pressure, friction and shear, applied externally to the skin surface are the most important factors contributing to ulcerations.[10]

Shear force results from non-uniformed forces pushing one part of the body in one direction and another part of the body in the opposite direction.[13] Shear is affected by the amount of pressure exerted, friction between materials contacting each other, the extent at which the body makes contact with the supporting surface, as well as gait velocity and internal muscle activity. Increased shear force can result in insults to the blood supply causing ischemia, cellular death, and tissue

necrosis, increasing the likelihood of foot ulcerations. It has been claimed that shear force diminishes vascularity from an area of tissue more significantly than normal vertical pressure.[12, 14, 17]

Previously, there has been a focus on vertical pressure as the prime agent in the development of diabetic foot ulcerations. Studies that have tried to associate the vertical stress component with ulcer occurrence did not yield promising outcomes due to relatively low correlation between maximal pressure sites and potential ulceration sites.[11] We now understand increased shear force may play a primary role in the development of diabetic foot ulcerations. However, the lack of efficient methods of shear force assessment poses a significant clinical and research challenge.[12]

Lack of evidence for shear force as a prime factor in ulceration is most likely due to difficulty in finding effective ways to measure shear. The purpose of this paper is to review recent methods for assessing shear force and the effectiveness of shear reducing insoles for preventing diabetic foot ulcerations. Prior experiments have measured skin vascularity, modeled analysis of internal stress, and the use of multilayer viscoelastic insoles.[12,15,16] We now have a greater need to elucidate the mechanisms of injury or pathogenesis of ulcer formation from shear and not direct trauma or vertical force.

METHODS

Utilizing the MeSH advanced search building tool within the PubMed interface, an initial search of the literature for "shear force" with the Boolean operator "and" employed to include the terms "foot ulceration" yielded 13 articles. An additional search utilizing the same Boolean operator and terms was performed on Google Scholar and yielded 116 articles. A final search, congruent to the previous two, from the Cochrane Databases yielded 3 articles. After individual analysis of each article, employing the inclusion and exclusion criteria, only 4 articles remained. The inclusion criteria for the study required that articles be written in English, be clinical studies involving diabetic patient populations, and be studies that measure the outcomes of repetitive shear stress on the plantar surface of the foot or devise a technique to assess shear and vertical stresses. A clinical study was excluded if patients were not diagnosed with Diabetes Mellitus Type II, or if the study failed to distinguish between repetitive vertical forces and shear forces. Papers published prior to 1985 were excluded from the study.

RESULTS

In an attempt to establish a novel model for assessment of plantar shear forces, Wang et al. developed a method of independently assessing plantar pressure and shear stress with a fiber optic sensor.[17] Utilizing the bend-loss technique (an operating motif based on the facets of force-induced fiber deformation), the authors assessed the power loss from the core mode to the radiation mode of their model. [17] In this complex model, the

deprivation of energy produced from a light-emitting diode is proportional to the bend of the optic fibers. This deprivation is assessed using a fiber-based macrobend sensor that determines light-intensity attenuation.[17] In order to distinguish between the two prevailing forces: vertical force and shear force, the model was created in a multi-layered fashion so that the distortion of the fiber-optic mesh in one layer is measured with respect to the other layer.[12] This relative assessment was crucial in the model to determine whether the effect of bend, measured as attenuation of light-intensity, was the result of vertical force or shear force. More simply stated, any misalignment noted between the two layers would be a key indicator of shear force. [17] To help diminish extraneous variables, the fiber-optic sensor described above was placed between two pads constructed of gel/polymeric compounds.[17] It is important to note that the authors compensated for the refractive index produced by the fiber-optic channels (200μ), as this oversight would have impacted the results of the study.[17] Force was then applied to the gel sandwiched fiber-optic device with an electromagnetic material testing unit for assessment of vertical force.[17] A subsequent test was preformed with a handheld force gauge for shear force.[17] The data collected from both force tests was performed continuously to compensate for any creeping that may occur and therefore confound the results. All data collected from both vertical and shear force tests was extrapolated and reconfigured into a 3-D force map utilizing MATLAB.[17] Assessing the results, the authors concluded that their novel model assessor of shear force was rather accurate at determining the amount of shear force applied onto a surface.[17]

Additional attempts to signify importance of shear force are described by Zhang et al. The authors' purpose was to investigate the variation of skin vascularity with the application of normal pressure and shear force. The distinction of blood flow to the skin following externally applied force was carried out with a Laser Doppler Flowmeter (LDF). [12] The relatively deeper vessels accounted for the majority of the flow measured. A rigid cylindrical indenter combined with a doppler probe was placed perpendicular to the skin and translated both pressure and shear force.[12] Pressure was applied by adding weights on top of the indenter. The application of weights connected to a string via a pulley system attached to the indenter produced varying shear forces. A shear force was applied and increased from 20-250g for 20 second intervals.[12] The laser doppler demonstrated consistent skin perfusion when 200g of pressure was steadily applied to the external device.[12] When shear force was initially applied to the indenter, a sharp increase in blood flow was noted followed by a steady decrease as shear force was maintained. A noticeable decline of skin perfusion was observed as increments of shear increased.[12] In regards to blood flow, authors noticed that both pressure and shear were inversely related to the amount of blood that reached the skin.[12] As the forces increased, the blood flow decreased. In conclusion, blood flow was reduced with both pressure and shear forces, but shear force in addition with pressure caused a greater decline in blood flow than compared to pressure alone.

The same authors also analyzed internal stress distribution following application of both shear force and pressure. Zhang et al. explained two models of compressive forces

using a theoretical method. In the first model, they applied vertical pressure to one location of the skins surface and applied an additional horizontal shear force to the same surface point.[12] They found that vertical pressure increased stress much deeper compared to shear force, which increased tissue stresses more superficially.[12] Furthermore, when pressure and shear force are applied on the same surface spot, the direction of forces (pressure vs. shear) appeared to be overlapping distal to the point of force application.[12] On the contrary, forces proximal to the point of contact appeared to travel in the opposite direction, indicating larger amounts of stress occurring distal to the point where force was exerted.[12] The second model uses two points of force application equi-distant from a center point (X). Shear force was then applied in opposite directions in relation to X.[12] When analyzing vertical pressure and shear force at different depths, the authors again found that shear force influences stress mainly in the superficial tissues.[12] In addition, as shear force was amplified, the stresses became more superficial. Shear force has a larger effect on the superficial area of soft tissue. This, in addition to the decrease of skin perfusion, implies that shear force, rather than direct vertical force, is more likely to be potentially damaging to this superficial region.

In an attempt to protect high-risk diabetic patients from ulcerations, Lavery et al. used two studies to compare several types of insoles, in attempt to reduce shear forces.[16, 17] The first of Lavery's studies was an 18-month randomized control trial where 299 diabetic patients (classified as either Group 2 or Group 3 using the International Working Group on the Diabetic Foot's Risk Classification) were assigned to receive either a standard insole or a shear-reducing insole. The majority of the participants were classified as risk group 2 according to IWGDF which includes both neuropathy and foot deformity. Only a minority of the participants had previous ulcerations (IWGDF group 3). The same physician evaluated each group every 10-12 weeks and all received the same therapeutic shoes. The insoles were assembled similarly with an upper pad made of 35-durometer EVA (ethyl vinyl acetate), a lower pad consisting of 45-durometer EVA, and a 20-durometer closed cell polyethylene foam top cover.[16] The shear-reducing insoles were slightly different as they included two thin nonstick sheets placed between the upper and lower pads, held together with elastic binders.[16] Results demonstrated that ulcerations were less likely to occur and fewer amputations were indicated in patients wearing shear reducing insoles, compared to patients wearing standard insoles.[16] Lavery et al. stated "patients with standard insoles were actually 3.5 times more likely to develop an ulcer compared to patients treated with shear-reducing insoles."[16]

Lavery's second study compared three multi-layered viscoelastic insoles to the shear reducing "Glide-soft" insoles. The multi-layered insoles were constructed with a bottom layer of firm-density plastazote and a top layer consisting of medium density plastazote.[17] Three distinctive middle layers, comprised of firm density plastazote, 45-durometer ethyl vinyl acetate (EVA), and 20-durometer poron, were used.[17] The Glide-soft design was prepared with two thin sheets of low friction material that are able to slide well over one another. A fiberglass sheet coated with Teflon was placed between the two layers.[17] The insole was then secured with elastic bindings. Glide-soft's function was to

reduce shear force by allowing the top portion to move with the foot relative to the lower portion.[17] The elastic bindings distend and eventually arrest the relative motion within the insole, causing redirection of the shear force more vertically (similar to that of pressure). Daily measurements of pressure were assessed via F-Scan and shear was measured with placement of the insole on a custom-designed shear tester.[17] The authors concluded that Glide-soft significantly reduced shear force when compared to the standard insoles, up to almost 43%. [17] Of the three standard insoles studied, poron proved to reduce most shear force when compared to EVA and plastazote.[17]

DISCUSSION

Shear force is an unfavorable factor in the etiology and pathomechanics of diabetic ulcerations. The results from both studies by Zhang et al. demonstrate that shear force has a greater stress effect on superficial soft tissue, in particular, the tissue just distal to where the force is applied.[12] The reduction of blood flow over a stressed area raises concern for the superficial, ischemic soft tissue since insensate diabetic patients are more likely to develop ulcerations from increased vertical and shear forces.

Until recently, there were limited methods for direct shear assessment. For this reason, theoretical models only suggested countermeasures for reduction of shear and vertical stresses through the use of shear-reducing insoles, especially in diabetic patient populations who experience neuropathy, PVD, and structural foot deformities. Lavery et al. acknowledge that in patients with sensory neuropathy and structural foot deformity, the incidence of ulceration ranges from 3-6% a year. However, when compared to a patient that has a history of foot ulcerations, the incidence increases to 19-40% per year.[16] Although therapeutic insoles and footwear in high-risk diabetic patients have shown to decrease the incidence of ulcerations, there is still significant room for improvement. Lavery et al. were able to demonstrate that the displacement of layers within the insole (shear reducing insole and the Glidesoft insole) served to minimize the potential for injury from shear forces, while retaining vertical pressure reduction similar to that of standard insoles. The displacement of the upper pad relative to the lower pad, controlled by the elastic binders, play an imperative role in reduction of peak shear force, which would otherwise affect the surface of the skin throughout ambulation.

Fortunately, the recent discoveries by groups such as Wang et al. have elucidated various other methodologies for measuring shear force.[17] These novel methods may be used in the future to gain invaluable information with regard to cellular breakdown in patient's with various chronic disease management needs (diabetes, PVD, CVD, etc). The data from such future proposed studies would provide the opportunity to develop products more effective in reducing shear force in the lower extremity. Such preventative efforts could serve to dramatically reduce the possibility of ulceration and consequential infection in at risk populations.

A few limitations were present in the studies contained in this review. In the article by Wang et al, the authors freely disclose that their methods of assessing shear force were somewhat compromised by not calculating

the possibility for edge effect. Patients included in the study by Lavery et al. were those that had been prescribed shear-reducing insoles. This may have contributed to a selection bias, as it is known that only a small percentage of patients who are eligible for shoes and insoles actually receive them.

CONCLUSION

Diabetic foot ulceration is one of the most common components in the pathway to limb loss, therefore, treatment and prevention of ulcers is the focus of amputation prevention. Until recently, shear forces have been disregarded or underestimated. Currently, there are no well-accepted measurements of shear forces. Reducing pressures on the soles of the feet with therapeutic footwear and shear reducing insoles are pivotal in the prevention of foot ulcerations.[12,16,17] In addition, diabetic patients should be screened for loss of protective sensation and treated appropriately.

AUTHORS' CONTRIBUTIONS

JA and JF contributed equally to the competition of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors of this paper declare no competing interests, such as but not limited to, organization affiliations or financial restitution.

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The Use of a Dehydrated, Decellularized Human Amniotic Membrane Allograft for a Non-Healing Surgical Wound in a Diabetic Patient: A Case Study

Michael T. Rossidis, BS and Gabrielle Laurenti, BS

Abstract

Introduction
Diabetic wounds can be incapacitating for patients and very difficult to treat. Factors contributing to the delayed healing of diabetic wounds include dysregulation of collagen production, disruption of inflammatory responses, decrease in nitric oxide (NO), as well as a change in the plasma proteins with an alteration in blood viscosity. For these diabetic wounds healing can take weeks or even months due to these physiological changes making it difficult for clinicians to manage. Here we analyze the use of a dehydrated, decellularized human amniotic membrane (DDHAM) to accelerate the healing of a diabetic wound.

Objective
To prove that the use of a DDHAM can enhance and accelerate the closure of a non-healing surgical wound in a diabetic patient following an amputation of the hallux due to osteomyelitis.

Methods
A 57-year-old Hispanic male with Diabetes Mellitus Type II had osteomyelitis of the hallux requiring an amputation up to the first metatarsal phalangeal joint. After a period of prolonged healing, the use of advanced wound healing via DDHAM allograft was applied. Moreover, a literature review was conducted to determine the efficacy of DDHAM for the treatment of a diabetic wound.

Discussion
According to Letendre et al., the majority of diabetic wounds treated with DDHAM showed decreased healing time with no adverse reactions. After prolonged healing and the use of conventional treatment post-amputation, application of DDHAM successfully reduced closure time of the open-amputated surgical site.

Conclusion
Currently, there are many ways that aid in the healing of diabetic wounds. Our case study suggests that using a DDHAM can not only expedite the healing process, but heal the wound with decreased scarring for better cosmetic results. DDHAM should be considered as the standard of care for non-healing diabetic wounds. Randomized controlled studies need to be conducted to further prove the efficacy of this product.

Key Words
Dehydrated, decellularized human amniotic membrane, diabetic foot ulcer, ulceration, amputation

Level of Evidence: 4

INTRODUCTION

Diabetic wounds can be incapacitating for patients and very difficult to treat. Diabetics ulcerate at a rate of 15% to 25% over one's lifetime, and 15% of those patients will likely end up with an amputation.[1] Amputation rates are so high due to that fact that these patients not only carry multiple co-morbidities, but diabetes itself can interfere with the normal healing process. Factors contributing to the delayed healing of diabetic wounds include dysregulation of collagen production, disruption of inflammatory responses, decrease in nitric oxide, as well as a change in the plasma proteins with an alteration in blood viscosity. According to Shah, advanced wound care therapies should not be considered until 4 weeks of conservative therapies have failed to decrease the wound size by at least 50%.[2] Advanced therapies include negative pressure wound therapy, hydroconductive dressings, hyperbaric oxygen, growth factors, biological dressings, skin substitutes, and regenerative materials.[3]

Physicians today have a myriad of skin substitutes to choose from when deciding on how to heal a diabetic wound. Xenografts are tissues derived from one species used on another species, and are most often indicated for temporary (2-4 days) coverage of a clean, partial-thickness wound.[4] Most often xenografts come from porcine dermis or intestine. Autografts are grafts that come from the patients themselves, and are most often divided into split-thickness skin grafts, full-thickness skin grafts, and cultured autologous skin grafts. Allografts are grafts from genetically non-identical individuals of the same species and can consist of epithelial/epidermal, dermal, or a composite of the two. Human amniotic membrane is considered an epithelial/epidermal allograft. Composite allografts, which are constructed of bovine type I collagen, living neonatal fibroblasts and keratinocytes, are considered the closest match to living skin.[4] Lastly, synthetic monolayer and bilayer substitutes are acellular matrices used to promote growth of host tissue and protect the wound from drying and infection.

Human amniotic membrane has been used since 1910 in order to treat burns, neuropathic ulcers, ophthalmic complications, and have been used as wound dressings.[4-6] The innermost layer of the fetal membrane is composed of an avascular tissue called the amniotic membrane, which, in turn, is composed of five layers: the epithelial monolayer, acellular basement membrane, compact layer, mesenchymal cell layer, and spongy layer.[6] Amniotic membrane contains both antimicrobial and anti-inflammatory factors such as: IL-1ra and IL-10 (potent anti-inflammatory cytokines), human β-defensins (mucosal surface anti-microbial) and elafin (antiprotease and antimicrobial).[6,7] Moreover, the membrane provides a fibronectin and collagen matrix, which can mimic normal dermal function and provide a foundation for epithelial growth.[4]

Dehydrated, decellularized human amniotic membrane (DDHAM) allograft is derived from a full-term, healthy pregnancy, and has been shown to expedite the closure of diabetic foot ulcers with biweekly application of the membrane. In-vivo and in-vitro experiments established that DDHAM contains soluble factors that stimulate mesenchymal stem cells for advanced wound healing.[8] Our goal in this study is to prove that the use of dehydrated, decellularized human amniotic membrane allograft can enhance and accelerate the

closure of a non-healing surgical wound in a patient with type II diabetes mellitus following an amputation of the hallux due to osteomyelitis. Healing was defined as complete re-epithelialization of the wound.

CASE STUDY

Presentation

A retrospective chart review is presented of a 59-year-old male with multiple co-morbidities suffering from a long-standing ulcer located on the plantar surface of the right hallux. The patient also complains of pain in the affected hallux. He reported having past ulcerations bilateral sub 1st metatarsal heads that have subsequently healed without complication. He reported having been to podiatrists in the past.

The patient's past medical history includes uncontrolled type 2 diabetes mellitus despite being on multiple oral agents and hypertension, which is controlled. The patient also suffers from bilateral peripheral artery disease and diabetic peripheral neuropathy. The patient denied smoking or ever having smoked.

On initial physical examination, the patient had non-palpable dorsalis pedis (DP) and posterior tibialis (PT) pulses on the right with ¼ DP and PT on the right. The patient presented with an ulceration on the plantar aspect of the right hallux. The area showed no signs of clinical infection. We performed basic wound care and referred the patient to a vascular surgeon to be evaluated.
The patient returned after undergoing an atherectomy to re-vascularize his right lower extremity. At this time, the ulcer was re-evaluated. The ulcer had grown in size and was erythematous, warm, painful, and purulent. The patient was diagnosed with osteomyelitis of the hallux. The decision was made to admit the patient to the hospital for treatment of infection and surgical intervention.

After amputation of the right hallux, the patient was discharged with intravenous Vancomycin to be followed with outpatient care. The patient then returned to the office for a post-operative follow-up. Unfortunately, the surgical site on the 1st MPJ dehisced with no infection and went on to poor healing. The patient's subsequent weekly visits consisted of sharp debridement, forefoot offloading with Darco shoe gear and sterile dressings without noticeable signs of closure for 4 weeks.

Treatment

After 4 weeks of standard wound care therapy, it was decided to use a DDHAM allograft to expedite the closure of the dehisced surgical site (Figure 1). The wound was carefully debrided in order to make sure any fibrotic and hyperkeratotic tissue was removed. We also confirmed the absence of any infection or osteomyelitis in the surrounding bone before application. The patient was seen and evaluated weekly and dressings were changed with decreasing size of wound site.

Results

On day 1, the dimensions, before application of the DDHAM allograft, were 3.4cmX3.5cmX0.5cm (Figure 1). The patient returned at 4 weeks with the new dimensions

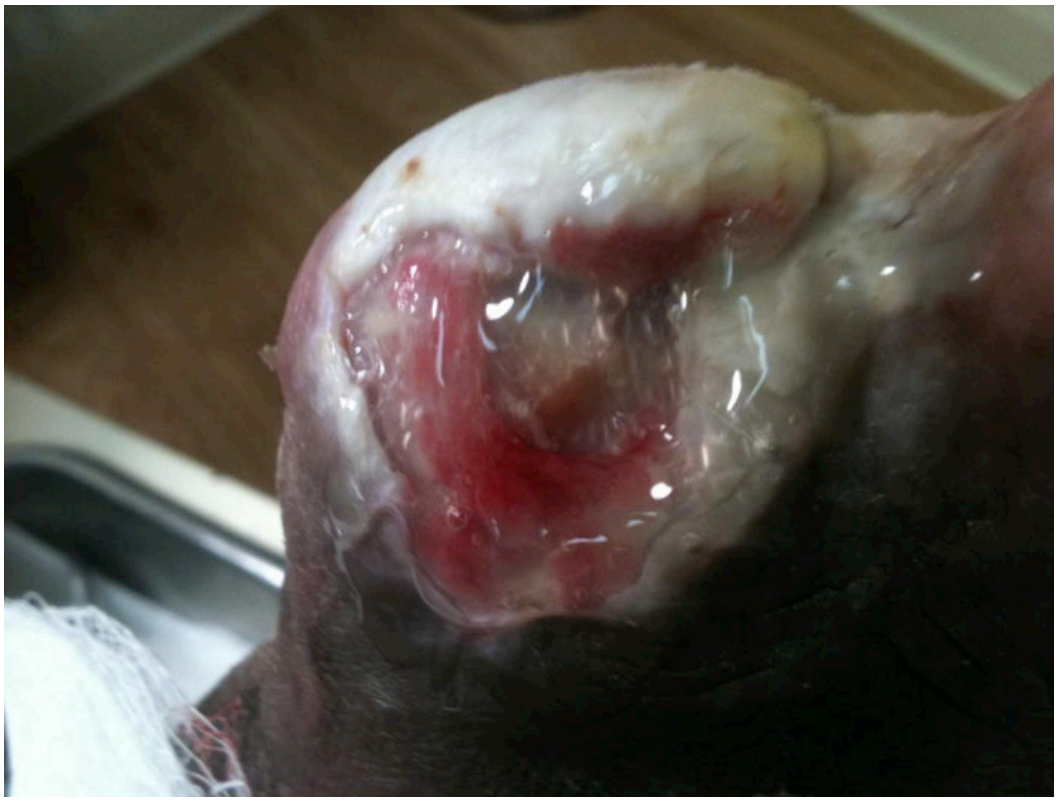

Figure 1: Day 1 after application of BIOVANCE Dehydrated Human Amniotic Membrane Allograft

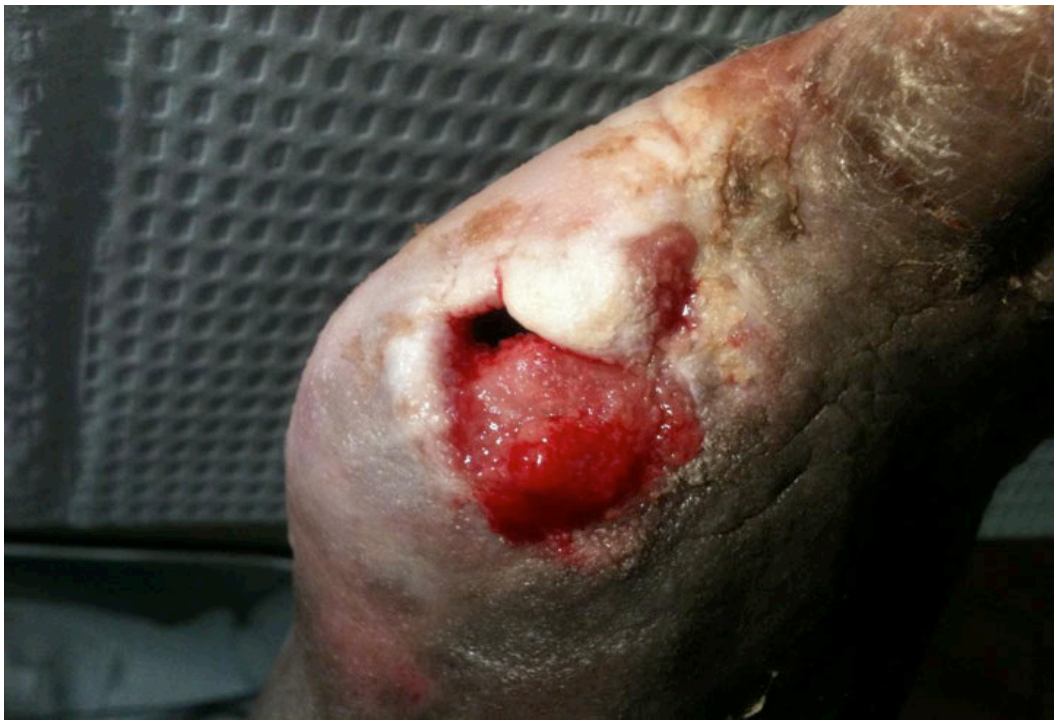

Figure 2: Four weeks after application of allograft

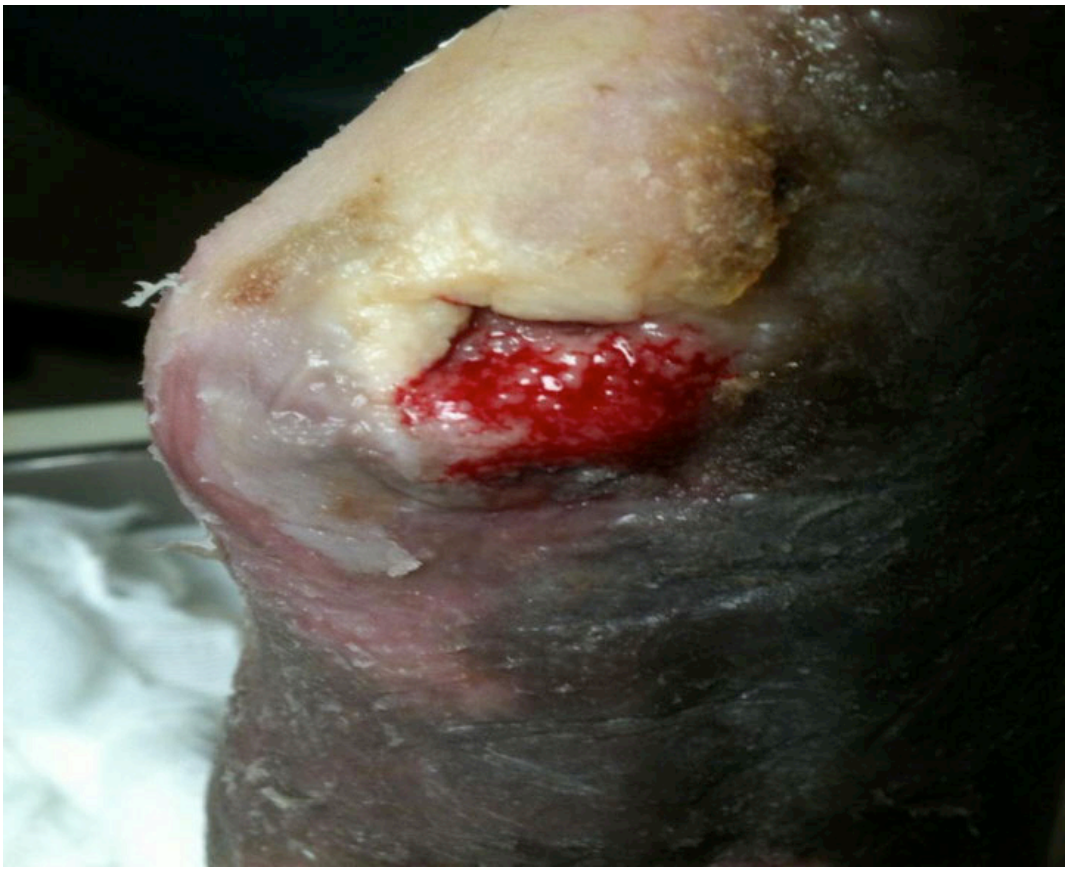

Figure 3: Five weeks after application of allograft

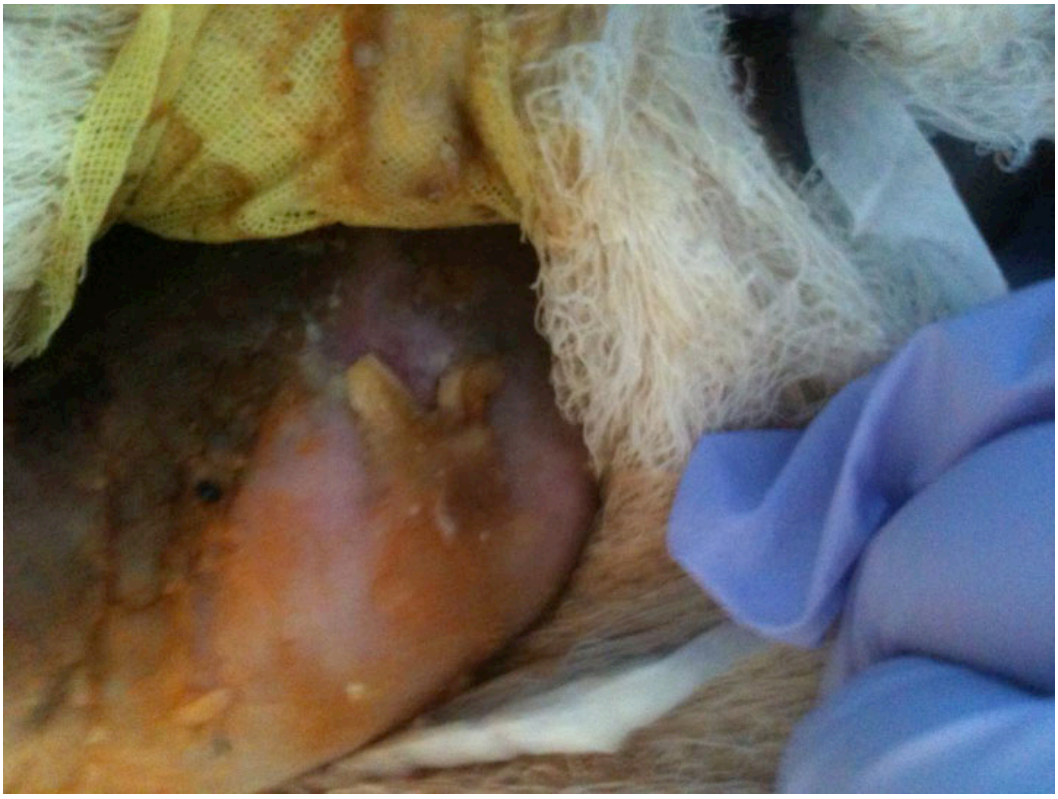

Figure 4: Six weeks after application of allograft; ulceration has healed

reading of 2.2cmX2.7cmX0.1cm (Figure 2). At this time, there were no signs of infection, and there was a granular base noted. At 5 weeks post-allograft application, the wound measured at 2.6cmX2.4cm (Figure 3). The wound became superficial with a healthy granular base. Full wound closure and healing was noted at week 6 indicating a successful outcome (Figure 4).

DISCUSSION

The literature states that wounds failing to heal to 50% of its original size over a 4-week period of conservative treatment necessitate the use of advanced therapy.[8] Recent literature shows that amniotic membranes have been used in a variety of situations, such as, but not limited to, burns, diabetic wounds, gynecologic surgery, orthopedics and eye surgery.[2] There have been many advanced wound therapies and products, including human skin equivalents, wound modulators, and growth factors. All have shown to accelerate healing, but cannot be considered a true replacement of skin. Most importantly, no one substitute exists to solve all wound presentations.[1]

Gruss et al. discussed that the DDHAM showed ultrasonic and functional similarities between fetal skin and amnion, purposing the idea that DDHAM can be considered a fetal allograft.[5] Zelen et al. reported in a prospective, randomized comparative study that the weekly application of DDHAM to patients with diabetic chronic foot ulcers healed in an average of 2.4 weeks versus a biweekly application, which healed in 4.1 weeks. Moreover, 90% of the participants in the weekly application group showed complete healing versus only 50% in the biweekly group.[8] When compared to a composite allograft, Veves et al. found that patients treated with weekly graft changes for up to four weeks had only 56% of patients healed at the 12-week mark.[9]

DDHAM has shown to have anti-microbial agents, such as lysozyme, progesterone, and allantoin.[5] In 1973, Robson et al. showed that when compared to other allografts and xenografts, human amniotic membrane decreased bacterial counts in open granulating wounds more in xenografts, but the same amount in allografts.[10,11]

This case study showed promising use of DDHAM with one time application in an uncontrolled diabetic patient with a chronic non-healing ulcer. Although most studies report multiple applications of DDHAM with complete healing, we show that with proper one-time application complete healing can occur in a chronic wound. Future studies need to investigate the cost-benefit analysis of using DDHAM versus other skin allografts on the market. Moreover, multicenter, randomized control studies need to address the efficacy of DDHAM versus composite allografts and other autografts. Although the concept of using human amniotic allografts has been around for decades, more research needs to be conducted to further evaluate the effectiveness of DDHAM for chronic non-healing ulcers of a variety of origins.

CONCLUSION

DDHAM has been shown to be cost-effective, easy to handle, has long-term shelf life, and requires no refrigeration. Reducing healing time of diabetic ulcers with advanced skin substitutes will ultimately reduce healthcare

costs, decrease the chances of further infections, and improve patient satisfaction. For these reasons, DDHAM should be a go-to treatment option in the arsenal of advanced wound care therapy for physicians treating chronic diabetic wounds.

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AUTHORS' CONTRIBUTIONS

MR and GL contributed equally to the writing and literature review of this manuscript. AI was the podiatric surgeon responsible for the case and subsequent office and hospital evaluations.

STATEMENT OF COMPETING INTERESTS

The authors of this paper declare no competing interests, such as but not limited to, organization affiliations or financial restitution.

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Prognostic Factors of Ewing Sarcoma in the Foot: A Systematic Literature Review

Sara Cathcart, BA, Kelly Noonan, BS, and Emily Sanphy, BS

Abstract

Introduction
Ewing Sarcoma (ES) is the second most common primary malignant bone cancer in adolescents. It is most often diagnosed anatomically in long bones, while its manifestation in the foot is rare and recorded to be approximated 5% of all anatomic locations. The rarity of this neoplasm in the foot often contributes as a factor in delayed or missed diagnosis. The purpose of this paper will be to give a comprehensive literature review and analyze the prognostic factors of ES in the foot, location of the tumor and delay of diagnosis.

Study Design
Systematic Review of the Literature

Methods
A PubMed search was conducted using key words 'Ewing Sarcoma' and 'Foot' as well as 'Ewing Sarcoma' and 'Tarsal bone'. Inclusion criteria involved case reports or case series written after 1990 and concerned Ewing sarcoma in the foot bones. Particular attention was given to articles pertaining to pathogenesis and to diagnosis of Ewing Sarcoma. Exclusion criteria were Ewing Sarcoma reports not involving the foot or articles dated prior to 1990. Articles written before 1990 were excluded due to the lack of diagnostic testing and treatment options available prior to that time.

Results
A total of nine case reports were included for analysis.. Ewing sarcoma most commonly occurs in long bones of adolescents between the ages of 5-20 years old, rarely manifesting in the foot. Ewing Sarcoma of the foot was found to grow 10-20 times slower than bone cancers in other locations. Radiologic evaluation seems to have less of a prognostic power in the outcomes of treatment when compared to the location of the lesion.

Conclusion
Ewing Sarcoma has a significantly slower growth rate in the bones of the foot than in other parts of the body. Delayed diagnosis and location of the tumor appear to affect the prognosis of Ewing Sarcoma in the foot; however, based on the reviewed cases, no conclusions can be made to differentiate the importance of radiographic imaging, timing of diagnosis and affective treatment on the prognosis of Ewing's Sarcoma of the foot. Recommendations for the future should include higher level of studies and research into additional factors that may affect the prognosis of Ewing Sarcoma in the foot.

Key Words
Ewing Sarcoma, Foot, Tarsal bone.

Level of Evidence: 4

INTRODUCTION

Ewing Sarcoma (ES) is currently the second most common primary tumor in children and adolescents. ES is most likely to manifest in the long bones and the pelvis with a predilection for the diaphyseal portion of the bone.[1] In less than 5% of patients the lower limb is the primary site of the tumor, making ES of the foot an extremely rare manifestation. The mean age of diagnosis occurs in the second decade of life for all skeletal locations of ES and it is almost twice as common in males as in females.[1,2]

Clinical Presentation

Clinically, ES will usually present as a localized, non-mechanical, painful swelling for several months. In children, this pain can often be mistaken for "bone growth" or common childhood injuries.[1] More nonspecific symptoms such as fever and general malaise may occur in one third of the patients, and are usually associated with a more advanced stage of ES.[1]

Diagnosis

Diagnostic tests of ES include imaging modalities such as X-ray, CT, and MRI. Classic radiographic features include lytic bone lesions, periosteal reaction, cortical bone destruction, and a possible soft tissue mass.[3] These findings are more classically present in metatarsals and phalanges. However, according to Baragas et al, when present in the more proximal tarsal bones, a more atypical appearance can occur. From these results, it was suggested that such atypical findings may lead to a misdiagnosis in hindfoot ES and therefore could lead to a worse prognosis. Further imaging studies of the chest, along with bone scans, are utilized to look for metastasis, a common complication of ES. Metastasis on initial visit is present in ~25% of cases, with the most common sites being the lungs, skeletal system, and bones or bone marrow.[1] Only 10% of patients diagnosed with ES have multiple bone involvement.[4] It has been hypothesized by Jalal et al that patients who have "skip lesions," a secondary area of known tumor cells within the same bone as the primary lesion, may confer a worse prognosis even if there is absent metastasis.

A definitive diagnosis of ES is confirmed upon biopsy via fine needle aspiration, core needle biopsy, or open biopsy. It requires a trained pathologist to identify ES in its early stages as it can be difficult to diagnose. Histologically, ES is composed of small round blue cells arranged in sheets.[1] 95-100% of cases of ES are positive for the cell-surface glycoprotein CD99. Cytoplasmic glycogen can be found in a Periodic Acid Schiff (PAS) stain and is indicative of ES. In addition to biopsy, molecular genetic studies such as fluorescence in situ hybridization (FISH) or reverse transcription-polymerase chain reaction (RT-PCR) may be used to definitively diagnosis Ewing Sarcoma. In 85% of ES tumors there is a translocation of chromosomes 11 and 22, and in 20% of those cases, an additional translocation of chromosomes 1 and 16 is present.[1] In t(11;22), the *ews* gene on chromosome 22 is rearranged to come in contact with *flil* or an *flil*-related gene. These genetic markers allow for appropriate diagnosis of ES.[1]

Common clinical differential diagnoses include: essential bone cysts, osteomyelitis, rheumatic osteitis, and rhabdomyosarcoma.[6] ES has also been misdiagnosed as a healing

fracture, a hemangioma, trauma, Lyme disease, gout, tubercular infection of bone and tendonitis.[1,6-9] Given the similar clinical and radiographic findings, the most common misdiagnosis of ES is osteomyelitis.. In 2003 Metcalfe reviewed twelve cases of ES in patients over a 30 year period. Seven of the patients were originally treated as osteomyelitis, but were later re-evaluated when they did not respond to antibiotic treatment.[10]

Treatment

Treatment options for patients with ES of the lower extremity include chemotherapy with adjunct surgical resection and/or radiation therapy. Prior to chemotherapy becoming a main component of treatment for ES, less than 10% of all patients survived.[1] This high percentage of deaths was startling due to the proven radiosensitivity of the tumor, however most patients were deceased within two years due to metastases of the tumor.[1] When planning amputations, below knee amputations (BKAs) are generally reserved for local relapse of disease.[2] Local recurrence is rare and often fatal, however approximately 80-90% of patients treated with local surgery or radiation will relapse in a distant location.[2] The National Cancer Database states there is a 5 year survival rate of 50.6% for patients with Ewing sarcoma across all sites in the body.[2]

Amputation at one time was considered the gold standard for local treatment of ES, but innovations in medical procedures and technologies have led to limb salvage having a more prominent role. Amputation alone does not lead to better survival results.[6] According to San Julien et al, limb salvage allows the patient to have a better functional outcome without compromising the clinical result.[6] In order for limb salvage to be optimally performed, there must be necrosis caused by chemotherapy treatment.[6] Using clear surgical margins after appropriate chemotherapy treatment, surgeons are now able to perform limb salvage procedures that do not affect the patient's likelihood of local recurrence.[6] According to a study performed by Casadei et al in 2004, patients who were treated with a combination of chemotherapy, radiotherapy, and surgery had the best outcomes as compared to patients treated with the combinations of chemotherapy and radiation, amputation and chemotherapy, chemotherapy and surgery, and/or solely a below knee amputation.[11]

In review of prognostic factors influencing survival rate, there is limited data available. This is likely due to atypical presentations that can be seen on X-ray, delay in diagnosis, and misdiagnosis. On radiography, ES of the tarsal bones often does not present with the same features as ES of a long bone.[12] As x-ray is one of the first steps towards diagnosing diseases of the bone, radiographic confusion can lead to a delay in correct diagnosis for patients with ES. Of all the bones of the foot, the calcaneus is the most commonly affected by all osseous tumors.[12] However, there are other more common diseases affecting the bones of the foot that mimic ES, and other bone tumors, both in a clinically and radiological manner. Because of this mimicry, there is often a delay in diagnosis of ES of the foot.

In 2004 Casadei et al presented on the prognostic factors of tumor site and treatment, of 36 patients with ES treated at their clinic in Italy from 1973-2000.[11] However, they were unable to come to any definitive conclusions

and to date, there are no further studies on this topic. Therefore, the purpose of this paper will be to analyze the prognostic factors influencing ES of the foot with particular attention to timing of diagnosis, onset of symptoms and location of the tumor.

METHODS

Three authors conducted independent literature searches using the online PubMed database with MeSH terms 'Ewing sarcoma' and 'foot'. The initial search for solely 'Ewing sarcoma' revealed 6,692 articles. By adding the MeSH term 'foot' the number of results decreased to 105. Inclusion criteria consisted of case reports or case series written after 1990 and involved ES manifestations in the foot bones. Based off of the title and abstract, eight cases fit this inclusion criteria. Any reports published prior to 1990 were excluded as were cases that focused on patients with comorbidities. To find additional case reports the search was further defined with the key words 'Ewing sarcoma' and 'tarsal bone' which returned 34 articles, one of which fit the inclusion criteria.

RESULTS

Nine case reports were reviewed from eight publications between 1990 and 2011. The average age of the patients in the cases was 15 years, with a range between ages 10 and 23 years, of which five were males and four were females. There were six right feet and three left feet involved. Four cases involved the calcaneus; two involved metatarsals; one involved the phalanx; one involved the cuboid; and one was multifocal and involved the cuneiforms, metatarsals, phalanges, and talus. Information including reference, age and sex, primary location of tumor, time lapse from onset of symptoms and diagnosis of ES, presence of metastasis at time of diagnosis, treatment modality, and outcome of each of these cases were summarized in Table 1.

The average time lapse between the onset of symptoms and diagnosis was 5.8 months, with the delay in diagnosis ranging from 1 month to over 12 months. Four of the nine cases were misdiagnosed, either as osteomyelitis, tuberculosis or calcaneal fracture, on initial visit. Two of the nine cases reported metastasis at the time of diagnosis. Eight of the nine cases were treated with chemotherapy, while the remaining case did not include any information on treatment plan. Of the eight reporting cases, five of the treatment plans included additional local control by surgical removal only; two with adjunct radiation therapy only; and one case included local control with both surgical intervention and radiation. Two of the nine reports failed to include follow up visits or patient status. Of the seven reporting cases, five patients were alive at the time of their follow up. Two of the nine reports documented the patient's death to ES-related problems.

DISCUSSION

According to a study by Brontzmann in 2013, it was found that patients with a delay in diagnosis of less than one year, versus greater than one year, failed to show a significant difference in 5-year and 10-year survival rates.[12] Brontzmann also noted a 2-6 times

Source	Age/ Sex	Primary Tumor Location	Initial Diagnosis	Time between onset of symptoms & diagnosis of ES	Metastasis present at time of diagnosis (Y/N)	Treatment	Outcome
Goodwin 1990[7]	10/F	Right 3rd metatarsal	Healing fracture	2 months	No	N/A	N/A
Cara del Rosal 1994[8]	23/M	Left 1st distal phalanx	Ewing Sarcoma	6 months	No	Amputation +chemotherapy	Alive at 10 years
Exner 1998[13]	12/F	Right 1st and 2nd metatarsal	Ewing Sarcoma	4 months	No	Chemotherapy, resection + reconstruction	Alive and well 41 months
Metcalfe 1998[10]	11/M	Right calcaneus	Osteomyelitis	8 months	N/A	Chemotherapy + radiotherapy	Alive at 6 years
Metcalfe 1998[10]	17/F	Left cuboid	Osteomyelitis	3 months	N/A	Chemotherapy + BKA	Alive at 5 years
Gupta 1999[14]	19/M	Right calcaneus	Tuberculosis	> 8 months	No	Chemotherapy + radiotherapy	Death 10 months after treatment due to pulmonary metastasis.
Rammal 2008[4]	10/M	Cuneiforms, cuboid, 2nd metatarsal, 1st phalanx & talus of left foot	Ewing Sarcoma	>1 month	Yes: multiple lesions found in lungs	Chemotherapy + BKA + radiation of lung	1 year follow up: free of local & systemic disease.
Jalal et al 2011[5]	14/M	Right calcaneus	Ewing Sarcoma	12 months	Yes; skip lesion metastasis to Talus	Chemotherpy + BKA	Death 6 months after diagnosis
Traki et al 2011[15]	16 F	Right calcaneus	Ewing Sarcoma	>1 year	No	Chemotherapy + planned surgical resection	N/A

Table 1: Overview of Nine Case Reports

longer delay in diagnosis of ES in the foot as compared to other sites of the body, but found that the death rate of ES in the foot was still "in the same range of sarcomas at other sites."[12] San Julian also concluded that delay in diagnosis was not statistically associated with a poorer prognosis.[6]

In both of the cases that reported patient death, the calcaneus was the primary location of ES. The 19 year old male described by Gupta et al in 1999 presented with a five-month history of heel pain and was originally diagnosed with tuberculosis of the heel based off increased leukocytosis and increased ESR in lab studies, as well as expansion and

sclerosis of the calcaneus on X-rays.[14] When three months of tuberculosis treatment failed, biopsy was performed and revealed ES. Although this patient was alive at a 6 month follow up after chemotherapy and radiation (the patient had refused amputation), he died 10 months after treatment due to lung metastasis. In the second case report by Jalal et al in 2011, a 14 year old boy with a year-long history of pain and swelling of the right foot was initially diagnosed with ES.[5] Metastasis to the talus was present at the time of diagnosis. Treatment included chemotherapy and below knee amputation. Although this patient was reported to have no signs of local recurrence or metastasis at his follow up, this patient reportedly died six months after treatment also due to lung metastasis.

Overall, four cases of ES in the calcaneus were reviewed. Three of the patients had reported follow ups, while one case was still undergoing the treatment process at the time of the article's publication. Of the three cases with known outcomes, one patient was alive and cancer free at the 6 year follow up, while the other two patients were deceased due to lung metastases. The patient who was living at the 6 year follow up showed no evidence of metastases, to the lung or other areas of the body. The same patient was diagnosed in less than 8 months and began treatment with chemotherapy and radiation. The two cases in which the patients were deceased had an 8 month or greater delay in diagnosis before they were able to begin the appropriate treatment.

In contrast to the aforementioned case of talar skip metastases present at diagnosis, a case report was reviewed from 2008 on a 10 year old male who presented with lung metastasis at the time of diagnosis.[4] This patient, as described by Rammal et al, had symptoms for about one week before seeking medical attention, and was diagnosed with ES a little after one month.[4] ES was found in several bones including the hallucal phalanx, the second metatarsal, cuboid, cuneiforms and the talus of the left foot, along with metastatic pulmonary lesions. The calcaneus was not affected in this case. Treatment included chemotherapy, radiation therapy, and a BKA. At a one-year follow up, this patient was found to be disease free with no signs of recurrence.

A review of these nine case reports also suggest that the time of diagnosis after start of symptoms and location of primary tumor are not mutually exclusive. Although the two case reports that resulted in death involved the calcaneus, both patients showed symptoms for at least eight months before a proper diagnosis. In addition, the patient with multifocal ES in several bones of the left foot that did not include the calcaneus had lung metastasis at the time of diagnosis and still had a positive outcome at the time of follow up. However, this patient was diagnosed with ES in under two months. Therefore, we cannot separate location and time lapse before diagnosis in consideration of prognostic factors.

Our analysis of prognosis of ES in the foot was restricted by the limited number of case studies and case reports available regarding ES in the foot. We attribute this limitation to the rarity of ES manifestation in the lower extremity, especially in the foot bones. Of the nine cases obtained, two of them were lost to follow up, thereby leaving relevant analysis of only seven cases of ES in the foot.

CONCLUSION

Based on a review of case reports from 1990 to the present on ES manifestations in the foot, we find that the two major factors include: location of the primary tumor, specifically the calcaneus, and delay in diagnosis. As ES is a rarely occurring tumor in the bones of the foot, it is difficult to obtain a large enough sample size in order to fully identify the most important prognostic factor. Based on the literature review, these case reports do not have supportive evidence to pinpoint one specific prognostic factor that, if altered, could affect the prognosis or survival rate of ES.

With the daily advent of new technology in the medical field, we recommend that more research be done on the varying prognostic factors of ES of the foot. Based on the errors in diagnosis of the reviewed case reports these should include but are not limited to: the affected bone of the foot, the radiographic findings, the delay to correct diagnosis, use of inappropriate treatments for incorrectly diagnosed diseases, and location of metastases. Future studies should be conducted so that in the rare occasion of treating a patient with ES of the foot, the appropriate diagnosis and prognosis can be made in a timely manner.

AUTHOR'S CONTRIBUTIONS

All authors contributed equal parts of research, writing, and compilation of this literature review.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Minimally Invasive Surgical Options for Chronic Plantar Fasciitis: A Literature Review

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Abstract

Introduction
The purpose of this study is to review the current literature of minimally invasive surgical options for chronic plantar fasciitis treatment. This study aims to compare the efficacy of three procedures: endoscopic plantar fasciotomy, radiofrequency nerve ablation, and cryosurgery.

Study Design
Qualitative Systematic Review of the Literature

Methods
An English language general literature search using the online search database PubMed was performed. Inclusion criteria included: articles written after 2007, heel pain for at least 6 months and failed conservative treatment, measurement of pain using the visual analog scale (VAS), a follow-up time of at least 4 months. Exclusion criteria included: subjects with prior surgery in the heel area/region, subjects with peripheral neuropathies and radiculopathy, or measurement of pain through a scale other than a VAS.

Results
Six articles were obtained through the PubMed database that met the criteria for the study. Visual analog scale scores measured preoperatively and postoperatively were used comparatively among the studies reviewed. Endoscopic plantar fasciotomy, radiofrequency nerve ablation and cryosurgery all proved to decrease pain based on VAS score and have minimal adverse effects.

Conclusion
It was evident from this review that endoscopic plantar fasciotomy, radiofrequency nerve ablation and cryosurgery are all optimal procedures for the treatment of chronic plantar fasciitis and improving heel pain. Due to their minimally invasive nature, they decrease surgical trauma, operating time, and time to return to weight-bearing activities.

Key Words
Plantar fasciitis, heel pain, radiofrequency nerve ablation, endoscopic plantar fasciitis, cryosurgery

Level of Evidence: 4

INTRODUCTION

Podiatrists frequently encounter plantar heel pain as one of the most common presenting complaints in the foot and ankle. In fact, approximately 11-15% of adult foot symptoms which require professional care are ultimately diagnosed as plantar fasciitis (PF).[1, 2, 3, 4] It has been estimated that 1 in 10 individuals will develop PF during their lifetime.[5] Regardless of the high prevalence of PF, the exact pathogenesis of it is still unknown.

The plantar fascia has a direct proximal fibro-cartilaginous attachment to the calcaneus. It originates from the medial process of the calcaneal tuberosity and separates distally into five separate strands, which attach at the forefoot. The skin overlying the heel is innervated by the medial calcaneal nerve. If compressed, this may present with heel pain and symptoms similar to PF. Baxter's nerve, which is the first branch of the lateral plantar nerve, may be at risk for compression as well because it lies between abductor halluces and the medial belly of the quadratus plantae muscle.[6]

The diagnosis of PF is typically made clinically and rarely requires further investigation.[7,8] The patient with PF complains of pain on the plantar aspect of the heel, which may be medial or lateral. The pain is usually most noticeable on initial steps after a period of inactivity and lessens with increasing level of activity during the day.[9] Symptoms may become worse following prolonged weight-bearing, and are often precipitated by an increase in weight-bearing activities. PF is usually unilateral, but up to 30% of cases have a bilateral presentation. Occasionally the pain may spread throughout the entire foot including the toes. The clinician may be able to elicit pain over the medial calcaneal tuberosity with palpation and the pain may exaggerate on dorsiflexion of the toes or standing on tip-toes.[10]

The clinical course for most patients is resolution of symptoms within a year with employment of conservative measures.[11] However, the resolution time may be anywhere from 6 to 18 months and sometimes longer.[10] An abundant number of conservative interventions have been described and are used for treatment of PF. These interventions include: rest, heat, ice pack, non-steroidal anti-inflammatory drugs (NSAIDS), heel pads, night splints, walking cast, taping, plantar and Achilles stretching, ultrasound, and steroid injection.[2,5] When conservative treatments fail to be effective after 6-12 months, minimally invasive PF treatments may be considered to resolve heel pain. These include: endoscopic plantar fasciotomy, radiofrequency nerve ablation, and cryosurgery. Unfortunately, few high-quality randomized, controlled trials have been made to support these therapies.

Endoscopic plantar fasciotomy (EPF) is a minimally invasive surgical treatment for chronic plantar fasciitis. The procedure was first described and recommended by Barrett and Day in 1991 as an alternative to the traditional open technique for release of the medial fascia. EPF is optimally performed under general or regional anesthesia, with the patient in supine position. A vertical incision is made anterior and inferior to the medial calcaneal tubercle and lateral aspect of the heel, and a blunt dissection is performed to the level of the fascia. A fascial elevator is used to create a channel immediately inferior to the plantar fascia. An arthroscope is then

introduced from the medial portal for visualization of plantar fascia. A hook knife through the lateral portal is used to divide the medial half of the plantar fascia from medial to lateral direction. The lateral half of the fascia remains intact. Incisions are closed with one suture and dressings applied to the foot. Patient should begin weight-bearing to tolerance (WBTT) within the first 24 hours.[12]

The radiofrequency nerve ablation (RFNA) procedure is performed by inserting a probe into the area of tenderness (generally the medial calcaneus), and the electrode creates a local agitation converting electrical energy into heat. Protein denaturation and cell death of the tissue occurs as a result of heat agitation. Multiple different radiofrequency nerve ablation systems exist but all utilize this general principle. Each RFNA study reviewed used a different system, and differed minimally from one another. RFNA has been employed in the management of various podiatric medical conditions including Morton's neuroma, verrucae, and ingrown toenails. RFNA has been used as a treatment option for plantar fasciitis that has not been relieved by conservative measures. RFNA targets and disrupts sensory nerves in the area of chronic inflammation. With the elimination of the neurogenic cause of the heel pain, relief can be achieved.[13]

Cryosurgery uses the same principle as cryotherapy to apply an analgesic effect to much deeper layers of the body while being minimally invasive. Cryosurgery involves inserting a handheld cryoprobe percutaneously to destroy pathologic tissue or cells at temperatures reaching –70°C. These extreme temperatures are useful in freezing the intracellular elements of a nerve, and can be employed as a minimally invasive treatment in plantar fasciitis (PF). By using a cycle of freezing, thawing, and freezing again, axons and cellular elements will rupture and, in theory, alter the pain pathway. The epineurium and perineurium remain intact, which prevents neuroma formation. When applied to PF treatment, the cryoprobe is used on the nerve that is responsible for registering the pain felt, most commonly branches of the medial calcaneal nerve. It has been postulated that cryosurgery also has the ability to destroy inflammation along the plantar fascia.[14]

The purpose of this study is to review the current literature of minimally invasive surgical options for chronic plantar fasciitis treatment. This study aims to compare the efficacy of three procedures: endoscopic plantar fasciotomy, radiofrequency nerve ablation, and cryosurgery. The procedures were compared based on advantages, disadvantages and negative outcomes reported by the literature. Visual analog scale scores measured preoperatively and postoperatively were also used comparatively among the studies reviewed.

METHODS

All three authors performed an English language general literature search using the online search database PubMed. Search terms included "plantar fasciitis," "heel pain," "radiofrequency nerve ablation," "radio-frequency nerve ablation," "endoscopic plantar fasciotomy," and "cryosurgery." General searches yielded 54 results. Based on inclusion criteria determined by the authors, papers fulfilling the following conditions were included: articles written after 2007,

subjects with heel pain located at the plantar aspect of the heel for at least 6 months, measurement of pain on a visual analog scale, subjects who were resistant to conservative treatments, and a follow-up time of at least 4 months. Based on exclusion criteria decided by the authors, articles containing any of the following characteristics were excluded: subjects with prior surgery in the heel area/ region, subjects with peripheral neuropathies and radiculopathy, or measurement of pain through a scale other than a VAS. When applying these criteria, 6 papers were retained and included in this review via PubMed.

RESULTS

After reviewing the six articles that fit our criteria, a chart comparing study design, recruitment of patients, sample size, age, sex, study duration, and mean preoperative and postoperative VAS scores was created (Table 1). The VAS score results reported in each article reviewed were averaged preoperatively, at one month, at three months and at one year based on the procedure. The averages for VAS score are represented in the histogram below (Figure 1).

DISCUSSION

Endoscopic Plantar Fasciotomy Results

A prospective study by Othman et al. compared the results of 37 patients who underwent either EPF or extracorporeal shock wave therapy (ESWT) in the treatment of chronic plantar fasciitis. Seventeen (8 males and 9 females) patients chose to undergo endoscopic release of plantar fascia. For the

	Endoscopic Plantar Fasciotomy		Radiofrequency nerve ablation			Cryosurgery
	Othman et al.	Fallet et al.	Erken et al.	Cione et al.	Landsman et al.	Allen et al.
Study Design	Prospective Cohort	Retrospective Cohort	Prospective Cohort	Retrospective Cohort	Prospective RCT	Prospective Cohort
Recruitment	Madina National Hospital and Al-Rahma Hospital, Al-Madina Al-Munawara, KSA.	Oakwood Annapolis Hospital, Oakwood Healthcare System	Anadolu Medical Center	Podiatry Associates of Belleville, Belleville NJ	Division of Podiatric Surgery, Cambridge health alliance	Oakwood Healthcare System
Total sample size	17 patients	22 patients (23 feet)	29 patients (35 feet)	75 patients	17 patients	59 patients (61 feet)
Mean age	42 years (range 29-59)	50.3 (range 16-69)	47.4 years (range 30-88)	55 years (range 24-83)	Not Stated	46.6 years (range 24-74)
Sex	9 females 8 males	15 females 7 males	15 females 14 males	50 females 25 males	Not Stated	42 female 17 male
Study Duration	14 months	1 year	2 years	36 months	4 months	1 year
Pre-op VAS Score	9.1	7.26	9.2	9	7.38	8.38
Post-op VAS Score	1.6	0.29	1.3	1	1	1.26

Table 1: Study Characteristics and Outcomes

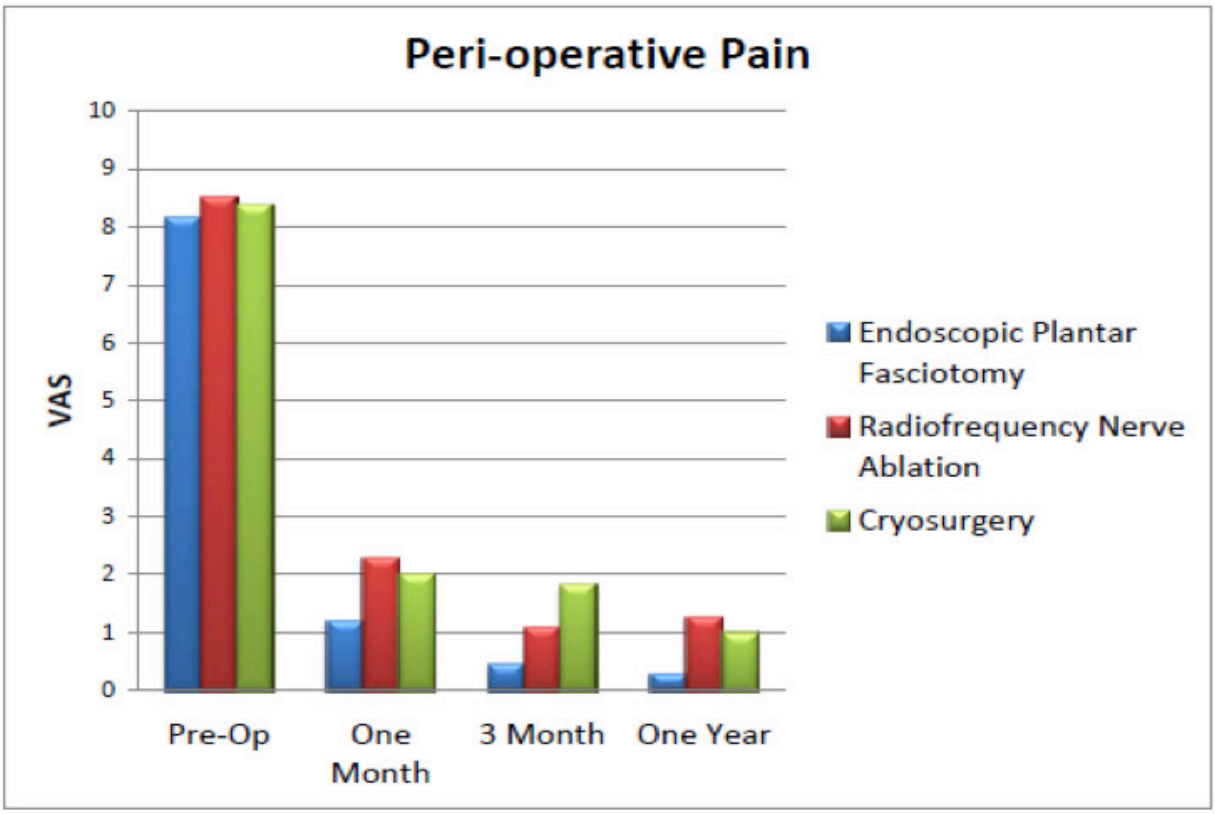

Figure 1: Histogram comparing perioperative pain in patients undergoing Endoscopic Plantar Fasciotomy (n=39 patients [40 feet]), Radiofrequency Nerve Ablation (n=121 patients [127 feet]), Cryosurgery (n=59 patients [61 feet]), VAS (visual analog scale).

results, patients in the study completed a questionnaire preoperatively, at 3 and 6-month follow-up visits. Pain level was evaluated using VAS scale when getting out of bed, at rest, and after activity. The mean follow-up for the patients who underwent EPF was 11 months (range 8-14 months). The average preoperative pain was 9.1, ranging from 8-10 on the VAS scale. Postoperatively, the pain decreased to an average of 1.6 (range 0-6). According to patient's questionnaire, 64.7% of patients (11 patients) had severe limitation of activities, and 35.3% of patients (6 patients) had moderate limitation of activities preoperatively. Ten patients had no functional limitations postoperatively, and six patients had minimal functional limitations. Only one patient had moderate functional limitation postoperatively.[15]

A retrospective study by Fallat et al. compared the postoperative outcomes of 53 patients (55 feet) who underwent surgical treatment of plantar fasciitis by either open fasciotomy with heel spur resection (OFHR) or EPF. The authors reviewed charts of patients who underwent either EPF or OFHR by the same surgeon (L.M.F.) from July 2007 through December 2009. Data were collected from the patients' medical records, which included pain levels using the visual analog scale (VAS) preoperatively, and at 1, 3, 6, and 12 months postoperatively. The EPF group included 22 patients (23 feet), 7 males and 15 females, with a mean age of 50.3 years. For

the purpose of this review we looked at the results only of the EPF group. The mean preoperative pain level in the EPF group was 7.26 (range 6.46 to 8.07). The mean pain intensity at the first postoperative visit of one month was 1.57 and 0.45 at 3 months postoperatively. The average one year postoperative VAS score was 0.29. The average time to return to full activity was 3.37 weeks (range 2 to 7) for patients who underwent EPF.[16]

Radiofrequency Nerve Ablation Results

Erken et al. prospectively evaluated the results of RFNA treatment used on 35 feet in 29 patients between 2008 and 2011. For the results of this study, a statistical analysis of VAS scores was performed. The average VAS scores of the patients as a whole were 9.2 ± 0.8 before treatment, 1.2 ± 1.3 at 1 month after the procedure, 1.5 ± 1.7 at 1-year follow-up, and 1.5 ± 1.6 at 2-year follow-up. The VAS scores prior to treatment, at 1 month after the procedure, and at 1-year and 2-year follow-up, were determined to be statistically significant. In the evaluation of the patients' feet, 85.7% of the patients (30 of 35 feet) rated their treatment as very successful or successful. Erken et al. deemed the radiofrequency nerve ablation treatment successful at both 1-year and 2-year follow-up due to the post op VAS score.[17]

Cione et al. performed a retrospective analysis of 75 consecutive patients with recalcitrant plantar heel pain caused by calcaneal neuritis, all who were treated with radiofrequency thermal lesioning (RTL). The median age of the cohort was 55 (range 24 to 83) years, 25 (33.3%) of the patients were male, 50 (66.7%) of the patients were female, and 15 (20%) of the patients were treated for bilateral heel pain caused by medial calcaneal neuritis. The median duration of follow-up was 18 (range 12 to 36) months. Each patient was asked to rate his or her heel pain using a 10-cm VAS. The median preoperative VAS score was 9 (range 2 to 10), whereas the median long-term postoperative VAS score was 1 (range 0 to 8). The authors of this study determined this difference to be significant (P=0.0001). Pain was reportedly reduced by approximately 79.7%, based on the 10-cm VAS pain measurement pre- and postoperatively. Recurrent plantar heel pain was reported by 5 of the patients who underwent the procedure. The 5 patients, who reported recurrent heel pain, did not experience any other complications related to the RTL procedure. The procedure relieved plantar heel pain in 93.3% of the patients. Cione et al. determined that RTL was a safe procedure and associated with a rapid return to regular shoes and weight-bearing activity.[18]

Landsman et al. conducted a multi-center, randomized, prospective, double-blinded study with crossover. Seventeen patients were divided into two groups, with eight initially receiving RFNA treatment and nine initially receiving sham treatment. If no improvement was observed after 4 weeks, a crossover was offered. All of the participants were asked to rate their level of pain before enrollment in the study and at each visit regarding the first step in the morning, overall maximum (peak) pain, and the average pain level. Evaluations were performed on a 10-point visual analog scale. Pain evaluation was performed by the patient and also by a clinician who was not the treating physician to maintain a double-blinded status. When examining the outcomes after active treatment, the authors observed a dramatic change in relative pain after the first step of the day (i.e., post-static dyskinesia), average pain, and peak pain, as recorded by

the physician and the study participant. The initial average pain of the treatment group had a VAS pain score of 7.38. After 4 weeks, pain improvement was seen in the treatment group, with a VAS score of 3.06. After 16 weeks post-active treatment, VAS score decreased to 1.00. Changes in pain levels were found to be statistically significant ($P<0.05$). The authors reported a statistically significant improvement in the symptoms of plantar fasciitis in patients actively treated with RFNA and no significant improvement in the sham-treated group. More importantly, those treated with sham subsequently demonstrated statistically significant improvement after subsequent RFNA treatment.[19]

Cryosurgery Results

Allen et al. performed a 1-year prospective study on 59 patients (61 heels) to evaluate the efficacy of cryosurgery on patients with painful, recalcitrant plantar fasciitis. Before the procedure, the area of maximal tenderness was identified; 56 patients had maximal pain near the medial to central band and 3 patients had pain near the lateral band. The procedure consisted of inserting a probe in a percutaneous fashion and 3 minutes of freezing, 30 seconds of thawing, and another 3 minutes of freezing. The surgical site was then irrigated with a mixture of steroid and local anesthetic. A compressive dressing was applied and removed in 24 hours. The patients were allowed to bear weight to tolerance and wear regular shoe gear. Pain was evaluated on a VAS scale at day 0, 1, 7, 28, 90, 180, and 365 after the cryosurgery procedure. The average pain before cryosurgery was 8.38 (standard deviation [SD]=1.64) on the VAS. From day 90 to 365, the average pain level decreased from 1.82 (SD = 2.38) to 1.26 (SD =1.89). The authors concluded that 90% (N=55) of the heels had a pain rating of 4 or less on the VAS at day 365 of follow-up. There were 32 patients who required no additional treatment, and had 0 pain on the VAS. The authors reported that several patients required additional conservative treatments consisting of either 1 corticosteroid injection or NSAIDs for 2 weeks, after which their heel pain resolved.[14]

Visual Analog Scale Outcomes

All pain outcomes reported by patients based on the visual analog scale decreased following each minimally invasive procedure (Figure 1). From the articles reviewed, endoscopic plantar fasciotomy had the largest decrease in pain one year postoperatively, from 8.2 to 0.3 on the VAS scale. Radiofrequency nerve ablation had a decrease in pain from 8.5 to 1.3 on the VAS scale. The average pain was reduced from 8.4 to 1.0 on the VAS scale for cryosurgery. No procedure had the ability to completely resolve pain to 0 on the VAS.

Advantages and Disadvantages of Minimally Invasive Procedures

The advantages of endoscopic plantar fasciotomy include significantly minimizing surgical trauma, operating time, and time to return to regular activities compared to conventional heel spur surgery. Patients are also allowed to immediately weight-bear with less pain and discomfort. One disadvantage of EPF that was reported in the study by Fallat et al. was recurrence of plantar fasciitis in one patient; however, the pain was less severe than before surgery and the patient was overall satisfied with the results.[15]

The advantages of RFNA include not only pain relief, but also immediate weight-bearing the day after the procedure. This procedure can be performed quickly and in a time-efficient manner. The patient does not need a surgical shoe or heavy postoperative bandages. Disadvantages associated with RFNA are accidental ablation of motor nerves, periosteal burn, superficial ulceration, and fat pad atrophy.[17,18]

An advantage to cryosurgery is the ability to decrease heel pain without altering the plantar fascia itself. This, therefore, decreases any chance of instability and lateral column pain that may be encountered when the plantar fascia is partially released, such as is done in endoscopic plantar fasciotomy. Another advantage is that motor function is not affected and sensation remains intact to the skin. In addition, there is a short recovery time, which was reported to be 2 to 3 days and immediate weight-bearing. Disadvantages to cryosurgery may be the possibility of recurrence. Although the study performed by Allen et al. did not have any specific reports of recurrence by the patients being treated for plantar fasciitis pain, it was stated that some degree of recurrence was reported when cryosurgery was used for treatment of paroxysmal trigeminal neuralgia. This leads to a limitation in stating disadvantages of cryosurgery for treatment of plantar fasciitis, and a longer-term clinical outcome study should be conducted. An additional disadvantage was continued pain. For some patients this pain resolved after a corticosteroid injection or NSAIDs for 2 weeks. Three patients requested surgical intervention 3 to 5 months following the cryosurgery procedure. These patients all went on to have an open plantar fasciotomy with heel spur resection.[14]

Adverse Effects of Minimally Invasive Procedures

In the endoscopic plantar fasciotomy articles reviewed, adverse effects reported are as follows: superficial wound infections that resolved completely after oral antibiotics were given, numbness in the area of the medial side of the heel that was relieved completely after 6 weeks, lateral column pain, which was relieved by conservative treatment.[15,16]

Adverse effects reported from RFNA studies include: hematoma at the procedure site, neuropathic pain, transient discomfort, ecchymosis at the injection site, dizziness and vasovagal response associated with fear of injections.[19]

Adverse effects encountered after the cryosurgery procedure as reported by Allen et al. were soft tissue abscess development by two patients and migratory pain resulting in lateral fasciitis by four patients. The soft tissue abscesses cleared up after debridement and oral antibiotic therapy, and the lateral fasciitis was resolved by performing an additional cryosurgery procedure lateral to the original area of maximal tenderness.[14]

Limitations

The limitation of comparing three minimally invasive procedures for treatment of plantar fasciitis and heel pain includes the lack of longer-term follow-up for all procedures and the use of a subjective pain scale, VAS. To better compare each procedure, future studies should use pain measurements that are objective in nature, such as the American Orthopedic Foot and Ankle Society (AOFAS) score. Additionally, all of the studies under

review for radiofrequency nerve ablation utilized different methods to carry out the research. Variability in methodology makes it difficult to accurately compare results. Lastly, longer-term studies will allow for any potential adverse effects to present themselves.

CONCLUSION

In most patients with plantar fasciitis, conservative treatment is usually sufficient. However, when pain persists, minimally invasive treatment is a viable option to be employed by the clinician. This review suggests that the endoscopic plantar fasciotomy procedure had the greatest improvement in pain based on the VAS score. However, this was only a subjective measurement and is not significant to conclude that EPF is a superior procedure to RFNA and cryosurgery.

It was evident from this review that EPF, RFNA and cryosurgery are all optimal procedures for the treatment of chronic plantar fasciitis and improving heel pain. Due to their minimally invasive nature, they decrease surgical trauma, operating time, and time to return to weight-bearing activities.

AUTHOR'S CONTRIBUTIONS

The authors, A.B., E.B., and C.G., equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Most Efficacious Endovascular Atherectomy Modality for the Diabetic Population: A Systematic Review

Loyd Tomlinson III, BS and Christopher Wolf, BS

Abstract

Introduction
Atherectomy is a surgical method of removing, mainly, atherosclerosis from a large blood vessel within the body. Atherosclerosis is the chief etiology of peripheral arterial disease and a leading comorbidity of diabetes. As diabetes continues to grow as a population subset in the U.S., it is important to understand the most efficacious modality for treating poor blood flow to the lower extremities. The purpose of this paper is to review infrainguinal atherectomy outcomes in the diabetic population.

Study Design
Systematic Review of the Literature

Methods
Two authors conducted independent literature searches utilizing the online databases PubMed, PubMed Central, Google Scholar and The Cochrane Library with keywords including 'Atherectomy,' 'Lower Extremity,' 'Diabetics,' and 'Revascularization.' Articles were included if they used specific tools for atherectomy and noted their results on a diabetic population. Literature that was excluded either had a population that was not diabetic, did not revascularize lower extremity vessels, atherectomy was not the only technique used, or the modality itself was not FDA approved.

Results
Diabetic patients have a very high incidence of peripheral artery disease as a comorbidity, which leads to an increased prevalence of claudication and critical limb ischemia among the population as a whole. Though all of the atherectomy techniques that were reviewed had a high correlation amongst the total population, the directional atherectomy technique had the best 12-month vessel patency results with 77% and 78% of the population with and without diabetes, respectively.

Conclusion
Podiatrists have a great opportunity to serve the diabetic population by detecting, classifying, and treating PAD when it presents in their office. Atherectomy affords the diabetic patient the same opportunities as the non-diabetic patient when it comes to limb salvage and the occlusion of a lower extremity vessel.

Key Words
Lower extremity, Directional Atherectomy, Orbital Atherectomy, Rotational Atherectomy, Diabetes, Endovascular Atherectomy

Level of Evidence: 4

INTRODUCTION

Diabetes mellitus (DM), the most prevalent risk factor for PAD, currently affects 382 million people and this number is expected to rise to 592 million by 2035.[1] PAD now affects 1 in 3 patients with diabetes.[2] Annually, 150,000 patients in the US undergo lower extremity amputation due to advanced peripheral artery disease (PAD).[3] Diabetic patients with PAD remain a challenge to treat. The diffuse atherosclerotic lesions that restrict blood flow to the lower extremities in PAD often produce symptoms that range from intermittent claudication to critical limb ischemia (CLI), which is characterized by pain at rest, non-healing wounds, and gangrene.[4] PAD that results in CLI is associated with significant morbidity and mortality; within the first year of a CLI diagnosis, 25–30% of patients will die and 30% will undergo amputation.[5] So far it is known that even after successful intervention, the prognosis for patients with DM might be worse compared to patients without diabetes.[6] To improve the overall technical outcome of peripheral intervention, various techniques have been promoted including pure balloon angioplasty, nittinol stents, drug-eluting stents, drug-coated balloons, laser, and atherectomy to treat complex peripheral artery occlusive disease.[7,8,9,10,11,12] Atherectomy is a surgical method of removing atherosclerosis from a large blood vessel, and for our purposes, within the lower extremity. The purpose of this review is to focus on studies of endothelial atherectomy and its effects on the diabetic population in relation to their non-diabetic counterparts. To this date, the atherectomy techniques that are FDA approved include directional, orbital, rotational, and laser ablative.[13]

Classification Systems

Critical limb ischemia (CLI) is a manifestation of peripheral arterial disease (PAD) that describes patients with typical chronic ischemic rest pain or patients with ischemic skin lesions, either ulcers or gangrene. The term CLI should only be used in relation to patients with chronic ischemic disease, defined as the presence of symptoms for more than 2 weeks.[3,4] In classifying this disease progression, the common scales used are the Fontaine's stages and Rutherford's categories (see Table 1). The one most often cited in the literature is that of the Rutherford scale because it is clinically the easiest to correlate with the patients' specific symptoms. It is important to note that this classification system is known to be a clinically significant finding and must be confirmed by taking an ankle-brachial index (ABI) prior to diagnosing a patient with CLI.[3] Taking toe systolic pressure or transcutaneous oxygen tension can also assess CLI.[4] Pain rarely occurs from CLI in a patient with ankle pressure greater than 50mmHg or toe systolic pressure greater than 30mmHg.[3]

Directional

Directional atherectomy is mainly represented in the market by the Medtronic SilverHawk catheters with different sizes and capabilities to properly treat the different densities of CLI plaque from soft to heavily calcified plaque.[13] This catheter is connected to a battery driven cutter driver and can be used to treat vessels of 2 mm to 10 mm in diameter. As the plaque is shaved using this device, there is minimal or no distal embolization.[13] Directional atherectomy is represented in this review by the DEFINITIVE LE study.[14] It is the largest prospective non-randomized PAD

Fontaine		Rutherford		
Stage	Clinical	Grade	Category	Clinical
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild Claudication	I	1	Mild Claudication
IIb	Moderate to severe Claudication	I	2	Moderate Claudication
III	Ischemic rest Pain	I	3	Severe Claudication
IV	Ulceration or Gangrene	II	4	Ischemic Rest Pain
		III	5	Minor Tissue Loss
		III	6	Major Tissue Loss

Table 1: Classification Systems for CLI

atherectomy device study assessing the effectiveness of directional atherectomy in the management of lower-extremity arterial disease.

Orbital

The Orbital Atherectomy System (OAS) developed by Cardiovascular Systems, Inc. (CSI) uses a rotational technique causing preferential sanding of the calcified plaque, resulting in a fixed luminal gain.[13] The catheter tip has an eccentrically placed diamond-coated crown, which is driven by a pneumatic powered console. This device requires a proprietary wire to advance the catheter to the desired segment and lubricant to avoid thermal damage to the vessel wall. The rotational speed can range between 60 kilo-rotations per minute (krpm) and 200 krpm.[13] Sanding the plaque results in microscopic particulate matter that is flushed by the bloodstream and hence large-size distal embolization are minimal.[13] Orbital atherectomy offers a versatile solution for removal of peripheral plaque.

Rotational

The Jetstream System is a rotational atherectomy device that has differential and circumferential cutting blades to debulk both hard (calcified, fibrotic) and soft (thrombus plaque) tissues with minimal damage to the vessel wall.[13] The tissue debris are aspirated through the side port and disposed into the bag attached to the pathway console. The pathway device is better at being able to adapt to different sizes with each clockwise (2.1 mm) and counter-clock (3.0 mm) rotation.[13] This device has two units, the main console and a single-use catheter electrically driven

with a central pod. The main console is reusable and includes the main power supply as well as the infusion and aspiration chambers. The atherectomy catheter is advanced over the wire proximal to the diseased segment and cautiously driven back and forth maintaining the rotational speed rate (70 krpm) for better outcome.[13]

Laser Ablative

The excimer laser became FDA approved after the LACI (Laser Angioplasty for Critical Limb Ischemia) multicenter trial.[17] The laser is used to ablate the plaque and thrombus, restoring the flow in occluded segments. Laser is delivered through a flexible fiber-optic catheter using short bursts of ultraviolet energy, which vaporizes the plaque into small particles with minimal thermal injury in the surrounding tissues. Hence there is less chance for distal embolization. As of now, the laser atheroablative technique is used only in conjunction with a percutaneous transluminal angioplasty.[18]

Purpose

The primary goal of any revascularization therapy in CLI is the restoration of pulsatile, laminar flow to the foot to assist wound healing, relieve rest pain, and avoid major amputation. The choice of a surgical or endovascular strategy may depend on many variables.[19] Bypass surgery has generally been considered the ‘‘gold standard’’ treatment; however, this approach is associated with significant morbidity and mortality.[20, 21] In addition, as many as 37% of CLI patients may be considered poor surgical candidates owing to many factors.[19] The purpose of this study is to outline the most suitable type of endothelial atherectomy for diabetic patients. To this point, there has been no comparison studies performed between different atherectomy techniques on diabetic patients. This review sets out to bring to light the best choice atherectomy device for the diabetic patient by comparing the outcomes of each diabetic population from each device’s respective multicenter studies.

METHODS

Four searches of literature in English were performed on the PubMed database search engine. The first search utilized the Boolean operator "and" for the terms directional atherectomy "and" lower extremity. The first PubMed search provided 23 articles. The second search utilized the Boolean operator "and" for the terms orbital atherectomy "and" lower extremity. The search provided 8 articles. The third search utilized the Boolean operator "and" for the terms Rotational atherectomy "and" lower extremity. The search provided 46 articles. The fourth search utilized the Boolean operator "and" for the terms laser atherectomy "and" lower extremity. The search provided 41 articles. Exclusion criteria consisted of articles that didn't have diabetic population represented in their study, if atherectomy wasn't the primary procedure with standalone patients and non-English articles. Inclusion criteria consisted of studies with atherectomy, infrainguinal vessel intervention, diabetic population and the term "Lower extremity.” The 118 articles yielded from PubMed search were evaluated against the inclusion/exclusion criteria leaving 3 total articles for qualitative review. (Figure 1)

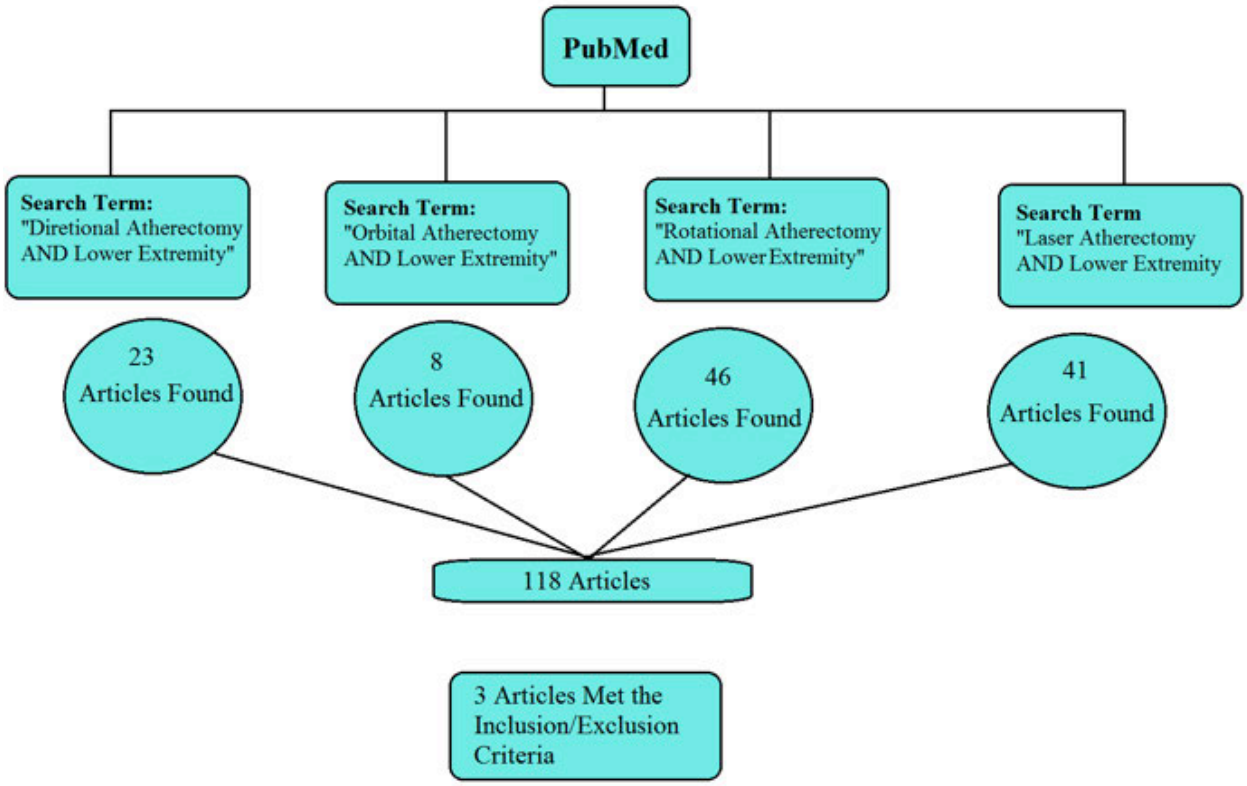

Figure 1: Systematic review of the literature

RESULTS

Directional

The DEFINITIVE LE study has been the largest study to date that took an in-depth look at the directional atherectomy device and compared it to patient outcomes. This study, using sonographic and angiographic independent core lab adjudicated events, enrolled 800 subjects with infrainguinal lesions reaching up to 20 cm in length. Patients underwent revascularization using directional atherectomy and post-treatment ultrasound examinations occurred at 30 days, 6 months, and 12 months. A range of data was obtained at each evaluation. The study broke up data points between diabetic and non-diabetic patients as well as the types of vessels that were affected in each group before treatment.[13, 14]

Orbital

CSI sponsored three consecutive prospective registries utilizing orbital atherectomy from October 2009 to June 2011: CONFIRM I, II, and III.[15] These registries were not constrained by inclusion or exclusion criteria. In total, 3135 procedures collected at more than 200 US institutions involving 4766 lesions are represented in the dataset, making the combined CONFIRM registries the largest and most unique resource of its type in existence.[15] The study used ABI and the Rutherford classification to categorize the severity of the lesion in each patient prior to treatment. The study also focused on such

factors as demographics, comorbidities, and lesion length. The average lesion length was 7 cm with a range of 0.1-60.0 cm and 66% of the patients involved with the study had diabetes.[15]

Rotational

The Pathway PVD Study for Percutaneous Peripheral Vascular Interventions was a multicenter prospective efficacy study including 172 patients with Rutherford class I to V lower-limb ischemia. All patients had more than 70% stenotic lesions up to 10 cm long for the above-knee or 3 cm for the below-knee segment. The reference vessel diameter was between 3 mm and 5 mm and the mean lesion length treated was 2.7 cm with 31% being total occlusions. At 30 days, 6 months and 1-year, follow-up data was collected on both the diabetic and non-diabetic patients.[16] The study Pathway PVD Study for Percutaneous Peripheral Vascular Interventions focused on the diabetic population and their non-diabetic counterparts throughout the study.

DISCUSSION

The treatment of PAD was compared amongst the Directional, Orbital and Rotational atherectomy. Being that each study was conducted independent of one another, comparative common ground needed to be established. To verify the validity of each study, the total number of patients and the total diabetic patients enrolled in each study were compared and listed in Table 2. Of the three studies, the largest study consisted of 3135 total patients with 3089 diabetic patients. The second largest study consisted of 800 total patients with 418 diabetic patients. The third and the smallest study had a total of 172 patients with 80 diabetic patients. It is apparent that each study has a large enough patient base and diabetic patient sample size to derive significant conclusions from their results. To establish validity between each study, the total target lesions treated and mean lesion length listed (in Table 2) were compared. The total lesions treated were 1022, 4766 and 210 with a mean treated lesion length of > 5cm, 7.2cm, and 3.5 cm.[14,15,16] It is important to acknowledge that comparisons made between DEFINITIVE LE study and CONFIRM study will have more validity than comparisons made with the Pathway PVD study based on the total lesions present and the mean lesion length's treated. PAD of the lower limb is further compared between the studies based on the location of the vessel that the lesion was treated in. The superficial femoral artery (SFA), popliteal artery (PA) or infrapopliteal artery (IPA) consist of the infra-inguinal vessels treated. To adequately contrast the three studies, the mean lesion length and patients treated in each respective vessel listed on Table 3 were compared. There was a strong majority of the patients in each study having lesions treated in the SFA based on Table 3. Two of the mean lesion lengths were very close; 71mm in DEFINITIVE LE study and 77.1mm in CONFIRM study with an outlier of Pathway PVD study being 27.35mm. This again reinforces the strength of comparisons made between CONFIRM study and DEFINITIVE LE study. Pathway PVD study in data in table 3, however, was not specific to SFA as the study provided a mean lesion length for all infra-inguinal vessels. Popliteal artery lesions had a fair amount of patients present with the lowest mean lesion length in all of the studies across the board. This may be attributed to the vessels overall length being less than that

Study/Atherectomy Technique	Total Patients	Total target lesions	Mean lesion length	Total diabetic patients
DEFINITIVE LE/ Directional[14]	800	1022	>5cm	418
CONFIRM/ Orbital[15]	3135	4766	7.2cm	3089
Pathway PVD/ Rotational[16]	172	210	3.5cm	80

Table 2: Compares the study/atherectomy techniques in total patient base, total diabetic patient base, target lesions treated and mean lesion length.
(Data provided from literature references in the manuscript, citations shown in table's 2 through 6 as study entries)

Lesion location	Study/ Atherectomy Technique	Patients	Mean Lesion Length (mm)	Patency of vessels post atherectomy (%)
Superficial femoral artery	DEFINITIVE LE/ Directional[14]	209	71	74%
	CONFIRM/ Orbital[15]	2213	77.1	63%
	Pathway PVD/ Rotational[16]	134	27.35*	61.8%*
Popliteal artery	DEFINITIVE LE/ Directional[14]	64	69.5	62%
	CONFIRM/ Orbital[15]	786	53.6	64%
	Pathway PVD/ Rotational[16]	58	27.35*	61.8%*
Infrapopliteal artery	DEFINITIVE LE/ Directional[14]	61	70.5	83.50%
	CONFIRM/ Orbital[15]	1708	74.3	67%
	Pathway PVD/ Rotational[16]	10	27.35*	61.8%*

Table 3: Illustrates the study/atherectomy technique against the breakdown of lesion location. Compares the lesion location breakdown against the patients, mean lesion length in mm and patency of vessels post atherectomy.
(* Is to indicate that the numbers presented were an average of all lesion locations)

of the other two vessels. The next most prevalent vessel to the SFA was the IPA. The IPA interestingly enough had a mean lesion length closely associated with the SFA mean lesion length. With the DEFINITIVE LE study having a IPA lesion length of 70.5mm and a SFA lesion length of 71mm compared to the CONFIRM study having a IPA lesion length of 74.3 mm and a SFA lesion length of 77.1. Based on the comparisons made from the data listed on Table 3, it is concluded that DEFINITIVE LE study and CONFIRM study were closely related in comparison to Pathway PVD study in lesion length across all vessels.

Once congruency was established between each study, the treatment methods for PAD were compared based on patency of vessel post atherectomy, ABI score and Rutherford classification improvement pre to post atherectomy, and adverse events within each study. The post atherectomy patency of the SFA, PA and IPA between each study were compared based on the data provided in Table 3. DEFINITIVE LE study has a higher patency post atherectomy in the SFA by 11% and IPA by 16.5%. The post atherectomy PA patency was highest in CONFIRM but there was a considerably less of a difference seen as it was only 2% higher than the other studies. It was concluded based on the comparisons made from Table 3 that DEFINITIVE LE study was superior in restoring patency of vessels in comparison to the other two studies.

The Ankle Brachial Index data on Table 5 was then compared between studies. The ABI pre-atherectomy for DEFINITIVE LE study, CONFIRM study and Pathway PVD study was .65, .6 and .59 respectively. The ABI at 12 months post atherectomy for DEFINITIVE LE study, CONFIRM study and Pathway PVD study was .83, N.A., .82 respectively. ABI is an essential test to the diagnosis of critical limb ischemia in patients with peripheral artery disease. On top of the relevance of the ABI test, each study has a very similar patient base start point with an ABI prior to treatment ranging from .65 to .59 between studies. The end point at post 12 months atherectomy for DEFINITIVE LE study and Pathway PVD study were very close with a .01 difference between them. Thus, based on the ABI both DEFINITIVE LE study and Pathway PVD study displayed effective and equivalent treatment of the occlusion. No conclusions could be drawn for CONFIRM study as there was no 12 month post atherectomy ABI taken.

The Rutherford classification is a standard measurement in assessing PAD.[3] Thus, to draw further conclusions; the Rutherford classification data on Table 6 was evaluated between studies. Pre-atherectomy the Rutherford classification for DEFINITIVE LE study, CONFIRM study and Pathway PVD study was 3, 3.51 and 3 respectively. The Rutherford classification 12 months post atherectomy for DEFINITIVE LE study, CONFIRM study and Pathway PVD study was 1, N.A. and 1.5 respectively. DEFINITIVE LE study and Pathway PVD study patients pre-atherectomy were both scored as 3 and thus substantial conclusions can be made. CONFIRM study's patients started with a 3.51 but no post atherectomy Rutherford classification was taken for these patients and thus no conclusions were drawn for this study. The 12 months post atherectomy Rutherford classification was 1 for DEFINITIVE LE study and 1.5 for Pathway PVD study. Thus, DEFINITIVE LE study in regards to the Rutherford

Study/ Atherectomy	Emboli	Dissection	Perforation	Aneurysm
DEFINITIVE LE/ Directional[14]	3.80%	2.30%	5.30%	0.40%
CONFIRM/ Orbital[15]	2.20%	11.10%	0.70%	N/A
Pathway PVD/ Rotational[16]	9.8%	8.70%	2.30%	0.60%

Table 4: Compares the adverse events specifically emboli, dissection, perforation and aneurysm between each study
(The adverse events listed above were provided at different points between each study. DEFINITIVE LE study provided its' adverse events at the 30 days post-op, the CONFIRM study provided it's adverse events seen intra-operatively and the Pathway PVD study provided its' adverse events at 6months post-op.)

Study/ Atherectomy Technique	Emboli	Dissection	Perforation	Aneurysm
DEFINITIVE LE/ Directional[14]	3.80%	2.30%	5.30%	0.40%
CONFIRM/ Orbital[15]	2.20%	11.10%	0.70%	N/A
Pathway PVD/ Rotational[16]	9.8%	8.70%	2.30%	0.60%

Table 5: Compares atherectomy studies/ techniques based on pre-atherectomy to 12 months post-atherectomy Ankle Brachial Index's

Study/ Atherectomy Technique	Pre-Atherectomy Rutherford Classification	12 Months Post Atherectomy Rutherford Classification
DEFINITIVE LE/ Directional[14]	3	1
CONFIRM/ Orbital[15]	3.51	N/a
Pathway PVD/ Rotational[16]	3	1.5

Table 6: Compares atherectomy studies/techniques based on pre-atherectomy to 12 months post-atherectomy Rutherford Classifications

classification is superior to the Pathway PVD study by .5 points on the Rutherford classification scale.

Adverse events listed on Table 4 were then compared between studies. The adverse events experienced within the atherectomy procedure consisted of emboli, dissection, perforation and aneurysm. The outliers between the studies in reference to Table 4 were that the DEFINITIVE LE study had a higher perforation event at 5.3%, CONFIRM study had a higher dissection event at 11.10% and Pathway PVD study had a higher emboli event at 9.8%. It can be concluded that there is a strong association between emboli in rotational atherectomy and dissection in orbital atherectomy as these events were increased in comparison to the other two studies. The Pathway PVD study across the board also had increased adverse events listed in Table 4. It should be noted that the adverse events listed on Table 4 were taken at different times within each study. The DEFINITIVE LE study provided its' adverse events at the 30 days post-op, the CONFIRM study provided it's adverse events seen intra-operatively and the Pathway PVD study provided its' adverse events at 6 months post-op.

Directional

The DEFINITIVE LE study set out to make direct comparisons between the outcomes of its patient population treated with diabetes to the patient population treated with the direct atherectomy that had other co-morbidities. The study's primary endpoint was 12-month patency post atherectomy. The studies secondary endpoint included Rutherford classification at 12 months, ABI at 12 months, amputation-free survival in subjects with claudication at 12 months, wound healing at 3 monthly intervals, major adverse events at 30 days, and quality-of-life measurement Walking Impairment Questionnaire.[14] The main comparison made within the study between diabetic patients and non-diabetic patients enlisted was at the study's primary endpoint. The 12 month primary patency for diabetic subgroup was 77% compared to the 12 month primary patency of 78% for the non-diabetic subgroup.[14] No direct comparisons were made between the diabetic and non-diabetic subgroups within the study's secondary endpoints. The results of this study in comparison to the results of the other atherectomy devices show that direct atherectomy is efficacious as a standalone revascularization technique. That said, it should be noted that within the study adjunctive procedures including percutaneous transluminal angioplasty was performed on several cases based on physician discretion. The exact number of percutaneous transluminal angioplasty's performed and which subgroups they were performed on were not disclosed within the article.

Orbital

The CONFIRM study which outlined the use of Orbital atherectomy for PAD was the next reviewed. No direct comparisons were made between the diabetic subgroup and the other patient subgroups. Since the total diabetic patient population lesion number was 3089 out of the 4766 patient lesions, any conclusions made about the study will more likely reflect diabetic patient outcomes, as they are the standing majority (65%) of the patients treated. This study discussed the intra-operative benefits of orbital atherectomy and when compared to the other studies, had a

significant decrease in adverse effects on emboli and perforation. Post atherectomy patient follow up within this study was not done. Thus, the study lacks evidence supporting positive outcomes for the patients after the initial date of the procedure. Furthermore, 79% of the lesions treated with orbital atherectomy required adjuvant therapy, and thus, justifying the conclusion that orbital atherectomy is not an efficacious stand-alone procedure.

Rotational

Of all three of the papers reviewed, the Pathway PVD study was the most concerned with the outcomes of the diabetic patients in relation to the non-diabetic patients. The study's primary endpoint consisted of freedom of major adverse effects (MAE) including any death, heart attack, target lesion revascularization (TLR), and index limb amputation at 30 days.[16] Ultimately the study focused on the rate of freedom from TLR at the 6-month post procedure date. As a baseline, diabetics and non-diabetics were split into separate categories and compared based on Rutherford class, Walking Impairment Questionnaire scores, Adverse Events, ABI, and lesion characteristics.[16] These baseline numbers not only showed similarity between the diabetic and non-diabetic patients, but also allowed for the difference in outcome and prognosis to be analyzed based on the comorbidity over time. The Pathway PVD study showed that after using this type of atherectomy, diabetic patients had a lower incidence of TLR at 6 and 12 months in comparison to their non-diabetic counterparts. Diabetic patients had an average increase in ABI from .6 to .81 at 12 months while non-diabetic patients had an increase in ABI from .59 to .84 at 12 months.[16] These numbers are further compared to the other atherectomy devices (Table 5), showing that this modality is an efficacious revascularization procedure. The Pathway PVD study shows no apparent difference in diabetic patient prognosis when compared to their non-diabetic counterparts. Also, the results of this study when compared to results in the aspects of side effects and efficacy profile, proved that rotational atherectomy works as a viable and efficacious stand-alone revascularization technique.

Limitations and Suggestions

The hardest part in determining which atherectomy technique is most suitable for diabetic patients is that each study had different primary end points. For the DEFINITIVE LE study the primary end point was a peak systolic velocity ratio of <2.4 while the Pathway PVD study focused on a proximal flow velocity of >2.4. The CONFIRM 360 study sought more of a plaque characterization prior to surgery, to predict outcomes. Another important aspect in relating the studies to each other was the population size in each study and the actual data points that were included in each study. Though the Pathway PVD study analyzed every aspect of the diabetic patient versus the non-diabetic patient, their sample size was so small that it did not provide the best confidence interval. Adding a control group and using the same inclusion criteria and primary endpoints for each atherectomy technique could make a stronger case for which atherectomy technique is the best for the diabetic patient.

CONCLUSION

All three studies demonstrated that the respective diabetic patients fared similarly compared to the respective non-diabetic patients. Of the three atherectomy techniques, directional atherectomy seemed to be the safest procedure based on adverse events alone. The CONFIRM 360 study had the highest amount of lesions that underwent atherectomy out of the three studies with most of them being diabetic.[15] The DEFINITVE LE study had a high sample size that was specifically chosen to provide a higher confidence interval when comparing the diabetic patients to non-diabetic patients. Based on the common data sets that all three studies provided, directional atherectomy proved to be the most efficacious. Orbital atherectomy has great short-term patency rates but was unable to prove its efficacy in a long-term setting because the study failed to follow up patients post operatively. Rotational atherectomy was the one that provided the most data comparison between diabetic and non-diabetic patients. The Pathway PVD study did not fair well with long-term adverse effects. Since the directional atherectomy study also showed that primary patency rates at 12 months were the same regardless of whether or not diabetes was present in the patient, directional atherectomy provided data that it is the most efficacious endovascular atherectomy technique for the diabetic patient. A further study would need to be done in order to confirm the conclusions made in this paper.

AUTHOR'S CONTRIBUTIONS

The authors, L.T. and C.W., equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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The Effect of Light Therapy on Recalcitrant Plantar Warts

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Abstract

Introduction
Plantar warts can be resistant to treatment, requiring many patients to undergo numerous treatment modalities to eradicate them. An extensive search of the literature was performed to compare and contrast four modalities of light therapy on recalcitrant plantar warts that have failed previous topical and non-topical treatments.

Study design
A qualitative systematic review of electronic databases was performed to compare light therapy on recalcitrant plantar warts.

Materials and Methods
A search was performed using PubMed and ScienceDirect databases. Inclusion criteria consisted of recalcitrant warts, yttrium-aluminum-garnet (YAG) laser, photodynamic therapy (PDT), CO_2 laser, and pulse dye laser (PDL) restricted from 1985 to present. Inclusion criteria were not limited to a particular type of a study for this literature review; criteria were open to case report, cross sectional study, randomized trials, and double-blinding study. Studies were excluded if their patient population was: immunocompromised on hemodialysis, taking immunosuppresants, had systemic illness, were pregnant, breast-feeding, or if they had photosensitivity.

Results
The search on PubMed for 'Plantar Warts' and 'Laser Therapy', and 'Plantar Warts' and 'YAG' yielded 44 and 7 articles respectively. From a combined total of 51 articles, 11 met the parameters of the inclusion criteria. An additional search on ScienceDirect resulted in 144 articles, and only 1 article fulfilled the criteria. Overall, 12 articles were selected for further qualitative review.

Conclusion
All light treatment option studies demonstrated reasonable outcomes to be used as alternative treatment modalities for recalcitrant plantar warts. However, there are minor differences amongst these different light types and studies. Although CO_2 therapy demonstrated effective results, its side effects were notable: post-op pain, scarring and pigment changes. PDL demonstrated similar treatment outcomes as CO_2 therapy, but yielded in significantly less side effects because it able to selectively injure the feeding vessels of the warts without damaging surrounding structures. YAG laser is ten times more selective for water than CO_2 therapy causing less thermal damage and minimizing adjacent tissue damage leaving minimal pain, scarring, and pigment changes. PDT is a new type of light therapy that displays effective clearance of recalcitrant plantar warts and causes less pain and discomfort compared to the above mentioned light-therapy armamentarium.

Key Words:
Yttrium-aluminum-garnet (YAG), photodynamic therapy (PDT), pulse dye laser (PDL), and 5-aminolaevulinic acid (ALA)

Level of Evidence: 4

INTRODUCTION

Viral warts are a common dermatologic problem with manifestations such as *Verruca vulgaris*, *Verruca plantaris* and palmoplantar warts.[1] They can cause social, cosmetic, and functional problems as well as possible painful lesions.[2] Viral warts are benign epithelial proliferations, most commonly caused by infection with different types of human papillomavirus in children and adults.[3] Human papillomaviruses (HPV) are deoxyribonucleic acid (DNA) viruses belonging to the group of papovaviruses.[4] HPV types 2, 27 and 57 occur most commonly as viral warts.[4] Histologically, warts have a dilated and congested capillary network in the dermal papillae that supply the warts.[1] Viral warts have a predilection for hyperkeratotic tissue with the most common sites of infection being the hands and feet.[2] The prevalence of HPV infection is 3.5% in adults; the frequency is higher in children.[2,5,6] Fabbrocini et al. indicated that viral warts increase in incidence and prevalence during childhood, peak in adolescence, and decrease in the older populations.[7]

Spontaneous resolution is seen in about two-thirds of warts within a 2-year period, however most patients will generally seek a medical professional to remove their viral lesions before this occurs.[2] The basic therapeutic strategy for treating warts is removal of the epidermal stem cells infected by the HPV.[8,9] Treatment for viral warts should reflect the benign character of HPV infection and be effective with minimal

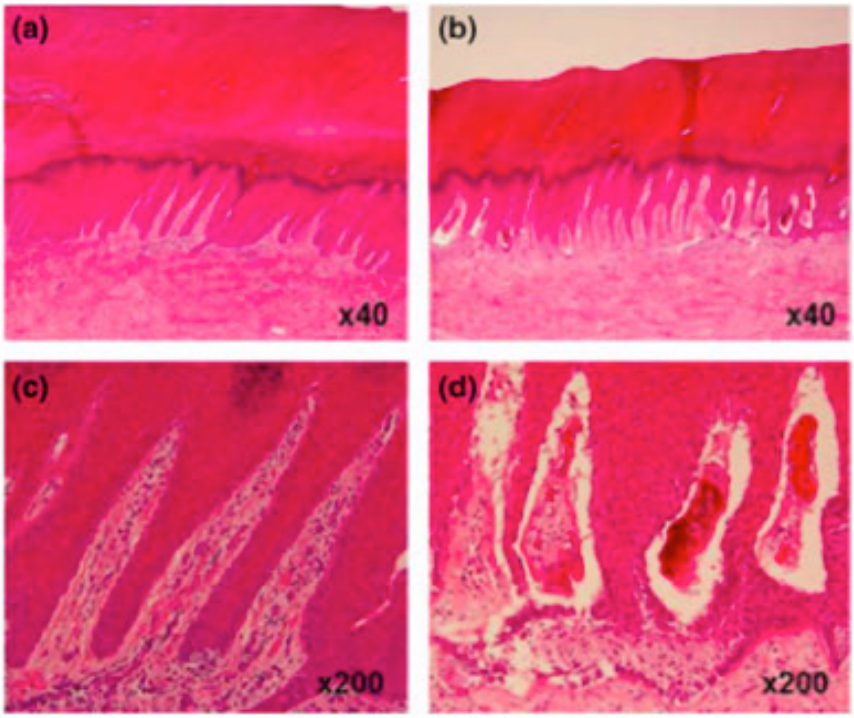

Figure 1: Histopathological evaluation (hematoxylin-eosin) of specimens taken pre- and post-laser irridation. (a, b) shows lower magnification (x40) for pre- and post-laser irridation. (c, d) shows higher magnification (x200) for pre- and post-laser irridation.
*Reprinted with permission from *The Journal of Dermatology*, 2014[8]

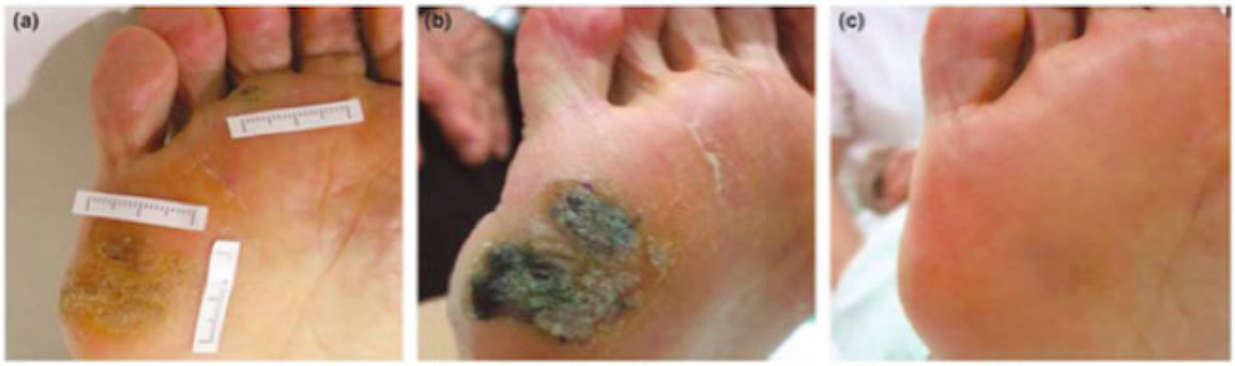

Figure 2 Treatment progression at various time points. One treatment at 160 J/cm^2 and 15msec was performed on a 78-year-old women with palmoplantar mosaic warts. (a) Baseline, (b) 2 weeks post-final treatment (c) 12 weeks post-final treatment.
*Reprinted with permission from *The Journal of Dermatology*, 2014[8]

adverse reactions.[2] Initial therapies for viral warts include paring of warts, cryotherapy and keratolytic topical agents or any combinations of these three. [2] Common keratolytic topical agents include salicylic acid, trichloroacetic acid, electrosurgery, intralesional bleomycin and interferon, podophyllin, cantharidin and topical 5-fluorouracil.[1,10]

Warts are considered recalcitrant when they persist for several years despite numerous treatments.[2] For this reason, four modalities of laser therapy on recalcitrant plantar warts will be investigated in this review. Lasers are an effective, safe and well-tolerated procedure for treatment of recalcitrant warts.[1] Yttrium-aluminum-garnet (YAG), photodynamic therapy (PDT), pulse dye laser (PDL), and 5-aminolaevulinic acid (ALA) will be analyzed for their treatment protocol, outcomes and side effects.

CO_2 therapy was popular for treatment of viral warts in the 1980's and 1990's, and was more successful than conventional methods at the time. However recurrence was still seen in plantar warts. CO_2 laser provides some degree of coagulation of the surrounding tissue, known as residual thermal damage (RTD). This ensures a dry field, however, it compromises wound healing. Since the laser damages infected tissue and uninvolved tissues surrounding the wound, it lengthens the wound healing process. Basically RTD results in extension of the wound caused by the CO_2 laser and is often associated with infection, delayed healing, scarring and other complications.[1,11]

Pulsed dye laser (PDL) has been suggested for treatment of recalcitrant warts. The Mechanism of action is the selective destruction of superficial papillary capillaries of the warts, as well as thermal injury of the heat-sensitive virus.[2] PDL is a monochromatic light of 585nm that exhibits a non-destructive mechanism of action on wart tissue.[2] Oxy-hemoglobin selectively absorbs PDL and is able to injure these vessels without damaging surrounding structures, thereby reducing the risk of scarring.[1] Furthermore, PDL has immunomodulating properties that contribute to wart healing.[1] Ultrastructural studies showed increased levels of IL-4 and mRNA, indicating a T-

helper (Th-2) cell response. These activated Th-2 cells are known to fight cutaneous viral infections.[1] PDL is particularly useful in children because it does not cause much pain. [1]

Histologically, YAG laser causes coagulation and destruction of the blood vessels in the papillary dermis in the infected area. This separates the dermis and epidermis at the basement membrane eliminating the HPV infected epidermis from the dermoepidermal junction (Figure 1).[8] Minimal destruction of the surrounding tissue is characteristic of YAG therapy, which contributes to minimizing the risk of complications. This will be explored in a later section.[8] Figure 2 demonstrates the effectiveness of YAG therapy.

Photodynamic therapy (PDT) combines a photosensitizer and light in the presence of oxygen, which destroys tissues via free radicals. The combined use of PDT and 5-aminolaevulinic acid (5-ALA) has been successfully employed in the treatment of many dermatological problems including viral warts.

This review is unique because it compares the efficacy of four phototherapies with an emphasis on recalcitrant plantar warts. Some studies review the effectiveness of laser treatments of warts including, but not exclusive to plantar warts. Other studies review treatment modalities to plantar warts with no emphasis on any single treatment modality.[12,13,14,15] A thorough examination of the treatment protocol and outcomes for each treatment will be investigated, and a decision will be made as to which phototherapy has the greatest effect in treating recalcitrant plantar warts.

METHODS

A search was performed on PubMed and ScienceDirect to retrieve literature. The initial search on PubMed utilized the Boolean operator “and” to narrow results to only articles including the terms ‘Plantar Warts’ and ‘Laser Therapy’; ‘Plantar Warts’ and ‘YAG’. The subsequent search on

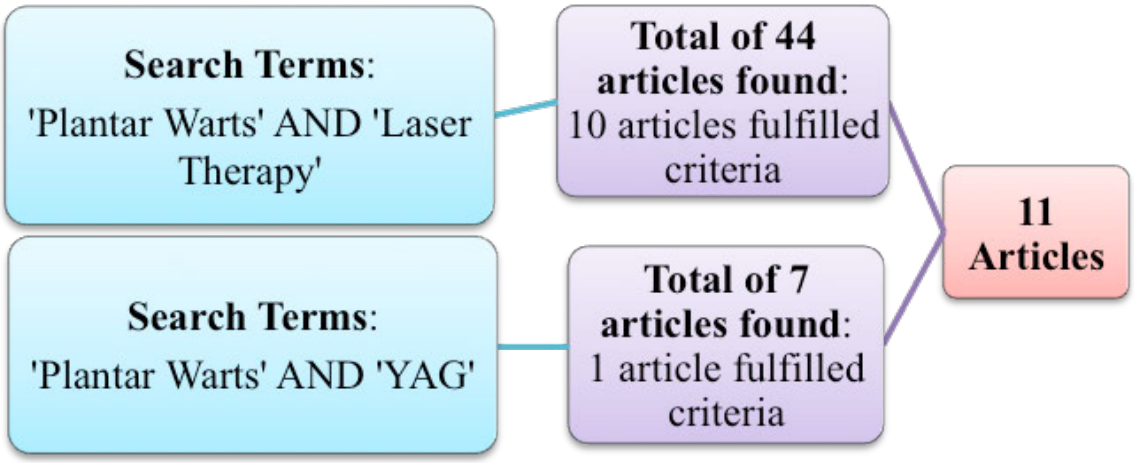

Figure 3. Acquisition of studies from PubMed

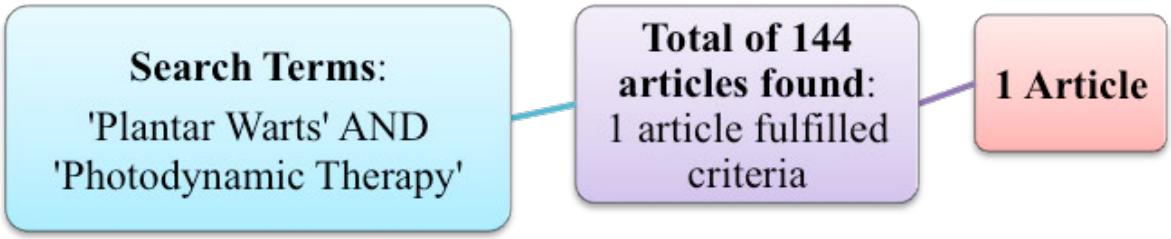

Figure 4. Acquisition of studies from ScienceDirect

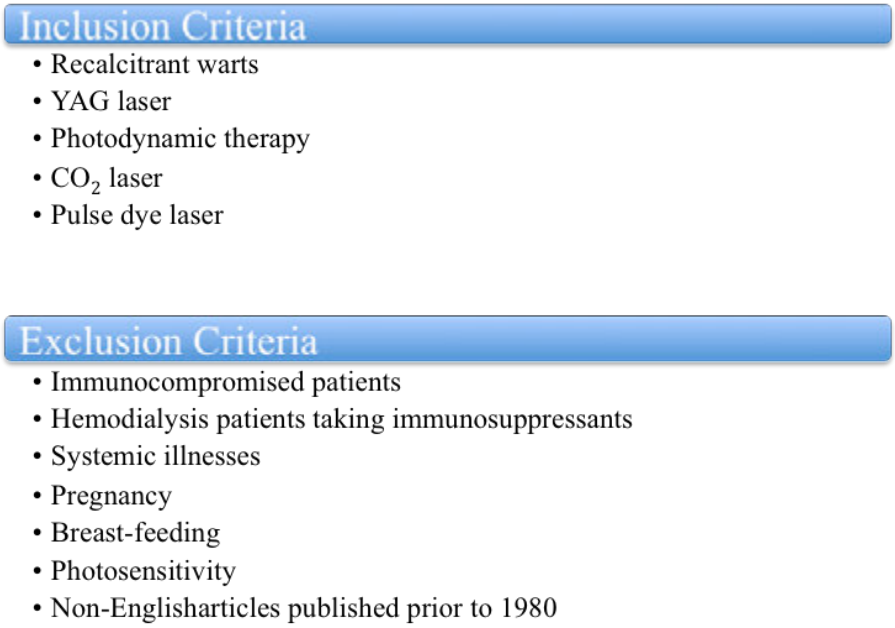

Figure 5. Inclusion and exclusion criteria

ScienceDirect also employed Boolean operation "and" for 'Plantar Warts' and 'Photodynamic Therapy' (Figures 3 and 4). Inclusion criteria consisted of studies involving: recalcitrant warts, YAG laser, photodynamic therapy, CO_2 laser, and pulse dye laser. Exclusion criteria consisted of studies on patients that were immunocompromised, on hemodialysis, had systemic illnesses, were pregnancy, breast-feeding or had photosensitivity. Non-English articles as well as those published prior to 1980, were also excluded. (Figure 5) As a systemic literature review, criteria for the type of study include systemic review, meta-analysis observational studies (i.e. cohort, case-control, and cross-sectional) and interventional studies (i.e. double-blind, randomized trial) from 1985 to present.

RESULTS

The search on PubMed for 'Plantar Warts' and 'Laser Therapy', and 'Plantar Warts' and 'YAG' yielded 44 and 7 articles respectively. From combined total of 51 articles, 11 fulfilled above mentioned criteria. In addition, search on ScienceDirect resulted in 144 articles, and only 1 article fulfilled the

criteria. Overall, 12 articles were selected for further qualitative review to compare and contrast the mentioned light therapies. The purpose of this review is to determine the light therapy that potentially yields the best treatment outcome.

CO_2 Therapy

Mancuso et al. [16] (Table 1) studied the results of 166 patients with plantar verruca who had a combined number of 494 lesions. Patients were classified into separate categories based on type of wart lesion. Combining the results in each classification and obtaining the average, clearance rate utilizing CO_2 laser for plantar warts was 75%. The ultimate success rate for all solitary lesions was 93% and all mosaic recalcitrant lesions was 62%. The authors recommended treating a wart in its solitary state and has not had previous treatments. Complications include excessive bleeding (1.2%), sterile abscess (4.2%), infection of soft tissue requiring antibiosis (1.2%), bone infection (0.6%), epidermoid inclusion cyst (1.2%), hyperkeratotic scar tissue (5.4%), and painful scar tissue (2.4%). Asymptomatic scar tissue was present in 90% of the patients.

Borovoy et al. [17] (Table 2) selected 31 patients with recalcitrant plantar warts. The lesions were classified based on their size, number and location (WB or non-WB). This study analyzed the effectiveness of the CO_2 laser therapy combined with curettage. After treatment, they applied sulfadiazine and covered the wound with Owens silk and dry sterile dressing. Follow-up protocol for this study included: 3 to 4 days post-therapy, followed by re-dressing one week later. Patients were placed on the pHisoHex whirlpool one week later. During this visit, patients were instructed to bathe regularly and change their dressing everyday. Follow-up was 1 month to 1 year (average of 5.7 months). 17 patients had multiple lesions in which 8 of them had clearance, 5 had recurrence, and the final 4 were lost to follow-up. Of the 14 patients with single lesions, 12 were cleared and 2 were re-infected with *Verrucae vulgaris*. 22 of 31 patients had lesions on weight-bearing areas. 12 of 22 had clearance with no scar formation, 6 had recurrence, and 4 were lost to follow-up. The rest had lesions on non-WB areas and 8 out of 9 had clearance.

Lavery et al. [18] (Table 3) conducted a literature review that evaluated the patients of Apfelberg, Borovoy, and Mueller and their results in treating plantar warts with CO_2 laser as a primary form of treatment for solitary and multiple lesions. Of all the studies done by the 3 clinicians, only 25 patients received laser therapy as a primary form of treatment. In this study, a primary lesion is defined as a previously untreated lesion or treated with another modality for 2 months or less. 97 plantar verrucae lesions were evaluated in which 60 were solitary and 37 were multiple. 84.8% clearance was noted on primarily treated solitary lesions. Primarily treated multiple lesions had a 74% clearance. Follow-up with these patients was a minimum of 3 months.

Mitsuishi et al. [3] (Table 4) selected 31 patients who had a combined total of 35 lesions with plantar warts for this study. Diagnosis of plantar warts was made by clinical examination and detection of HPV DNA via PCR. Duration of the lesions ranged from 6 months to 10 years. CO_2 laser was used to excise the lesional skin with a portion of adipose tissue and at least a 1-mm margin,

which included non-lesional skin. Artificial dermis was then applied over the defect to prevent scarring, quicker healing time, and minimal pain. Follow-up ranged from 3 to 10 months. Patients were then examined to analyze for the presence of HPV DNA from the upper epidermis at the post-operative site. 31 out of 35 lesions had complete clearance after one treatment session and the rest had recurrence within 3 months following initial treatment.

PDL

Borovoy et al (Table 5) monitored over 200 patients with plantar warts. A majority of these patients had mosaic lesions (81.4%) that were resistant to conservative treatments. The other 18.6% of these patients had solitary lesions that were also resistant to conservative treatments. Conservative treatments that these patients had undergone previously were cryotherapy, topical acid therapy, CO_2 laser vaporization and excision. Borovoy observed clearing of the lesions in both patient groups (*i.e.,* mosaic and solitary lesions) in 79.9% of the cases after an average of 2.38 treatment sessions. He also reported that a certain percentage of people had to receive more treatment sessions to have had their lesions cleared: 18.75% required 3 sessions, 5% required 4 sessions, and 1.25% required 5 sessions. He hypothesized this greater chance of treatment failure or need for prolonged treatment sessions was associated with the chronicity of the lesions and/or the number of previous failed treatments. The average follow-up period for these patients was approximately two years. A total of 160 subjects showed clearance and these subjects were mailed questionnaires. A total of 143 subjects replied back to the questionnaire forms. All of them reported no recurrence, which is equivalent to 89.4% assuming the other 17 patients had possible recurrence.[19]

Sethuraman et al (Table 6) also studied the effectiveness of PDL on recalcitrant warts. Sethuraman treated perineal warts, peri-anal, face, hands and plantar foot in children age between two and seventeen. He identified 61 patients that were treated with PDL from 1995 and 1999 by chart review and grouped them according to different body sites affected by the warts. First, the warts were pared by #15 blade until puncture bleeding was apparent. Then PDL was used to irrigate the warts. Sethuraman reported 75% complete clearance rate with the average of 3.1 treatments. The effectiveness of PDL therapy varied according to anatomical sites treated. They observed genital and facial warts responded best to PDL with 100% clearance rate whereas plantar warts demonstrated only 69% clearance rate. Sethuraman followed up with these patients from 12 to 66 months and reported that 75% of his subjects did not have recurrence over more than 24 months. He reported minimal side effects associated with PDL: mild pain, mild scarring (2%), hypopigmentation (8%), hyperpigmentation (2%) and itching but they were not common. Sethuraman stated that it was due to PDL's ability to selectively target blood vessels feeding warts and not damaging any other surrounding structures. Sethuraman reported that only disadvantage of using PDL therapy is the cost.[1]

Ross et al (Table 7) looked at 33 subjects with warts in three different locations (hand, digits, and plantar foot). Ross reported 48% complete clearance and 45% partial clearance. Of those subjects who had complete clearance, the highest clearance rate was demonstrated by those that had warts in

their hands, and lowest by those who had warts in the feet. The clearance rate was 75% and 20% respectively. They also reported that only 69% of the cases stayed wart free over an 11-month follow-up period.[10]

Togsverd-Bo (Table 8) and her team studied 89 subjects that had recalcitrant warts in either hands or feet to identify the difference in effectiveness of treating warts with paring alone vs. Paring plus PDL therapy. She reported there was no difference in either method of treatment. However, she reported that there was only 22% and 13.5% complete clearance in paring plus PDL and PDL alone respectively, which is not a statistically significant finding.[2] She also reported that there was no significant scarring or pigmentation as a result of the treatment, but there was significant pain associated with paring plus PDL.[2]

PDT

Schroeter et al. [4] (Table 9) observed 31 patients with a total of 48 recalcitrant plantar warts. All warts in this study have been treated previously several times with liquid nitrogen, salicylic acid, silver nitrate, and 5-FU. Furthermore, some patients had excision and curettage as a form of treatment. ALA was applied topically prior to PDT treatment. Blunt scraping was performed to enhance the penetration of ALA. A total of 6 patients were used as controls in which 2 were without ALA, 2 were without the PDT light, and 2 were only blunt scraping. Follow-up after treatment were scheduled at 1 day, 1 week, 1 month, and at 3 months. The final follow-up for all patients was an average of 15 months. Each wart was treated an average of 2.3 times. No significant side effects were noted in any case. Overall clearance was noted to be 88%(42/48 warts). A trend was seen between clearance and age, treatment time, and size of warts: Younger patients had higher clearance than older patients. Warts that were radiated for 19 minutes had higher clearance than warts that were only radiated for 16 minutes. This study also noted that the larger the warts, the more easily they were cleared. The clinicians noted PDT is less time consuming compared to other modalities and patients can go about their normal routine immediately after treatment.

Fabbrocini et al. [7] (Table 10) performed a randomized double-blind clinical study on 90 patients with recalcitrant plantar warts to confirm the efficacy, safety and tolerability of ALA-PDT treatment. Prior to treatment, salicylic acid was applied to the warts and kept in place for 7 consecutive days. Patients were divided into 2 groups. The morning of the treatment session, superficial curettage was performed to optimize the penetration in patients receiving the ALA cream. Treatment time for each wart was 15 minutes. Patients were followed up every 15 days to assess clearance. If clearance was not observed, the treatment was repeated every 15 days for a maximum of 4 times until satisfactory clearance was noted. Patients were followed up by 30 and 90 days, and then 6 and 24 months following the final irradiation session. Two weeks following the last irradiation session, 55/63 (87.3%) clearance was noted in the PEG+ALA group, whereas 9/52 (17.3%) clearance was noted in the PEG without ALA group. The warts were considered completely healed when the skin was free of hyperkeratotic tissue and irregular skin surface for at least 4 months. Patients in the ALA group experienced minor burning sensation or slight pain, but not so severe as to require local anesthesia or bring the study

to a halt. All patients confirmed this method had less pain and discomfort compared to other treatment modalities. The clinicians also noted that no scars were observed. No recurrence was noted in the PEG+ALA group after 24 months of follow-up.

YAG

Trelles et al (Table 11) studied at 121 plantar warts in 58 patients between the ages of 12 and 75 years old. All of these patients were previously treated with conservative therapies. They ablated the lesion with Er:YAG until they saw normal tissue and coupled the treatment with LED application to promote faster healing. LED application was repeated post-operatively at days 2, 6, and 10. Trelles reported 100% clearance rate at the initial therapy. This was possible because they were able to take out the lesion layer by layer until they saw normal tissue underneath the warts. No recurrence was observed at 6-month follow up, but there was ≤6% recurrence (3/58) over 2-year follow up period. Trelles stated the advantages of this technique were minimal thermal damage after treatment and immediate ambulation following bilateral therapy. Furthermore, they reported minimal drainage from the surgical site 2 days s/p, and the majority healed completely by 15 days s/p with minimal scarring.[11]

Wollina and her team (Table 12) also assessed the effectiveness of Er:YAG. Wollina combined Er:YAG with 0.5% podophyllotoxin topical cream. They looked at 35 patients between the ages of 17 and 50 with mean age 32.2 years old. Initially, they ablated the verrucous lesion with Er:YAG until they saw pin-point bleeding and waited until the lesion healed. Once the lesion was healed, they applied 0.5% topical podophyllotoxin cream. Each subject received an average of six cycles of podophyllotoxin treatment. Each cycle involved application of cream once a day for three days followed by four days of rest period. Her team reported 88.6% complete resolution rate with 5.7% (2/35) recurrence rate in three months follow-up. They stated that this was an improvement from the previous study, which resulted in 14% recurrence rate at 3-month follow up period when they only used Er:YAG without subsequent topical podophyllotoxin cream application.[16]

Kimura and his team (Table 13) used a different YAG technique (i.e., Nd:YAG). This particular YAG laser uses shorter wavelength (1064nm) compared to Er:YAG (2.94μm) that was discussed previously. Kimura and his team studied 34 subjects with a mean age of 40. All participants previously failed conservative treatments such as cryotherapy with NO, topical vitamin D, coix seed, salicylic acid, imiquimod for at least 6 months as well as some invasive treatments such as ultra-sonic scalpel and PDL therapy. They performed up to six sessions of Nd:YAG with four weeks interval in between sessions. Subjects were then re-evaluated after 24 weeks. They reported 56% complete resolution and 14.7% (5/34) cases worsened over time. 7 out of 19 cases that showed complete resolution were lesions located in the feet; however, 4 out of the 5 failed cases were also located in the feet as well. Although the exact mechanism of Nd:YAG is still unclear, one hypothesized that clearance of wart is probably due to coagulative necrosis caused by destruction of blood vessels in papillary dermis, which results in the separation of epidermis from dermis at the

junction as histopathological evidence shows.
[8]

CO_2 Tables

Type of Lesion	Single Treatment	Multiple Treatments	Overall Success
Solitary	81%	19%	93%
Solitary Recalcitrant	51%	49%	70%
Multiple	52.5%	47.5%	62%
Multiple Recalcitrant	40%	60%	75%

Table 1. Result Summary for Mancuso et al
N = 494 lesions
Overall success combining all classifications was 75%
Follow-up: Approximately 3 months was needed for recurrence to be noted.
4 out of 166 patients developed symptomatic plantar scar tissue.

Type of Lesion/ Location	Clearance	Recurrence	Lost to follow-up
Solitary	12	2(due to reinfection)	0
Mosaic	8	5	4
Non-weight bearing	8	unknown	unknown
Weight bearing	12	6	4

Table 2. Result Summary for Borovoy et al
n = 31 patients
Classification by category:
-Solitary = 14
-Mosaic = 17
-Weight bearing = 22
-Non-weight bearing = 9
Follow-up was about 1 month to 1 year with an average of 5.7 months.

Type of Lesion	Number of lesions	Clearance (%)
Solitary	60	84.8
Mosaic	37	74

Table 3. Result Summary for Lavery et al
n = 97 lesions
Follow-up was approximately 3 months

Number of Lesions	Clearance(number of lesions)	Recurrence(number of lesions)
35	31	4

Table 4. Result Summary for Mitsuishi et al
n = 35 lesions
Follow-up was approximately 3 to 10 months. 4 patients had recurrences within 3 months.

PDL Tables

Number of cases (n=160)	Treatment sessions per patient	Number of cases (n=160)	Treatment sessions per patient
30	1	30	1
50	2	50	2
70	3	70	3
8	4	8	4

Table 5. Result summary on Borovoy et al
N = 200
Demographics
A. Mosaic recalcitrant – 81.4%
B. Solitary recalcitrant – 18.6%
79.9% initial complete clearance with 2.38 treatment session on average
Follow-up (n=160)
- 143 (89.4%) no recurrence
- 17 (10.6%) lost to follow up

Location	Complete clearance, n (%)
Hands	13 (93)
Combined extremities	9 (60)
Plantar warts	9 (69)
Combined face and extremities	8 (67)
Genital	5 (100)
Face	2 (100)
Overall	**46 (75)**

Table 6. Result Summary for Sethurmann et al
N=61 (children only)
Follow-up (12-66 months):
75% no recurrence over 24 months

N=33
Result
- 48% complete clearance
  - Hand – 75%
  - Digits – 50%
  - Foot (plantar) – 20%
- 45% partial clearance

Follow-up
- 69% clearance over 11 months
- 32% recurrence over 6 months

Table 7. Summary results for Ross et al

Evaluation 6 weeks after last intervention (n=78)			
Intervention	No response	Partial response	Complete response
Paring plus IPL, n (%)	27 (65.9)	5 (12.2)	9 (22.0)
Paring alone, n (%)	28 (75.7)	9 (11.5)	14 (17.9)

Table 8. Result summary for Togsverd-Bo et al
Treatment response according to interventions with paring followed by IPL vs. Paring alone

PDT Tables

Treatment	Number of lesions	Clearance(number of lesions)
Currette + ALA + PDT	42	42
Curette + PDT	2	0
Curette + ALA	2	0
Curettage	2	0

Table 9. Result Summary for Schroeter et al

n = 48 lesions
Follow-up: Patients were followed up 1 day, 1 week, 1 month, and 3 months post-op. Each wart was treated an average of 2.3 times with no significant side effects. Final follow-up was an average of 15 months.

Treatment	Number of patients	Number of warts	Clearance (number of warts)
PEG+ALA+PDT	48	63	55
PEG+PDT	42	52	9

Table 10. Result Summary for Fabbrocini et al

n = 90 patients
Salicylic Acid was applied to all warts 7 days prior to treatment.
Curettage was done on patients receiving ALA the morning of the treatment.
Follow-up: Every 15 days to a maximum of 4 times till clearance was noted.
In patients who cleared with ALA treatment, no recurrence was noted after 24 months of follow-up.

YAG Tables

N=128 (58 patients)
100% clearance
Follow-up:
- 0% at 6 months
- ≤6% at 2 year

Table 11. Result summary for Trelle et al

N=35 patients
Result:
- 88.6% complete clearance
- 5.7% (2/35) recurrence at 3 months

Table 12. Result summary for Wollina et al

Level of improvement	Result on plantar warts, n (%)
Complete clearance (100%)	7 (39)
Marked improvement (81-99%)	3 (17)
Mild to moderate improvement (10-80%)	4 (22)
No change or worsened (≤10%)	4 (22)
Total	18 (100)

Table 13. Result summary for Kimura et al
N=34
Follow-up:
- 14.7% (5/34) no improvement or recurrence
  - 4/5 recurrence was plantar warts

DISCUSSION

CO_2

CO_2 is the earliest light therapy utilized to eradicate plantar warts. Success rates have been recorded as high as 80-90%. There were many studies performed with great results, but with these results came complications. CO2 laser is a light energy that changes to heat with a resultant nonspecific cellular destruction. In treating verruca, it is targeted towards epidermal cells that are hyperkeratotic due to the HPV virus. This method destroys the cells with heat and eventually kills the virus in the cell. One of the main complications in this therapy is the pain that comes along during the treatment. Local anesthetic block is usually given to the patient that corresponds to the location of the wart. Post therapy complications include excessive bleeding, sterile abscess, infection of soft tissue requiring antibiotics, bone infection, epidermoid inclusion cyst, hyperkeratotic scar tissue, and painful scar tissue as reported by Mancuso et al. The studies also reported highest success rates among patients with solitary lesions that had CO_2 therapy as an initial treatments as reported by Mancuso and Lavery et al.

Lowest success rates were among patients that had Mosaic recurrent plantar warts as reported by Mancuso et al. These results decrease the chances of patients with recalcitrant plantar warts to effectively be treated. Mancuso's study effectively classifies the best patient population in which the therapy is most effective, but the retrospective nature of the study decreases the validity of the study. A recent study done by Mitsuishi et al looks into a different approach to effectively apply CO_2 laser therapy and reduce post-op scarring and delayed healing with the use of a dermal application. Although this therapy reduced some complications, further evaluation of CO_2 therapy with ancillary measures is required to determine long-term efficacy

PDL

There were several studies performed to assess the effectiveness of PDL technique in treating warts of many different kinds. As it was mentioned in previous sections, this technique utilizes monochromatic light of 585*nm* to selectively destroy blood vessels that feed warts. For this reason, it not only destroyed the warts, but also minimized side effects such as post-op pain, scar formation, and hyperpigmentation. However, outcome of different studies revealed different results suggesting that we needed more investigation to determine its true efficacy. Borovoy et al reported up to 79.4% clearance rate after three average treatment sessions whereas Ross reported as little as 20% clearance rate. Gibbs explained that this is due to several factors.[21] First, there was high heterogeneity of the study subjects and these studies did not account for the spontaneous resolution of warts. Finally, there was an investigator-associated bias as a result of the study being non-randomized and non-controlled, which made the interpretation and validity of these outcomes uncertain. In contrast, Togsverd-Bo's study, a controlled RCT, avoided above problems and determined that PDL therapy did not make any difference compared to conventional treatment.

PDT

As explained by Schroeter et al, pulse dye laser therapy involves the combination of a photosensitizer and light in the presence of oxygen, during which time free radicals are generated thereby destroying the tissue. Aminolevulinic Acid, a photosensitizer to the cells containing HPV, is applied topically to the location of the wart before pulse dye treatment. The success rate in Schroeter's study was related to the age, treatment time and size of warts. Higher success rates were noted in patients that are young, longer treatment time, and larger warts. Fabbrocini et al compared the effectiveness of PDT +ALA with a control group in which ALA was not applied. His results were shown to have an 87.3% success rate in patients in which ALA was applied before PDT treatment with no post-op complications. Some complications were noted to occur during the treatment in both studies. These complications include slight burning and tingling sensations. There were virtually no post-op complications observed during both author's studies. This therapy proved to be more effective than previous light therapies that have been utilized with minimal complications. Both authors' studies were well constructed, but the size of Schroeter's study and control group may not be sufficient to legitimize the effectiveness of the treatment. A transparent presentation of the results of their power analysis would have

yielded a more powerful study, which addressed the suboptimal control group size. Fabbrocini's study has a larger study size in which nearly half the patients were utilized as the control group. Although the study just compares the effectiveness of PDT with and without ALA, it proves the effectiveness of the therapy. Schroeter et al had chosen his patients from a specific population which may distort the results in favor of the test, whereas Fabbrocini had randomly obtained his patients and performed a double-blind clinical trial study in which the study would not be favored. Based on the results, PDT turned out to be an effective therapy based on the results of the two studies, but a larger sample size will increase the validity of the treatment.

YAG

YAG is a newer and safer method of laser treatment that became popular in late 1990's and early 2000's. YAG can be divided into invasive and non-invasive technique depending on the wavelength it uses. And it is considered more invasive if higher wavelength is used. Typically, Er:YAG uses longer wavelength (2.94μm), which has greater penetration power compared to Nd:YAG (1650ηm). It is discovered to be a beneficial treatment option, especially Er:YAG with its higher penetrating power, for recalcitrant plantar warts as demonstrated by both Trelle and Wollinina. However, it is hard to conclusively determine its efficacy due to their study designs. They are all small retrospective studies with heterogenetic patient population where variable inclusion and exclusion criteria are used as well as different definition of study outcomes. Also, the non-controlled and non-randomized nature of their study design make it difficult to eliminate investigator-associated bias that causes interpretation and validity of the study very uncertain. Therefore, despite the evidence of some benefit of using YAG on treating recalcitrant plantar warts we need high quality controlled RCT to definitively determine its true efficacy.

CONCLUSION

In summary, results are inconclusive in determining the single best therapeutic light therapy option for recalcitrant warts. For definitive comparison one needs to perform a meta-analysis with minimum confounding factors and standardized outcome measures. Additionally, the articles used for this review were mostly small retrospective studies and patients had variable previous treatments with discrepancies in the follow-up protocols amongst different studies. Therefore, utilization of more RCT's with larger subject size and high degree of homogeneity could further strengthen the study outcome.

AUTHOR'S CONTRIBUTIONS

The authors equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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Management of Pyoderma Gangrenosum in the Presence of Comorbidities-A Case Study

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Abstract

Introduction
Pyoderma Gangrenosum is a rare ulcerative neutrophilic dermatosis which is very difficult to diagnose.[1] There are no diagnostic lab tests available, and most of the diagnosis is made by exclusion. The purpose of this study is to review management of pyoderma gangrenosum in a patient over the course of 2 yrs.

Study Design
Case report

Methods
The diagnosis of pyoderma gangrenosum was made based on exclusion and on the presence of primary and secondary criteria.[2] Primary criteria included the presence of an ulcer with an undermined wound-border. Secondary criteria included histological evidence and presence of certain comorbidities. Secondary criteria were fulfilled by the pathological report which confirmed the presence of neutrophil and lymphocytic infiltrates. In addition, the past medical history and the hematology reports of the subject confirmed the presence of endocrine dysfunction, arthralgia and metabolic syndrome.

Results
This article will offer a presentation of pyoderma gangrenosum in a 58 year old male over the period of 2 years. The article will include description and diagnosis of pyoderma gangrenosum as well as treatment options available for this disease. It will also include how the presence of different co-morbidities affects the healing of pyoderma gangrenosum.

Conclusion
The objective of this case report is to confirm the success of standard therapy for pyoderma gangrenosum. Standard therapy for this disease includes use of immunosuppressant drugs, wound care dressings and compression therapy. The failure of proper management of pyoderma gangrenosum in our case is strongly due to lack of patient's compliance and the presence of co-morbidities like diabetes which resulted in delayed healing. Further research assessing the treatment of pyoderma gangrenosum in the presence of co-morbidities will result in proper management and care for our patients.

Key Words
Pyoderma Gangrenosum, ulcer

Level of Evidence: 4

INTRODUCTION

Pyoderma gangrenosum is a rare skin disease that involves ulceration of the cutaneous tissue. It is an inflammatory disease whose manifestation has been suggested to involve the infiltration of the skin with abnormal neutrophils and immunological factors.[3] There is a greater predilection for adults, with females being more commonly affected than men. The incidence appears to be about 3-10 million per year.[4] Clinically, the disease is most commonly found in the lower extremity, with a greater occurrence in the pre-tibial area, however other areas of the skin may be involved. It starts out as sterile pustules which rapidly transform into painful ulcers with well-defined borders. The ulcer border is usually violet or blue.[5] There appears to be recurrent ulcerations that have a mucopurulent or hemorrhagic exudate. Erythema is usually noted around the ulcerations with severe pain. Patients normally present with systemic symptoms like fever, arthralgia and malaise.[5]

In the clinical settings, the course of pyoderma gangrenosum may present with an explosive on-set and rapid progression or an indolent on-set with gradual progression[3]. With the first type, the progression of the ulceration is rapid and necrosis is severe, whereas with the second presentation, the disease spontaneously regresses. In about 50% of the cases of pyoderma gangrenosum, there is an associated systemic disease, including inflammatory bowel disease, hematological and rheumatoid conditions.[2] However, there are cases of pyoderma gangrenosum that are drug induced or idiopathic.[5]

Pathophysiology

Pyoderma gangrenosum is considered an autoimmune disease of unknown etiology. There are many studies to support that pyoderma gangrenosum is linked to autoimmune diseases like inflammatory bowel disease, rheumatoid arthritis etc. In addition to that, tumor necrosis factor (TNF) has been shown to be increased in inflammatory bowel diseases and hence, it is not unexpected that anti-TNF medications have been shown to be effective against pyoderma gangrenosum. Also, it has been shown that patients taking immunosuppressants for the autoimmune disease often develop pyoderma gangrenosum, thus suggesting that there is a link between the autoimmune disease and pyoderma gangrenosum. Similarly, it has been found that in pyoderma gangrenosum, there is an increase in the T-cell lymphocytes which are targeted against certain autoantigen of unknown origin.[6]

Diagnosis

The diagnosis of pyoderma gangrenosum is a clinical one that will depend on the patient's history; however biopsies are supportive for the diagnosis. If a biopsy is obtained early in the disease stage, an infiltrate of chronic inflammatory cells in the dermis will be noted. A biopsy taken later in the disease stage will show an infiltrate of polymorphonuclear cells, with evidence of infarction and abscess formation.[5] However, the histopathological findings are non-specific for pyoderma gangrenosum and it is important to rule out possibilities including but not limited to venous disease, vasculitis, infectious disease, drug reaction and cancer.[4,5]

Main primary criteria	1. Primary sterile pustule or ulcer with livid, undermined wound-border
	2. Exclusion of other relevant differential diagnoses like chronic venous/ arterial leg ulcer, pyodermatitis, vasculitis
Additional secondary criteria	1. Histology of the wound-border: neutrophilic infiltration of the dermis with signs of vasculitis and accumulation of immunglobulins and/or complement factors beside the vessels
	2. Existence of relevant, associated concomitant diseases like chronic inflammatory bowel diseases, arthropathies, hematological disorders, neoplasia, endocrine dysfunctions, metabolic syndrome
	3. Response to a systemic immunosuppressive therapy or no response to a conventional ulcer-therapy
	4. Triggering of a PG by pathergy-phenomenon
	5. Extremely painful ulcer (VAS > 4 points)

Table 1: Showing Modified diagnostic criteria for Pyoderma Gangrenosum[1].

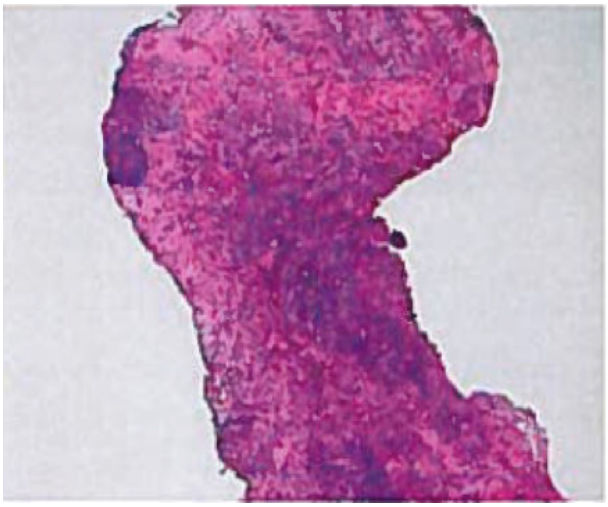
Differential Diagnosis

Pyoderma gangrenosum is mostly diagnosed clinically by exclusion. Since the most common manifestation of pyoderma gangrenosum is skin lesions, we have to rule out other conditions that could manifest similar to pyoderma gangrenosum. The histological manifestations of dermal infiltration of neutrophils and lymphocytes, which is seen in pyoderma gangrenosum, can also be seen in infection.[6] Hence adequate culture and sensitivity reports should be done to rule out any bacterial, viral or fungal infection.[5,6] Similarly, any vascular insufficiency, including venous or arterial, can also manifest itself in a similar ulcerative manner as pyoderma gangrenosum. Another differential should include cutaneous malignancies like squamous cell carcinoma or lymphoma.[7] Also, the presence of any systemic autoimmune disease like inflammatory bowel disease or rheumatoid arthritis should be taken into account before the diagnosis of pyoderma gangrenosum is made.[5]

Treatment

There is no one single treatment for pyoderma gangrenosum, however, the main goal of the treatment is to stop the inflammatory process and start the natural healing process. The treatment approach involves immunosuppression using topical and systemic steroids. Topical treatments used to slow down the progression of the disease include Triamcinolone. For patients with systemic symptoms, an oral corticosteroid, such as Prednisolone, has been reported to cause improvement. If treatment with corticosteroids fails, then other immunosuppressants should be utilized including Ciclosporine, Methotrexate, Tacrolimus.[5,8] The immunosuppressants have been known to not only reduce the dependence on corticosteroids but they are also helpful because the pyoderma tends to show resistance to treatment. Newer therapy approaches involve the use of biological elements like Tumor Necrosis Factor-α interleukins. Infliximab which is anti-TNF- α has been shown to help with some of the resistant ulcers.[9] A comprehensive list of most commonly used systemic immunosuppressants is shown in Table 2.[8] In a randomized clinical trial (RCT) it was found that treatment with Infliximab, a monoclonal antibody against Tumor necrosis factor-α, showed improvement in 20/29 patients.[5]

In a retrospective study done in Germany, it was found that 28.6% of the patients with pyoderma gangrenosum have diabetes mellitus. In the study, 32.6 % of the patients were obese and led them to believe that a possible correlation between metabolic syndrome and pyoderma gangrenosum.[1] In an earlier study done by Al Ghazal et al, diabetes mellitus, mostly type 2 was found in 25.5 % of patients and hypothyroidism was found in 6.9%.[1] Similarly, in another study done by Binus et al, underlying diabetes mellitus was found in 28.2% of all the patients. Again, these results show the correlation between co morbidities and pyoderma gangrenosum.



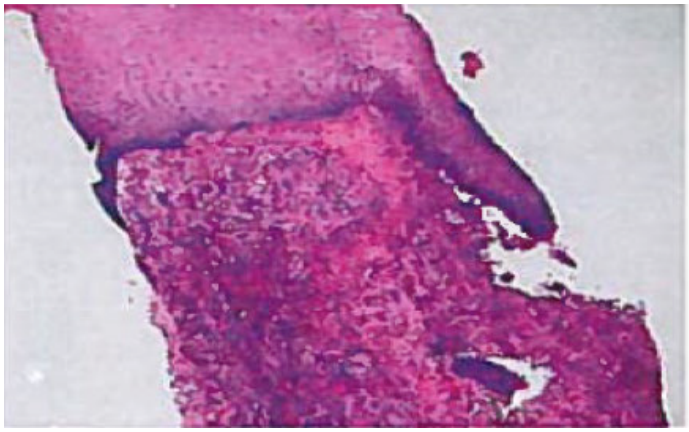


Figure 1 and 2: 2mm punch biopsy showing infiltrates of acute inflammatory cells along with lymphocytes and histiocytes

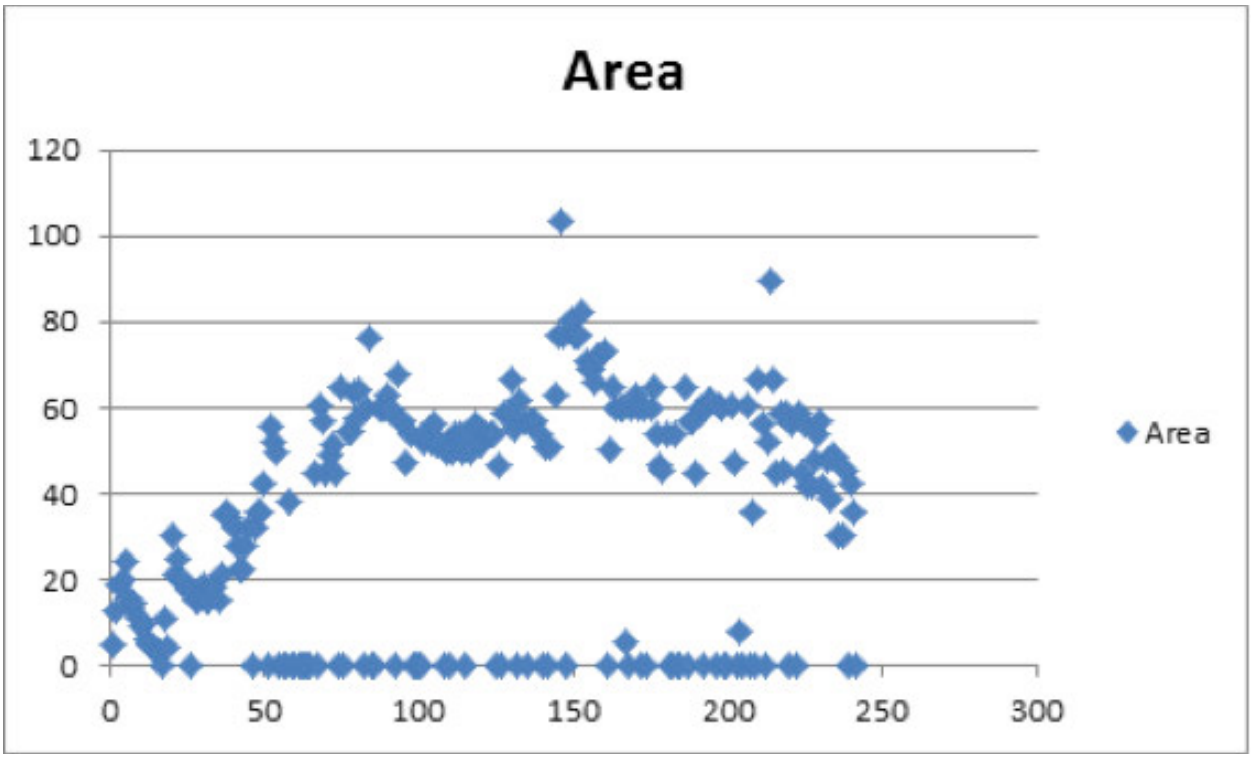
Anti-TNF-α (Etanercept, Infliximab, Adalimumab)
Anakinra
Azathioprine
Corticosteroids
Cyclophosphamide
Cyclosporine
Dapsone
Methotrexate
Minocycline
Mycophenolate mofetil
Sulfasalazine
Tacrolimus
Thalidomide

Table 2: comprehensive list of systemic immunosuppressants used for the treatment of Pyoderma[5] Gangrenosum

CASE REPORT (METHODS)

A 58 yr old male started coming to the podiatry clinic in 2006 for diabetic foot check-up including vascular, neurological, dermatological assessment and callus and nail debridement. On January 19, 2012 he presented with a fever, arthralgia and a painful ulcer on the lateral malleolus of the left foot which he stated started two weeks ago. Upon examination the ulcer appeared fibrous with a granular base, irregular macerated borders with serosanguinous scant. The initial ulcer dimensions were (Lx W x D) 2cm x 2.5cm x0.2cm. The ulcer was classified as UT grade 2C and Wagner grade of 2. Hyperpigmented, periwound scaling and +2 pittting perimalleolar edema was also noted. Medical history revealed a healed mid-foot ulcer, diabetes type 2, left hip replacement, obesity, peripheral venous insufficiency, hypothyroidism and a personality disorder. The patient was taking Amlodipine, Diovan HCT, Simvastatin, Lantus, Vit C, Vit D, Victoza, Percocet, Oxycontin, and Hydrocortisone at the time the ulcer appeared. The initial diagnosis was venous stasis ulcer, due to his history of peripheral venous insufficiency and was treated with Dicloxicillin (500mg), adaptic, Hydrofera blue dressings and compression therapy. The ulcer was routinely monitored and by May 2nd, 2012 the ulcer healed with a superficial scab.

He returned to clinic on May 17th, 2012 with a reopened ulcer at the healed site. The ulcer appeared macerated and was measured as 4.3cm x 2.2cmx 0.1cm. Microbiology reports confirmed Staph Aureus and a small episode of Pseudomonas infection of the ulcer site. Multiple hematology reports from 2012-2014 showed consistently high ESR, high HbA1c, high TSH levels, low T3 levels, low hemoglobin, low iron, low hematocrit, low lymphocyte % and high neutrophil count. An MRI was performed on September 30th, 2012 to rule out osteomyelitis but cellulitis could not be ruled out. PADnet studies conducted on November 13th, 2012 confirmed venous incompetency in the left lower extremity. Pathology reports ordered on September 27th, 2012 and July 22nd, 2013 showed increased number of small vessels and mixture of fibrin and acute inflammatory cells, along with superficial perivascular lymphocytic infiltrate composed of lymphocytes and scattered histiocytes (Figure 1). The diagnosis of Pyoderma Gangrenosum was made by exclusion and was confirmed by the presence of primary as well as secondary criteria (#1,2,3) as listed in Table 1.Treatment began with compression therapy along with Ciprofloxacin(500mg) and Clindamycin (300mg). Different topical creams like magic



Graph1: The area of the wound from 1/19/2012 to 12/29/2014

cream (consisting of, zinc oxide, Lidocaine and SSD and triple Abx), cellurate collagen powder and gel, Clobetasol ointment 0.05%, Phenytoin suspension 125mg/5m, LUZU (Luliconazole 1%) cream were also applied for the treatment of the ulcer. Various dressings including Adaptic, Calcium alginate, Prisma, Enluxtra humifiber on top of the silver dressing, Endoform, Hydrofera blue, Apligraf, Medihoney, Mepitel, MANUKApli, and Iodoform black gold along with gold dust particles were used and the ulcer dimensions were closely monitored for the next 19 months. The ulcer reached a peak measurement of 11.5cm X 9cm X 0.1cm.The measurement now as of December 29, 2014 was 6.5 cm X 5.5cm X 0.1cm. (Graph 1)

DISCUSSION

Pyoderma gangrenosum is an inflammatory immune-mediated disease which involves ulcerative skin lesions.[10] The unpredictable nature of the disease makes it very difficult to diagnose and provide proper treatment for it. The lack of a particular diagnostic tool for pyoderma gangrenosum causes clinicians to mostly rely on the histological lab reports and the presentation of the disease. Even though there has been no validated standard for treatment of pyoderma gangrenosum, most of the time the therapy relies on the use of topical as well as systemic immunosuppressants and biological materials. The skin graft and surgical debridement is often not used for the treatment of pyoderma gangrenosum because of the risk that the ulcers can be induced by trauma. Also, the draining nature of the ulcer can help determine what kind of dressing should be used for the ulcer.[8] With the use of

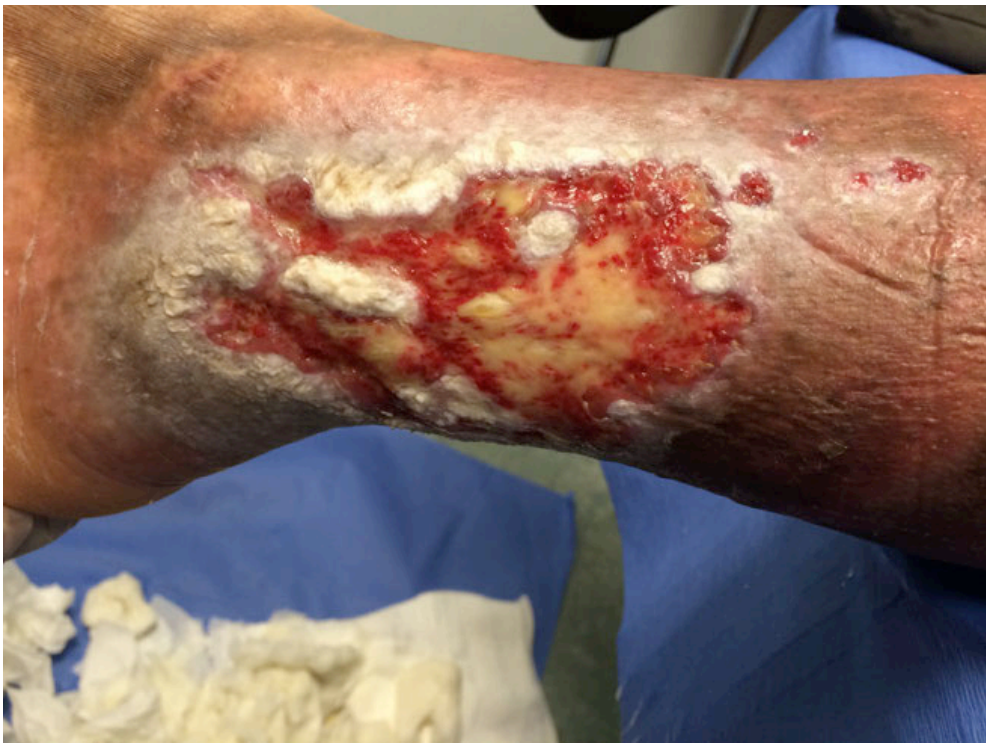


Figure 3: Picture taken on January 19, 2012

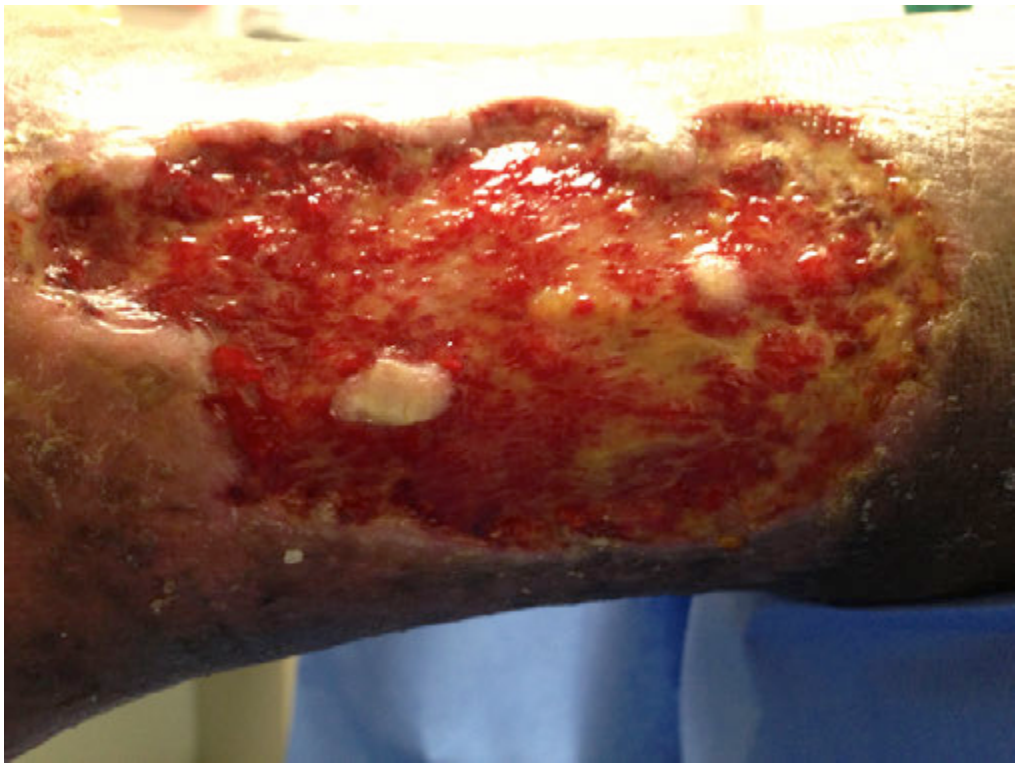


Figure 4: Picture taken on December 30, 2013

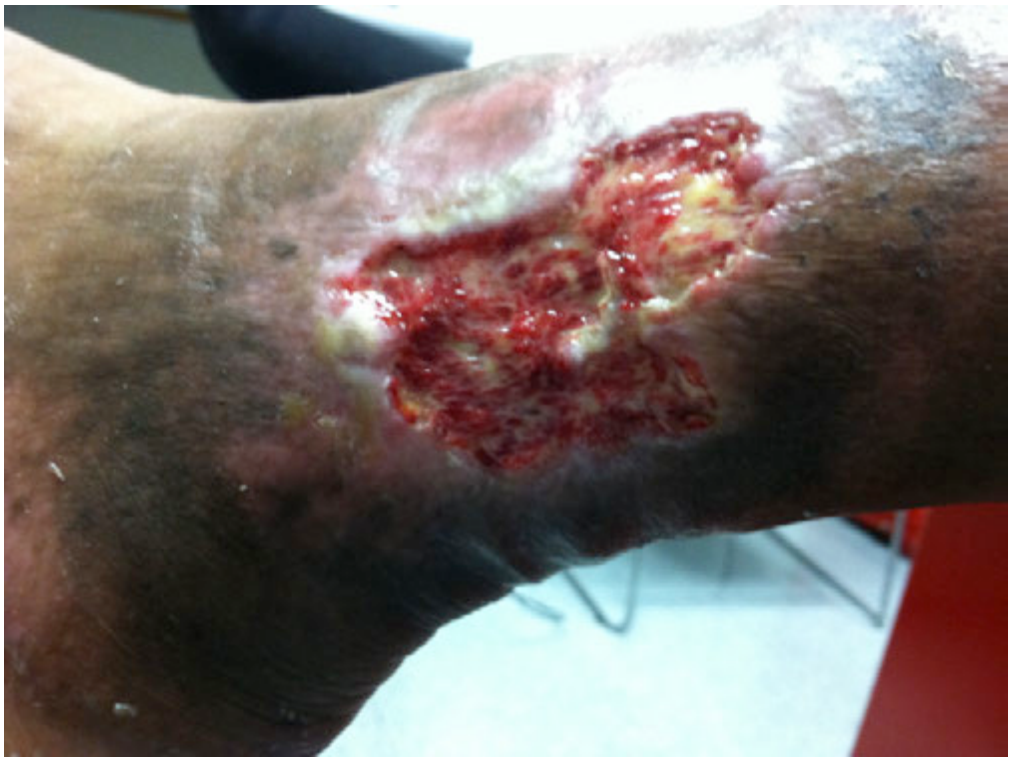


Figure 5: Picture taken on December 29, 2015

immunosuppressants, there is always a possibility of bacterial and fungal infections at the site of ulcer. Therefore, regular culture and sensitivity reports of the ulcer site can result in proper management of the disease without causing further infection.

In this case study, the recommended treatment plan for pyoderma gangrenosum was not followed because the patient refused the use of oral corticosteroids and immunosuppressants which made our treatment options very limited. Additionally, the initial ulcer healed within 5 months by the use of adaptic, hydrofera blue and unna boot application. But the ulcer reopened because of patient's failure to follow up on his visits. . The wound was addressed using the wound care protocol using the various dressings stated above. Although the ulcer appeared to heal, the ulcer reopened several times, indicating that another factor was playing a role. The non-compliance of the patience was evident in his consistently high HbA1c and his high BMI. Weight bearing also did not allow the ulcer to heal properly. It is essential to recognize the variable factors that may play a role in delayed healing of patient's wounds. In the case of our patient, the presence of venous insufficiency, multiple endocrine abnormalities, and a history of hip replacement, which caused him to have an abnormal gait, may have played a role in the delayed healing of the patient's wound.

CONCLUSION

The presentation of the ulcer along with the patient's history and biopsy report support the diagnosis. In this paper we follow the course

of ulcer formation and treatment in a patient with co-morbidities. We gain insight into how healing can be delayed and how various factors influence healing time. This case was interesting as it showed us how the diagnosis of pyoderma gangrenosum can be made, and that it is mainly made by exclusion. Ideally, further work would include following the use of all the available treatment options and to see the effect comorbidities have on the healing. However, in this case the patient's current refusal makes it difficult. Further research is needed to compile a standard diagnostic tool for pyoderma gangrenosum and compose a standard protocol for the management of this disease.

AUTHOR'S CONTRIBUTIONS

The authors equally contributed to the construction of this manuscript.

STATEMENT OF COMPETING INTERESTS

The authors declare that they have no competing interest associated with this manuscript.

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