New York College of Podiatric Medicine

Podiatric Medical Review

Volume 31 **2022-2023**

A systematic review of the current management of foot blisters in military personnel Julia Reczek BS, Pages 6-14

A Systematic Review of the Efficacy of Pegloticase as a Treatment for Chronic Gout Surujdevi Singh BS; Samantha Owens BS, Pages 15-22

Common etiology, Pathogenesis and Potential Effective Treatments for Calcaneal Fat Pad Deterioration: A Literature Review Harneet Jaswal BS; Jessie Laffey BA, Pages 23-31

Comparing treatment outcomes and subsequent sequelae for rheumatoid arthritis of the foot and ankle Sruthi Kosuru BS; Shivani Mahajan BS; Jyoti Borate BA; Srishti Ramthirthkar MS; Tamara Pavlovic BS, Pages 32-46

Combined Anticoagulant and Antiplatelet Therapy on Peripheral Arterial Diseases: A Literature Review Biao Zhang MS, Pages 47-57

Differences in Surgical Outcomes for Tarsal Coalition Based on Interposition Used: A Systematic Review of the Literature Jacques Blondet BS; Ahra Cho MS; Kai Higuchi BS; Sahil Mapkar BS; Pages 58-72

Evaluating the Efficacy of L-Arginine and Glutamine on Wound healing: A literature review Muhammad Umair Husain MPH; Naila Habeeb MS; Tuba Azaam BS, Pages 73-80

Evaluating the Implication of Copper in Wound Healing: A literature review Ronald Baraga Delannoy BS; Muhammad Umair Husain MPH; Pages 81-89

Efficacy of Foot and Ankle Orthoses in the Treatment of Gait Abnormalities in Children with Neurological Deficits: a Systematic Review Noran Abo-Donia BS; Jo-Yu Fang BS, Pages 90-100

Lower extremity amputation risk associated with using sodium-glucose cotransporter 2 (SGLT-2) inhibitors Jaqueline Harris BA; Kunali Patel BS, Pages 101-109

Fish Skin Graft Versus Tissue Matrix Allograft in the Treatment of Lower Extremity Diabetic Wounds: A Systematic Review Lauren Wasserman BS; Jennifer Bloom MA; Amanda Varveris BS; Srini Shah BS; Edgar Lu BS, Pages 109-126

Literature Review of Pediatric Obesity in Relation to Gait Morphology Anna Nicole Dartley BA; Annmarie Abodeely BS; Troy Gubler MS; Janice Therese Bautista DPM MPH, Pages 127-141

Posterior Tibial Tendon Transfers in Treating Foot Drop Patients: A Systematic Review. Christina Yerdon BS; Andrew Bastauross BS; Chiara Mercado BS; Milana Mayzlish BS; Sally Foad MD; Demiana Ishak MS, Pages 142-156

Podiatric Manifestations of Illicit Drug Use Harneet Jaswal BS, Pages 157-163

Rapid Detection of Methicillin Resistant Staphylococcus Aureus (MRSA) and Methicillin Sensitive Staphylococcus Aureus (MSSA) among Patients with Foot Infection. Opemipo Akin-Adejimi BS, Pages 164-173

SECOND RAY PATHOLOGY FOLLOWING 1ST RAY PROCEDURES AS RELATED TO METATARSAL PROTRUSION DISTANCE. DO PREOPERATIVE LENGTHS MATTER? Dolly Basaldua DPM; Emanoil Shafik DPM; Anthony Ghali BS; Andrew Bastauross BS, Pages 174-179

Stem cell based therapy for peripheral arterial disease: A literature review Ajay Patel BS; Caroline Downs BS; Taylor Furtado BS, Pages 180-191

Suture Button Versus Syndesmotic Screw for Ankle Fractures Laurin Larian DPM, Pages 192-200

The significance of bacterial diversity and foot ulcer localization in younger and older individuals with Diabetes Devondra Pitt MS; Shauna--Kay Rhooms BS; Betty Kim BS, Pages 201-209

The Difference in Dermatological Manifestations Between Kaposi Sarcoma and Diabetic Foot Ulcers: A Literature Review Faiyaz Mohammad Rahman BA; Jason Singh BA; Harman Manj BA; Muhammad Abdulla BA, Pages 210-219

"The Efficacy of Resveratrol on Wound Healing." Sebastian Sukdeo BS; Bryant Tufino Flores BA; Nikki Hammond BS; Naila Habeeb BS, Pages 220-227

The incidence of lower extremity injuries occurring on athletic turf in comparison to natural grass: A Literature Review Emil Gulman BS; Nikolay Igdalov MS; Muhammad Umair Husain MPH; Rodion Savelyev BS, Pages 228-235

Use of Deep Vein Arterialization for treatment of end-stage lower limb arterial damage Devondra Pitt MS; Shauna-Kay Rhooms BS, Pages 236-248

Using Botulinum Toxin as a Non Surgical Treatment for Diabetic Neuropathy: A Literature Review Olivia Chandler BA; Christian Elder BS; Tommy Oliver BS; Pages 249-255

STUDENT JOURNAL OF THE NEW YORK COLLEGE OF PODIATRIC MEDICINE

A Note from the Editors

"*While writing your research paper, don't forget that you are crafting a small piece of history. Your work, no matter how humble or grand, contributes to the legacy of human understanding.*"

-Carl Sagan

Podiatry is a unique field that is fortunate to benefit from the dedicated and skilled contributions of both women and men in the realm of podiatric research. The Podiatric Medical Review (PMR) has a long-standing history of consistently producing top-notch publications based on evidence-based medicine over the years. It is with a great sense of pride and honor that we bring you Volume 31 of our journal.

We wish to express our utmost gratitude, with sincere modesty, to the senior editors, junior editors, peer reviewers, and the faculty members of the New York College of Podiatric Medicine for their commendable dedication to this journal. Without your contributions to Volume 31, the progress of podiatric research would not have been possible, and this progress is essential for the well-being of our future patients. Our aspiration is to inspire all our readers to recognize the critical role of podiatric research in shaping the podiatric clinicians they aspire to become. Engaging in podiatric research is integral to staying current in understanding effective diagnoses and treatment outcomes for all our patients. The ultimate objective should be to enhance the health of our patients, as well as that of all podiatric medical students, residents, and attending podiatrists as we all advance in our noble careers.

With a tremendous amount of enthusiasm, we are delighted to present to you the forthcoming edition of the Podiatric Medical Review, Volume 31 edition.

Faiyaz Rahman

Kunali Patel

Congratulatory Note from our Faculty Advisor

Dear Readers of the *NYCPM Podiatric Medical Review*,

It is with great pleasure that I take this opportunity to congratulate and recognize all who contributed to the 2023 NYCPM *Podiatric Medical Review*. In addition, with the guidance and leadership from our Editor-in-Chief Faiyaz Rahman, and Co-Editor-in-Chief Kunali Patel, along with their editorial staff, and all those who contributed articles to the *Review*, including their clinical faculty reviewers…Thank you!

This publication is a tribute to the dedication and hard work of all who were involved in its preparation. The journal offers student written literature reviews, case reports, and original research…

In addition, the goal of publication is to steer students towards research and to get them comfortable with analyzing medical and scientific works. This enhances the education at NYCPM and helps to create well- rounded clinicians in the near future.

The Volume 31 NYCPM Peer Medical Review will reach a large audience. It will be distributed to many Podiatric Residency Programs and to other schools of Podiatric Medicine. The *Review* is a testament to the kind of outstanding work our students are capable of, and we are so pleased to see them all very accomplished.

Again, warmest congratulations on your achievements and to all who have been involved in making this publication a tremendous success.

Fraternally submitted,

Anthony R. Iorio DPM, MPH
Faculty Advisor NYCPM PMR

A Systematic Review of the Risk Factors and Current Measures to Prevent Foot Blisters in Military Personnel

Julia Reczek, BS

ABSTRACT

Introduction
It is commonplace for members of the armed forces to perform physically demanding marches at some point in their career. Friction blisters developed during these marches may seem inconsequential but can lead to debilitating pain or further disease if not treated properly. The purpose of this paper is to evaluate the current methods for reducing incidence of foot blisters and investigate the risk factors for developing blisters in a military environment.

Study Design
Systematic review of literature

Methods
A PubMed MeSH terms search with the query "(military personnel) AND (blister) AND (injury)" yielded a result of 14 articles. The inclusion criteria for selection were articles written in English and utilizing human subjects. Exclusion criteria were papers which focused on warfare blistering agents, blistering diseases, or those that investigated treatment of blisters and not their development. These criteria designated 10 articles to be reviewed.

Results
Each paper investigating the effectiveness of different sock materials determined that utilizing a sock made from synthetic fibers significantly reduced the incidence of blisters. The most effective type of synthetic material was not conclusively identified, with socks made from polyester, polypropylene, or BLEND (50% Merino wool, 33% polypropylene and 17% polyamide) all proving to reduce blisters compared to standard wool socks. The major risk factors for developing foot blisters were white ethnicity, female sex, using tobacco, pes planus, and younger age.

Conclusion
Synthetic sock fabrics have been shown to effectively decrease the number of blisters developed on marches. Other preventative measures such as antiperspirants are not recommended due to frequent skin irritation. Additional research should be done to ascertain the sock fabric which would put soldiers at lowest risk for forming foot blisters.

Keywords: Military personnel, blisters, socks, injury

Level of Evidence: Level 4

INTRODUCTION

Friction blisters are a skin pathology which are commonly experienced by people from all walks of life but are especially relevant and concerning among athletes. From runners to ballerinas, enduring a blister on a weight bearing surface can inhibit the level of performance and even lead to further injury or infection. A specific population in which foot blisters can be especially debilitating is among military personnel[1]. The unique working conditions and physical demand put upon soldiers makes them an important demographic to assess for the innovation of new injury prevention measures, which is the aim of this paper.

Blisters are a type of painful skin pathology which can arise from many sources. However, those from marching are caused by friction. Shearing forces acting upon the skin, such as a boot or sock moving against the sole of the foot, can cause separation of the epidermis into layers. This separation often occurs near the mid-Malpighian layer (stratum basal and spinous layers combined), leaving an overlying blister made of the stratum granulosum, spinosum and corneum.[2,3] The newly formed space between the separated skin has a lower pressure than its surroundings, so hydrostatic force creates an accumulation of transudate, exudate or blood here.[2] While this blister is currently sterile, continued frictional forces can cause a break in the top layers and the release of any fluid inside. The now open wound is at risk for infiltration by bacteria or any other foreign substances, which in a larger blister could cause serious consequences, such as sepsis or ulceration if not treated properly.[3]

Soldiers are often tasked with marching long distances while wearing ill-fitting boots and carrying heavy loads, which can promote the formation of numerous foot pathologies, including blisters. Moreover, the development of new weapons and armor technology over the years has caused soldiers to increase the weight of the loads they carry. Recently during the war in Afghanistan, soldiers carried up to 127 pounds of weight at once. This may not only increase the force applied to the feet, but also potentially affect the way the soldier walks, leading to more pathology.[1]

The negative effects of foot blisters on military personnel have been studied extensively, yet their development is still very common today. According to Brennan et al., a 1972 study stated that 10% of the admissions to Walson Army Community Hospital in New Jersey had a primary complaint of lower extremity skin lesions. Of this 10%, over half were noted to be friction blisters, thus indicating the presence of blisters severe enough to seek medical attention.[3] A different study reported that, after completing a 161-kilometer march over five days, 21% of the soldiers from Fort Liggett, California sought medical treatment for friction blisters.[3] This value is even more significant when studied from a monetary perspective. Brennan et al. continued to report a study which stated that blisters were seen among 5.4% of the US Marine Corps recruit training program members, which effectively cost the organization nearly $700,000 due to the injured recruits performing only light duty for several days while recovering.[3]

Clearly, foot blisters are a very common medical problem among active members of the military and should not be discounted as an inconsequential injury. Further work still needs to be done to advance current technologies to prevent the formation of foot blisters amidst the high physical burdens put upon soldiers today.[4] The common

modalities used today to reduce foot blister incidence are fitting boots properly, performing physical training in preparation for marches, using topical antiperspirants, and providing socks that function to reduce moisture and friction against the skin.[5] Throughout this paper, these methods will be assessed to determine which, if any, should be considered most effective in preventing foot blister formation, and the direction of any necessary further research in this field will be indicated.

METHODS

A MeSH terms search in PubMed with the query "(military personnel) AND (blister) AND (injury)" yielded a result of 14 articles. The inclusion criteria for article selection involved human subjects and studies published in English. Of these articles, three were excluded based on exclusion criteria outlined in Figure 1. Finally, this yielded 10 articles included in this literature review.

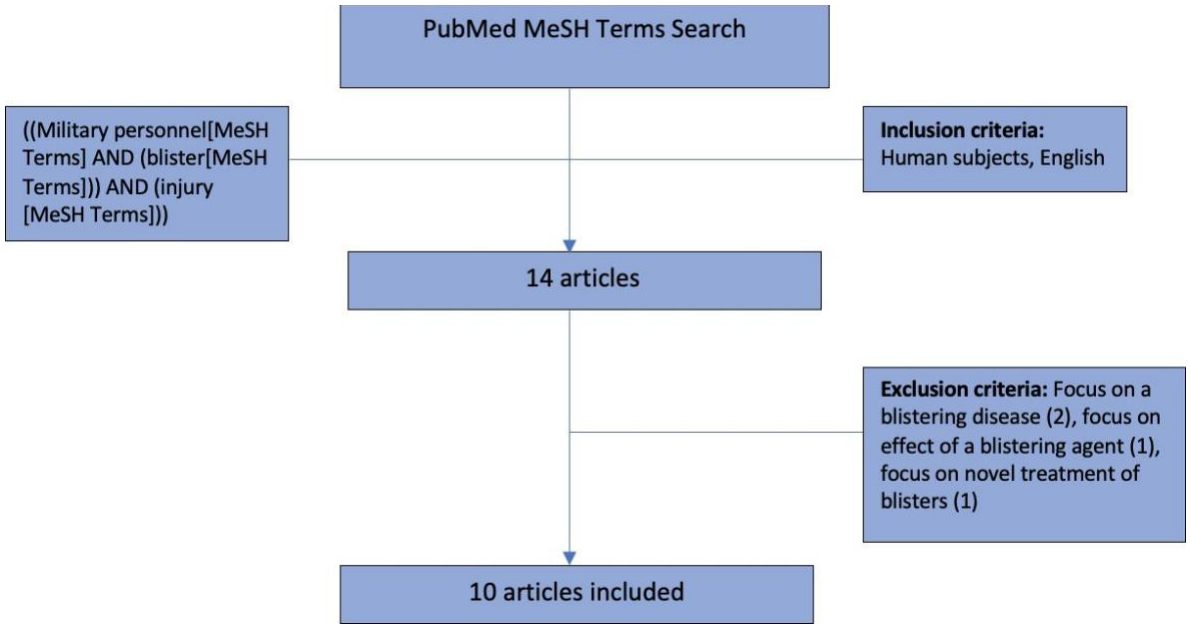


Figure 1: *PubMed Article Search with inclusion and exclusion criteria*

RESULTS

In his paper, "Injuries and Prevention During Foot Marching", Knapik analyzed the results of two studies focused on the incidence of injuries during road marches.[1] The first study was conducted following a 20-km march where 335 soldiers carried a load of 101 pounds, and in the second study 218 soldiers carried a 104-pound load for the duration of a 161-km march which took place over the course of five days. The total incidence of foot blisters in the first study was 35%. This made foot blisters the most common injury incurred from this march. Back pain was the second most prevalent injury, at 23%, followed by metatarsalgia at 12%.[1] In the second study, 50% of the soldiers experienced foot blisters, with three soldiers discontinuing their march before completion due to this injury. The second most prevalent injury was metatarsalgia at

17%, followed by knee pain at 7%. Knapik continued by giving recommendations to prevent the development of the most common injuries from each study. When discussing foot blisters, he stated that because blisters develop from the combination of moisture on the skin and applied friction, if these conditions were reduced, blister formation should be avoided. Possible measures to reduce friction and moisture included fitting issued boots properly, conditioning the feet for marches through athletic training, using socks made of a material that wicks away moisture, or applying antiperspirant to the feet.[1]

In another article by Knapik, entitled "Prevention of Foot Blisters", there was a more detailed explanation of methods to reduce the formation of blisters. Knapik stated that "blisters occur most often in feet that have not been properly conditioned".[5] As the skin builds tolerance to frictional forces, it grows thicker with stronger adhesion between layers and renewal of the outermost layer of skin more frequently. The two other measures examined to prevent blisters were sock choice and antiperspirants. Regarding socks, Knapik discussed a study done by the Marine Corps, where the effectiveness of three different sock systems at preventing blisters was examined. The first sock was a standard issue sock made of a mixture of wool, cotton, nylon, and spandex. The second sock was the same standard issue material but had a liner worn underneath made of polyester; the intention being to increase the wicking moisture away from the skin. The third sock was made of a mixture of wool and polypropylene material, and also used the liner introduced in the second sock system. Blisters were later seen in 24% of soldiers wearing sock system one, 11% of soldiers in system two, and 9% in system three.[5] The author states that the function of the liner was likely to reduce frictional forces on the skin, while the fabric blend used in the third system dispersed moisture from the skin surface.[5]

When discussing the use of antiperspirants, this same study by Knapik detailed a study done at the West Point military academy while cadets prepared for a 21-km road march where they would be also carrying a load of 72 pounds.[5] There were two groups in the study, with the first group applying an antiperspirant containing 20% aluminum chloride hexahydrate to their feet, while the second group received a placebo. After the march, 21% of the test group experienced blisters compared to 48% of the placebo group. While this was a significant result, the test group also had the undesirable side effect of skin irritation in 57% of their group, while the placebo group had 6% chance of skin irritation.[5] It was determined that while the antiperspirant was successful in reducing blisters, the skin irritation from the aluminum chloride makes it less advantageous than other potential measures.[5]

A study done by Van Tiggelen et al. highlighted specifically the effect sock choice could have on the formation of foot blisters. In this prospective case control study, six platoons (189 officer cadets) of the Belgian Royal Military Academy were separated into three groups and given different sock systems to wear.[2] The first group wore padded polyester socks made of a blend of 88% polyester, 11% polyamide, and 1% elastane material. Group two was given two pairs of socks to wear simultaneously. The inner sock was composed of a thinner material made from 45% polyester, 45% viscose, 8% polyamide and 2% elastase material. The thicker outer sock was made from a blend of 40% cotton,

40% wool, 18% polyamide and 2% elastane. The final group was the control, who were given standard army socks made of a 70% wool and 30% polyamide blend. [2] The socks were worn throughout a six-week long training program, and all participants experienced the same schedule, activities, and environment. When comparing the efficacy of different sock systems, it was found that the cadets who wore the first sock type, padded polyester, developed significantly less blisters than those in the double layer socks ($p=0.007$) and the control group ($p<0.001$). [2] When comparing the double layer to the control group, no significant change in blister formation was found. An assessment of risk factors among the cadets was also incorporated into this study in the form of a questionnaire. Cadets selected which risk factors applied to them, such as smoking, alcohol, recent lower extremity injuries, use of topical anti-blister treatments like antiperspirants, and prior military or athletic experiences. The only significant risk factor ($p<0.001$) was race, where Caucasians were at a much higher risk compared to those with an African background. The author noted other associations between blisters and pes planus/pes cavus foot types, and a slight correlation between female soldiers and increased blister incidence. [2]

In their retrospective cross-sectional study, Brennan et al. focused on highlighting risk factors and preventative qualities for foot blister development among soldiers who visited the 28th Combat Support Hospital in Baghdad, Iraq. [3] Soldiers receiving medical care in this hospital were asked to fill out a questionnaire concerning their activity level in the military and free time, if their boots had been broken in, their tobacco use, any blister history or measures used to prevent blisters. In total 872 of these questionnaires were completed and analyzed. Since the start of their time in Baghdad, 33% of the soldiers reported foot blisters and 11% of them received medical care for these wounds. The risk factors noted to increase the likelihood of developing blisters were being female, ages 26-34, not having boots broken in, and history of blisters on past deployments. Tobacco use and athletic/running activities did not show significant risk for blister development or avoidance. [3]

A different experimental study focusing on sock type was conducted by Bogerd et al., where 12 male military recruits wore specific socks while being asked to walk on a treadmill. Each participant carried a load of 21kg, consisting of their clothing and equipment. [6] The first sock was made of a 99.6% polypropylene and 0.4% elastane. The second sock, called BLEND, was composed of 50% Merino wool, 33% polypropylene and 17% polyamide. Some participants were instructed to wear the polypropylene sock on their left and BLEND on their right, while others were told to do the opposite. Skin temperature sensors were applied to each soldier's boots at five locations: near the medial cuneiform, distal to the phalanges, distal edge of the lateral malleolus, the dorsum of the third metatarsal and the distal anterior tibia. [6] After analyzing the temperature sensors, there was a significant difference in temperature at the dorsum of the third metatarsal and distal anterior tibia locations among the two sock types. The BLEND material showed higher temperature for the former, while the polypropylene sock had higher temperatures for the latter. The other three locations did not show any significant temperature differences. [6] Skin moisture data showed that the polypropylene socks absorbed less moisture than the BLEND socks ($p<0.01$), however the boots worn by soldiers were able to absorb more moisture

when worn with the polypropylene sock. Overall, these moisture differences led the authors to conclude there was no clinical difference in moisture absorption between the socks tested. [6] In a second paper by Bogerd, the same two sock materials were retested in a cohort of approximately 37 recruits, this time focusing on variations in moisture, temperature, and comfort perception. [7] Participants rated the BLEND sock to be more comfortable due to decreased temperature, dampness, and friction. Skin hydration was measured at three locations: plantar distal phalanx of the hallux, posterior calcaneus, and dorsal surface of the third metatarsal. The first location showed no difference in hydration between sock types, while the second two were both drier with the BLEND sock. [7] BLEND socks also absorbed 2.9±1.3 times more moisture than the polypropylene sock. This led the authors to recommend usage of the BLEND sock material in military settings. [7]

In a paper by Bush et al., a prospective study was performed to exemplify the prevalence, physical effects, and monetary cost of foot blisters among US Marine Corps recruits. There were 2,130 participants in this study, with the mean age being 18.4 years old.[8] These soldiers completed an 11-week course where they underwent intensive physical training for up to 20 hours each day. During training, 116 recruits received medical treatment for blisters, which were noted as the most frequent soft tissue injury and made up 10.7% of all diagnoses. Recruits being treated for a blister were likely to have other foot and ankle injuries as well.[8] Overall, blisters among these Marine Corp Recruits led to a total of 103 days of assigned light duty, 177 lost days of training, and 159 clinic visits. For this training program, it was estimated that blisters cost approximately $29,529. [8] Bush et al. stated that increasing educational measures about foot health could reduce the incidence of blisters. They also recommended breaking in boots properly before training and wearing 100% acrylic socks to reduce moisture on the skin surface. Finally, the authors noted an association between foot blisters and the development of subsequent severe injuries to the lower extremity. This may be the result of compensatory modifications to normal biomechanics when dealing with a painful blister. Therefore, Bush et al. emphasized the comprehensive significance of reducing blister incidence from a health and monetary perspective. [8]

Reynolds et al. performed a study on 218 soldiers while completing a 161-km march with a load of approximately 47kg.[9] Out of the 98 total injuries, 48% were from foot blisters which resulted in 10 total light duty days assigned subsequently. Soldiers also completed questionnaires before the march about their tobacco history as well as information about the footwear they would be using. Demographic data showed that white soldiers, soldiers younger than 24 years old, those who smoked cigarettes, and those with a lower body mass (<70.6kg) developed blisters more commonly.[9] There were no significant differences noted among different sock blends (standard issue wool versus cotton blend) or boot model.[9]

Birrell et al. conducted an experimental study to determine the types of injuries and level of discomfort experienced by soldiers during a two-hour treadmill march.[4] The participants each carried a load of 20-kg and were either interviewed about their experience (8 soldiers) or filled out a questionnaire (10 soldiers). 63% of the soldiers interviewed and 60% of those who completed a questionnaire reported development of foot blisters after the march.[4] The majority of the soldiers who

experienced blisters also reported that their boots felt adequately broken in, which led the authors to conclude that blister formation is dependent on other factors such as the load carried, stride length, distance marched, and speed.[4]

In a 1999 study by Knapik et al., the risk factors leading to foot blisters were assessed among 339 students beginning basic training at the US Military Academy.[10] The participants all filled out a questionnaire with demographic questions as well as those about foot type, prior illnesses, tobacco/alcohol usage, and previous military history. The cadettes then performed a 21-km road march while carrying a load of approximately 33kg. After the march, researchers determined that 44% of the participants developed new blisters while marching.[10] When investigating risk factors, it was found that being of black ethnicity reduced the risk of forming foot blisters compared to those of white (p=0.02), Asian (p=0.02), and Hispanic (p=0.08) ethnicities. When comparing individuals with pes planus to those with normal feet, the former had a higher incidence of blisters (p=0.05).[10] It was also found that individuals using smokeless tobacco products daily, those with no prior military experience, and those who experienced an illness in the past 12 months were at a higher risk of developing foot blisters.[10]

DISCUSSION

Foot blisters are a very common and often debilitating injury that have unfortunately become commonplace in military settings.[8] The distance which soldiers are required to march, as well as heavy loads of clothing and equipment put high levels of strain on the feet, which ultimately leads to friction blister formation.[4] There are several risk factors that have been identified as putting soldiers at a higher risk of forming blisters, which is information both healthcare providers and military personnel should be aware of. In their assessment of risk factors, Van Tiggelen et al. found that race was a significant risk factor for blisters.[2] Caucasians had a much higher risk of developing blisters, compared to individuals with an African background. This information is supported by the work of Reynolds et al. and Knapik et al. in their respective studies.[9,10] Soldiers of a younger age were also found to be more likely to experience foot blisters.[3,9] Foot biomechanics and the locations where the foot interacts with the ground can have a great effect on the integrity of the foot's skin. This was exemplified in two studies where individuals with pes planus were found to be at a greater risk for blisters than those with normal feet.[2,10] While Van Tiggelen et al. or Brennan et al. did not find a significant correlation between smoking/alcohol use and the likelihood for developing foot blisters, two other sources stated that tobacco products should be considered a risk factor.[2,3,9,10] Two studies reported that females were at greater chance for developing blisters than males, and several reported the importance of having well fitting, broken in boots to march in.[1,2,3,4,8]

All soldiers, especially those determined to be at higher risk, should be aware of effective methods to prevent the formation of foot blisters. One such measure that can reduce blister incidence is choosing socks that reduce moisture and temperature on the skin surface.[1,5] The 2014 study performed by Knapik proposed that a sock system made of a mixture of wool and polypropylene material plus a polyester liner reduced blister formation by 15% compared to a standard issue wool blend sock.[5] In Van Tiggelen's sock study, they found that a

padded sock made of a blend of 88% polyester, 11% polyamide, and 1% elastane material was significantly more effective at preventing blisters compared to a double layer and standard issue sock.[2] While Bogerd et al. completed two studies focused on sock material, only one showed a significant difference between the effectiveness of socks tested. There was no control utilized in these experiments, such as a standard issue sock, so any changes in temperature and skin moisture were only compared between the BLEND (50% Merino wool and 33% polypropylene and 17% polyamide) and the 99.6% polypropylene and 0.4% elastane sock.[6] In their second study, Bogerd et al. found that BLEND socks absorbed approximately three times as much moisture than the polypropylene sock, which led to their recommendation that BLEND material should be used in the military.[7] Bush et al. advised for the use of 100% acrylic socks due to their moisture wicking ability, but did not perform trials on this material's effectiveness.[8] While there is no overall consensus as to which sock material is superior for reducing blister incidence, each paper proposed a new synthetic blend instead of the standard issue sock, which is made of mostly natural fibers.[1,2,5,6,7] Synthetic materials distribute moisture and heat more evenly to help promote evaporation and create an more comfortable environment within the shoe.[6,7] In order to determine which of these sock materials is most effective at preventing the development of blisters, further comparison studies should be performed.

While several papers mentioned the use of antiperspirants to reduce friction blisters, one study showed a detrimental side effect that could negate their purpose for increasing foot comfort in soldiers.[1,2,5] Knapik stated that while topical antiperspirants did lead soldiers to experience 27% less blisters than those using a placebo, 57% of individuals in this test group also experienced skin irritation from the chemicals.

There are several limitations in this literature review. First, while the studies focused on risk factors often had large sample sizes, the experimental tests on sock types were performed in limited groups of soldiers. More studies that include statistical analysis on the efficacy of sock material at reducing blister formation should also be performed.

CONCLUSION

Blisters are a very common injury to the feet of military personnel around the world yet are frequently overlooked because they are often self-limiting. Before partaking in long distance marches, soldiers should be informed of the various risk factors for developing blisters such as white ethnicity, pes planus, younger age, using tobacco products, and not breaking in boots. Additionally, there should be preventative interventions implemented by military organizations to keep at-risk individuals from forming debilitating blisters. While synthetic blend socks have been shown to create an environment that makes the foot more resistant to blister development, it is not yet clear which material is most effective in doing so and thus requires further investigation. The use of topical antiperspirants has been considered another effective measure to reduce blister incidence, but the skin irritation associated with the active ingredients likely invalidates any benefit they could provide soldiers.

AUTHOR'S CONTRIBUTION

The author performed all evaluations and analyses required for this paper. The author

reviewed the final manuscript for submission.

STATEMENT OF COMPETING INTERESTS

The author declares that she has no competing interests associated with this manuscript.

REFERENCES

1. Knapik JJ. Injuries and injury prevention during foot marching. *J Spec Oper Med*. 2014;14(4):131-135.

2. Van Tiggelen D, Wickes S, Coorevits P, Dumalin M, Witvrouw E. Sock systems to prevent foot blisters and the impact on overuse injuries of the knee joint. *Mil Med*. 2009;174(2):183-189.

3. Brennan FH Jr, Jackson CR, Olsen C, Wilson C. Blisters on the battlefield: the prevalence of and factors associated with foot friction blisters during Operation Iraqi Freedom I. *Mil Med*. 2012;177(2):157-162.

4. Birrell SA, Hooper RH. Initial subjective load carriage injury data collected with interviews and questionnaires. *Mil Med*. 2007;172(3):306-311.

5. Knapik JJ. Prevention of foot blisters. *J Spec Oper Med*. 2014;14(2):95-97.

6. Bogerd CP, Rechsteiner I, Wüst B, Rossi RM, Brühwiler PA. The effect of two sock fabrics on physiological parameters associated with blister incidence: a laboratory study. *Ann Occup Hyg*. 2011;55(5):510-518.

7. Bogerd CP, Niedermann R, Brühwiler PA, Rossi RM. The effect of two sock fabrics on perception and physiological parameters associated with blister incidence: a field study. *Ann Occup Hyg*. 2012;56(4):481-488.

8. Bush RA, Brodine SK, Shaffer RA. The association of blisters with musculoskeletal injuries in male marine recruits. *J Am Podiatr Med Assoc*. 2000;90(4):194-198.

9. Reynolds KL, White JS, Knapik JJ, Witt CE, Amoroso PJ. Injuries and risk factors in a 100-mile (161-km) infantry road march. *Prev Med*. 1999;28(2):167-173.

10. Knapik JJ, Reynolds K, Barson J. Risk factors for foot blisters during road marching: tobacco use, ethnicity, foot type, previous illness, and other factors. *Mil Med*. 1999;164(2):92-97.

A Systematic Review of the Efficacy of Pegloticase as a Treatment for Chronic Gout

Surujdevi Singh, BS and Samantha Owens, BS

Abstract

Introduction

Gout is a medical condition defined as an abundance of uric acid that leads to its deposition in the joints. These deposits, most found in the 1st metatarsal phalangeal joint, lead to inflammation and pain. If untreated, Gout can cause destruction to the 1st metatarsal phalangeal joint and cause gait disorder and pain on ambulation. Gout attacks can arise suddenly and commonly occur at night. The first line of treatment for gout includes nonsteroidal anti-inflammatory drugs and corticosteroids. Patients that do not respond well to first line treatment methods or patients with chronic gout may benefit from receiving an intravenous therapy of pegloticase. Pegloticase works by lowering uric acid levels in the body. The methods of Pegloticase treatment for chronic gout will be reviewed and assessed utilizing clinical research articles. The effects of co-therapy with other gout medications, such as Methotrexate, Azathioprine, and Mycophenolate Mofetil will also be discussed. To analyze the efficacy of Pegloticase as a treatment method, the frequency of gout flares, changes in serum uric acid levels, adverse effects, withdrawal, and death will be evaluated.

Study Design: Systematic Literature Review

Methods

Utilizing the PubMed Database, a search was conducted for the phrases "gout" AND "pegloticase." The primary search query produced 183 articles. The Inclusion Criteria required that the research articles were English language systematic reviews published between 2010 and 2022, with human subjects. After the application of inclusion criteria, 11 articles were obtained. Two results were excluded from the search because they were repeated submissions for the same publication. One result was excluded because it did not discuss Pegloticase. The search yielded 8 articles.

Results

Most of the data published on the efficacy and safety of pegloticase, under the brand name of KRYSTEXXA®, was derived from the studies done by Botson et al. and Sundy et al. Studies have been performed on this drug with sample sizes of less than 50 patients. In the study done by Sundy et al., the confidence intervals were low, and although the p-value shows the data was statically significant, the research trials should be replicated with multiple trials. In research studies such as Sriranganathan et al. and Kydd et al, findings demonstrated that there were frequent events of adverse effects and infusion reactions that negatively affected patients and caused intolerance. Pegloticase has shown efficacy in treating refractory gout, but due to the intolerance of the drug more clinical research should be conducted to confirm the safety.

Conclusion

Pegloticase has been found to decrease urate concentration, reduce inflammation, and improve quality of life, making it a promising new drug for the treatment of chronic gout. Findings show that patients tolerated pegloticase better when receiving the drug monthly. Administration of pegloticase biweekly, however, resolved tophi with greater efficacy, but with higher occurrences of infusion reactions. Pegloticase has also shown efficacy in treating refractory gout but, due to the intolerance of the drug, more clinical research should be conducted to confirm the safety.

Keywords: Chronic gout, Pegloticase

Level of Evidence: Level 4

INTRODUCTION

Gout is a painful joint inflammation that often affects the 1st metatarsal phalangeal joint of the foot. Elevated uric acid levels in the blood contribute to the formation of urate crystals between joints which cause arthritic pain. Tophus, which consists of monosodium urate crystals, is a major symptom of gout. Oftentimes this is very painful for the patient suffering from gout. [1] Gout attacks or flares can occur suddenly and can last from days to weeks. [1] Treatment of acute gout flares typically consist of non-steroidal anti-inflammatory drugs to relieve pain and inflammation. [4]

Attacks may subside for months or even years; however, if left untreated, it can lead to chronic gout. To prevent chronic gout, the patient's diet and lifestyle habits should be assessed after an acute attack. [4] Additionally, medication is also commonly prescribed. One medication commonly used to prevent a recurrence of gout is allopurinol, although not all patients respond well to this treatment or to other medications currently available. The risk of gout increases when the uric acid levels in the blood exceed 7 mg/dL. Allopurinol, along with proper diet and lifestyle changes can keep uric acid levels below 6 mg/dL. Despite strict uric acid control, patients can still undergo gout flares and may have to continue to take medication for many years or for the rest of the patient's life. New medications such as Pegloticase are currently being researched to treat chronic gout. Pegloticase is administered as an injection every 6 months, converting the urate crystals into highly water soluble allantoin that is more easily excreted. [2]

Pegloticase is currently indicated for patients with chronic gout that have shown intolerance to other treatments for lowering urate levels. Efficacy and safety research has shown that pegloticase decreases urate concentration, reduces inflammation, and improves quality of life making it a promising new drug for the treatment of chronic gout. Pegloticase was FDA approved in 2010 and has been utilized in treatment of chronic gout, under the drug name KRYSTEXXA®.

METHODS

Utilizing the PubMed Database, the research topic search query was conducted using the phrases "gout" AND "pegloticase." The search query produced 183 articles. The Inclusion Criteria required that the research articles were English language systematic reviews published between 2010 and 2022, with human subjects. After the application of inclusion criteria, 11 articles were obtained. There were 2 results excluded from the search because they were repeated submissions for the same publication. One result was excluded because it did not discuss Pegloticase. The search yielded 8 articles.

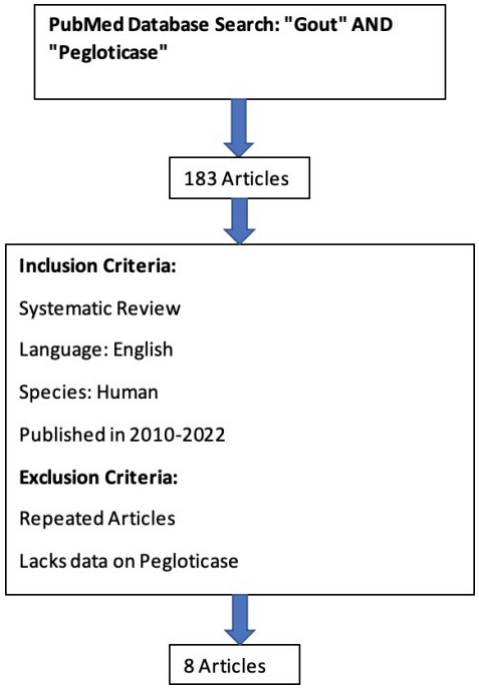


Figure 1: Summary of article acquisition with inclusion and exclusion criteria

RESULTS

In the systematic review by Richette et al., treatment guidelines were stated in relation to the severity of gout and the frequency of flares. In patients with gout flare, NSAIDs, colchicine, or steroids were recommended. In patients with frequent flares, NSAIDs, colchicine, or steroids were recommended with the addition of interleukin-1 blockers. Richette et al. also recommended that urate lowering therapy be initiated and serum uric acid monitored. SUA levels should be maintained at <6 mg/dL (360 µmol/L*)* and <5 mg/dL (300 µmol/L*)* in those with severe gout. [6] Allopurinol was recommended as a primary urate lowering therapy and its dosage adjusted according to renal function. If the SUA could be lowered to the recommended range with allopurinol, then febuxostat or a xanthine oxidase inhibitor should be prescribed. For patients with refractory gout, pegloticase was recommended. [6]

It is possible for patients to develop antibodies against Pegloticase causing concern that infusion reactions or an anaphylaxis response may occur. In a systemic review by Schlesinger et al, 6.7% of infusion reactions were reported in patients treated with intravenous Pegloticase.[4] The majority of these infusion reactions were considered mild to moderate and 0.35% of them were classified as anaphylaxis.[4] Despite Pegloticase having potential for immunogenicity, it still had significant efficacy in lowering serum urate levels, reducing tophi, decreasing pain, decreasing blood pressure, and improving the quality of life in patients with chronic refractory gout.[4]

To combat the immunogenicity properties of Pegloticase, treatment with an additional

agent might be beneficial. In the systematic review by Keenan et al., they found administering Pegloticase with an additional immune suppressing drug or immunomodulatory agent benefits patients' response to Pegloticase. [2] Specifically, 42% of patients treated with Pegloticase alone responded to treatment compared to 82.9% treated with Pegloticase with additional immunomodulation.[2] The immunomodulatory agents listed in order of successful response rates included Methotrexate, Mycophenolate Mofetil, SubA Methotrexate, Leflunomide, and Azathioprine. The proportion of patients that responded to pegloticase with an immunomodulatory agent ranged from 90.3% to 63.6%, all well above 42%.[2] Research has also shown that Pegloticase could have a higher efficacy when taken with methotrexate, highlighting that a cocktail of drugs might be beneficial for patients with chronic gout. [2] Studies have found that Pegloticase is effective with administration with methotrexate but has been contraindicated in patients with G6PD deficiency. In randomized clinical trials, 71% of patients receiving Pegloticase with Methotrexate showed improvement and 39% of patients receiving only Pegloticase showed improvement. [5]

As mentioned above, Methotrexate was found to be the most beneficial immunomodulatory agent when administered with Pegloticase and increased patients' response rate to treatment compared to Pegloticase alone. Boston et al. performed a clinical trial to study the efficacy and safety of using methotrexate in combination with pegloticase. Methotrexate was administered orally along with folic acid for four weeks before starting treatment with Pegloticase and continued throughout treatment. They reported 78.6% (11 out of 14) of patients still responded to pegloticase at the sixth month mark.[5] Gout flares at the three-month mark were reported as an adverse side effect but were less likely as treatment progressed. [5] No other adverse side effects were found in association with the combined treatment.

In the study by Sundy et al., the data had low confidence intervals and was one of the main referenced research articles for pegloticase. Two randomized clinical trials were conducted to observe the efficacy of pegloticase in decreasing serum uric acid levels below 6 mg/dL when administered biweekly or monthly. The primary end point was achieved in 36 of 85 patients in the biweekly group (42%; 95% CI, 32%-54%), 29 of 84 patients in the monthly group (35%; 95% CI, 24%-46%), and 0 of 43 patients in the placebo group (0%; 95% CI, 0%-8%; $P < .001$ for each comparison). [8] The confidence intervals were low for each group, but the p- value showed that the data could be replicable and was statically significant. Among patients with chronic gout, elevated serum uric acid level, and allopurinol intolerance or refractoriness, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower uric acid levels compared with placebo. [8] Additional research trials and a larger sample size would help to further corroborate these findings.

The efficacy and adverse effects were also investigated in Sriranganathan et. al. The study found that 14 % of patients had resolution of one or more tophi after receiving six months of treatment with pegloticase monthly compared with placebo. [3] The results showed 100% of people receiving pegloticase had adverse effects and 95% of people receiving the placebo had adverse effects. [3] Findings showed that patients tolerated pegloticase better when receiving the drug monthly. Monthly dosage had less infusion reactions than the biweekly dosage. However, receiving pegloticase

biweekly resolved tophi with higher efficacy. The drawback of pegloticase is seen in the gout flares that can occur when beginning this drug as well as the increased probability of an infusion reaction when receiving the injections of pegloticase.

To further compare the efficacy and safety of serum urate lowering therapies, a systematic review by Kydd et al. was referred. Allopurinol, febuxostat, and pegloticase were all effective at lowering serum urate compared to placebo, and febuxostat (≥ 80 mg) was more effective at lowering serum urate than allopurinol. [7] Regarding acute gout attacks, pegloticase and febuxostat (≥ 120 mg) resulted in more acute attacks than placebo. [7] These findings show that pegloticase has a higher chance of causing the patient discomfort and pain than as seen in allopurinol. Pegloticase was effective as a refractory gout treatment but was associated with more withdrawals due to adverse events and infusion reactions. This led to patients having lower tolerance to the drug and the need to change to an alternative.

DISCUSSION

Guidelines state that serum uric acid levels should be maintained at <6 mg/dL and <5mg/dL in those with severe gout. Therefore, urate lowering therapy should be initiated and serum uric acid level should be monitored appropriately. Allopurinol is the first line drug used for urate lowering therapy and should be adjusted according to renal function. If allopurinol fails to lower the serum urate concentration to appropriate levels, then febuxostat or a xanthine oxidase inhibitor should be prescribed.[6] Primarily, analgesics are used to treat discomfort, but with continuing frequency and severity, interleukin-1 blockers and pegloticase are prescribed.

One concern surrounding Pegloticase is its immunogenicity properties or the patient's ability to form antibodies to the medication. Infusion reactions were of specific concern considering the dangerous and severe nature of anaphylaxis reactions. In the systematic review by Schlesinger et al, it was found that Pegloticase treatment sometimes resulted in infusion reactions. Specifically, 113 infusion reactions occurred in 1695 infusions of pegloticase intravenously.[4] Out of these, 0.35% (6) were classified as anaphylaxis reactions.[4] They were classified as mild to moderate hypersensitivities and no fatalities were reported. Given this decently large sample size, infusion reactions and anaphylaxis do not seem to be a legitimate concern for treatment with Pegloticase. It has been seen that infusion reaction causes patients additional pain and intolerance to Pegloticase and can lead to the need to change medications.

Along with safety, the efficacy of Pegloticase was also a concern. Some patients developed antibodies against the medication and no longer responded to treatment; therefore, serum urate levels could not be lowered to less than 6 mg/dL. With that said, benefits were reported in patients who continued therapy despite developing immunogenicity. Gout flares were less common when Pegloticase was administered bi-weekly compared to monthly in patients who responded to Pegloticase and those who no longer responded. Pegloticase seems to have the ability to improve a patient's quality of life despite its immunogenic properties. In order to combat the immunogenicity of Pegloticase, treatment with an immunomodulator may be beneficial. Specifically, co-treatment with Methotrexate shows promise. Boston et al. found 78% of

patients co-treated with Pegloticase and methotrexate still responded to treatment at 6 months.[5] One limitation to this clinical trial, however, was the small sample size of 14 patients.

Pegloticase was seen to resolve tophi and reduced serum uric acid levels below 6 mg/dL more effectively when given biweekly, although it causes a higher occurrence of adverse effects. When looking at the studies performed to test the effectiveness and safety, most of the data published on KRYSTEXXA® was derived from the studies done by Botson et al. and Sundy et al. This novel drug has had research performed using sample sizes less than 50 patients per trial group. In the study done by Sundy et al., the confidence intervals were low and although the p-value shows the data is statically significant, the research trials should be replicated with multiple trials. In research studies, such as Sriranganathan et al. and Kydd et al, findings demonstrate that there are frequent events of adverse effects and infusion reactions that negatively affect patients and cause intolerance. Although these results show pegloticase as an unsafe drug option, the dosage period should be taken into consideration. Pegloticase has shown efficacy in treating refractory gout, but due to the intolerance of the drug more clinical research should be conducted to confirm the safety.

CONCLUSION

Pegloticase is a novel treatment option for patients with chronic gout that have shown intolerance to other treatments for lowering urate levels. It has been shown that pegloticase decreases urate concentration, reduces inflammation, and improves quality of life making it a promising new drug for the treatment of chronic gout. Findings show that patients tolerated pegloticase better when receiving the drug monthly. However, receiving pegloticase biweekly resolved tophi with higher efficacy. Pegloticase has shown efficacy in treating refractory gout, but due to the intolerance of the drug more clinical research should be conducted to confirm the safety.

AUTHOR'S CONTRIBUTION

Both authors contributed equally to the production of this literature review. Both authors approved the final submission.

STATEMENT OF COMPETING INTERESTS

The authors declare there were no competing interests associated with this paper.

REFERENCES

1. Anderson A, Singh JA. Pegloticase for chronic gout. Cochrane Database Syst Rev. 2010 Mar 17;2010(3):CD008335. doi: 10.1002/14651858.CD008335.pub2. PMID: 20238366; PMCID: PMC6599816.
2. Keenan RT, Botson JK, Masri KR, Padnick-Silver L, LaMoreaux B, Albert JA, Pillinger MH. The effect of immunomodulators on the efficacy and tolerability of pegloticase: a systematic review. Semin Arthritis Rheum. 2021 Apr;51(2):347-352. doi: 10.1016/j.semarthrit.2021.01.005. Epub 2021 Jan 27. PMID: 33601190.
3. Sriranganathan MK, Vinik O, Bombardier C, Edwards CJ. Interventions for tophi in gout. Cochrane Database Syst Rev. 2014 Oct 20;(10):CD010069. doi: 10.1002/14651858.CD010069.pub2. Update in: Cochrane Database Syst Rev. 2021 Aug 11;8:CD010069. PMID: 25330136.
4. Schlesinger N, Lipsky PE. Pegloticase treatment of chronic refractory gout: Update on efficacy and safety. Semin Arthritis Rheum. 2020 Jun;50(3S):S31-S38. doi: 10.1016/j.semarthrit.2020.04.011. PMID: 32620200.
5. Botson JK, Tesser JRP, Bennett R, Kenney HM, Peloso PM, Obermeyer K, LaMoreaux B, Weinblatt ME, Peterson J. Pegloticase in Combination With Methotrexate in Patients With Uncontrolled Gout: A Multicenter, Open-label Study (MIRROR). J Rheumatol. 2021 May;48(5):767-774. doi: 10.3899/jrheum.200460. Epub 2020 Sep 15. PMID: 32934137.
6. Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, Coyfish M, Guillo S, Jansen TL, Janssens H, Lioté F, Mallen C, Nuki G, Perez-Ruiz F, Pimentao J, Punzi L, Pywell T, So A, Tausche AK, Uhlig T, Zavada J, Zhang W, Tubach F, Bardin T. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017 Jan;76(1):29-42. doi: 10.1136/annrheumdis-2016-209707. Epub 2016 Jul 25. PMID: 27457514.
7. Kydd AS, Seth R, Buchbinder R, Falzon L, Edwards CJ, van der Heijde DM, Bombardier C. Urate-lowering therapy for the management of gout: a summary of 2 Cochrane reviews. J Rheumatol Suppl. 2014 Sep;92:33-41. doi: 10.3899/jrheum.140460. PMID: 25180126.
8. Sundy JS, Baraf HS, Yood RA, Edwards NL, Gutierrez-Urena SR, Treadwell EL, Vázquez-Mellado J, White WB, Lipsky PE, Horowitz Z, Huang W, Maroli AN, Waltrip RW 2nd, Hamburger SA, Becker MA. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. JAMA. 2011 Aug 17;306(7):711-20. doi: 10.1001/jama.2011.1169. PMID: 21846852.

Common Etiology, Pathogenesis and Potential Effective Treatments for Calcaneal Fat Pad Deterioration: A Literature Review

Harneet Jaswal, BS and Jessie Laffey, BA

ABSTRACT

Introduction

The calcaneal fat pad plays an important cushioning role in walking: one step has an impact of 110% of a person's mass and the fat pad can absorb around 80% of this movement (Balius et al., 2021). Two of the most common causes of plantar heel pain are calcaneal fat pad atrophy and plantar fasciitis (Yi et al., 2011). The calcaneal fat pad offers cushion, shock-absorption, and diffuses pressure while weight-bearing (Chang et al., 2022). It is located on the posterior plantar surface of the calcaneus and is composed of adipose tissue tightly packed into a collagenous septum with elastin fibers (Saad et al., 2021). To tell plantar fasciitis from fat pad atrophy, an ultrasound or magnetic resonance imaging (MRI) should be used (Balius et al., 2021). The purpose of this paper is to review how heel pad atrophy occurs and evaluate potential mitigation measures and treatment for it.

Study Design: Systematic Review of Literature

Methods

Five literature searches were conducted on the PubMed database using the key phrases "heel fat pad atrophy", "heel fat pad", "treatment heel pad atrophy" and "heel pain treatment" and "calcaneal pad atrophy obesity". The inclusion criteria consisted of articles related to heel fat pad atrophy and treatments for heel fat pad deterioration, while exclusion criteria included articles that didn't mention heel pad atrophy and those written before 1990. After applying the inclusion and exclusion criteria, 19 articles we available for review

Results

There are many causes of heel pad atrophy, such as aging, injury, prolonged and repetitive weightbearing, peripheral neuropathy, rheumatoid arthritis, and improper footwear (Chang et al., 2022). In addition, micro-traumas and repeated corticosteroid injections used for plantar fasciitis treatment are also common causes (Allam & Chang, 2022). Symptoms of heel pad atrophy include aching pain, tingling, burning and cold sensations, pain after a long walk, pain at night, and pain while resting (Yi et al., 2011). It is commonly seen in patients older than 40 years old as bilateral plantar heel pain (Yi et al., 2011). Some studies have found that fat grafting can be relatively successful in reducing pain and improving function (James et al., 2021). Pedal fat grafts can also act as preventative measures to prevent further deterioration (Minteer et al., 2018). Other treatments include manual therapies, foot orthotics, and taping (Salvioli et al., 2017).

Conclusion

Calcaneal fat pad atrophy is commonly seen with plantar fasciitis and can be due to a variety of causes. Although not as effective as an intact heel pad, there are various treatments for replacing the deteriorated adipose tissue. Additional methods are in the process of development and will

allow for more function and less pain for patients. Although it is difficult to circumvent heel pad atrophy altogether, the treatments listed here, as well as conservative measures, will allow patients to either improve or detain the progression of the degeneration.

Keywords: heel, atrophy, fat pad, calcaneal

Levels of Evidence: 4

INTRODUCTION

A notable advantage human beings obtained through evolution was the ability to move in a bipedal manner. This allowed for movement with only the lower extremities instead of all four limbs, expediting not only the ability to walk but also the potential to run long distances. Although standing upright allowed new and additional movements when compared to our four-legged ancestors, this new design arrived with imperfections. One example is the effect our body weight has on our feet, more specifically on our heels.

The calcaneal fat pad bears the biggest load when compared to other parts of the foot while a person is standing (Chanda & McClain, 2019). The fat pad is located below the calcaneus and mitigates the force the ground has on the foot when taking a step (Chanda & McClain, 2019). The fat pad is arranged into superficial and deep U-shaped septa, filled with adipose tissue and reinforced with elastic fibers (Lopez-Lopez et al., 2019). It contains 19-25% more unsaturated fatty acids than adipose tissue elsewhere in the body, which contributes to its unique function as a shock absorber and dissipater (Lopez-Lopez, 2019).

When initiating the gait cycle, the heel hits the ground during the first strike, leading to a constriction of the pad. Consequently, the fat pad absorbs just under 25% of the impact when walking. Due to its vital role, heel pain occurs more commonly than other types of foot pain (Chang et al., 2022). Around 3.6-7.3% of adults over the age of 18 have dealt with this affliction, and the number increases once a person passes middle age (Chang et al., 2022).

There are multiple factors that contribute to heel pain (Ozdemir et al., 2004). One main physiology of calcaneal fat pad atrophy is a loss in elasticity of the tissue, leading to increased compressibility and consequent heel pain (Balius et al., 2021). Calcaneal fat pad atrophy occurs in adults participating in sporting activities, those using improper footwear, and during any activity involving prolonged weight-bearing (Balius et al., 2021). Diabetic patients and the elderly also exhibit heel pad atrophy (Lareau et al., 2014). A combination of aging, weight, and increased physical activity can cause a decrease in water retention, collagen, and elastin from the fat pad, resulting in atrophy and decreased protection of the heel (Balius et al., 2021).

Heel pain experienced from calcaneal fat pad atrophy worsens during prolonged standing and increases at night (Yi et al., 2011). It often occurs alongside plantar fasciitis, however pain due to fat pad atrophy is more often bilateral when compared to plantar fasciitis (Yi et. Al, 2011). The plantar surface of the calcaneus is tender and pressing on the heel will exacerbate the pain (Choo et al., 2020). The central weight-bearing plantar surface of the calcaneal tuberosity is where the most pain is felt and is not exhibited with open chain motion of the foot, ankle, or toes (Lareau et al., 2014).

Treatment of pain from heel pad atrophy includes non-steroidal anti-inflammatory medications, rest, ice, and orthoses. Since pain from heel pad atrophy is commonly seen with plantar fasciitis, symptoms can be difficult to mitigate.

METHODS

Five literature searches were conducted on the PubMed database using the key phrases

"heel fat pad atrophy", "heel fat pad", "treatment heel pad atrophy" and "heel pain treatment" and "calcaneal pad atrophy obesity". The inclusion criteria consisted of articles related to heel fat pad atrophy and treatments for heel fat pad deterioration, while exclusion criteria included articles that didn't mention heel pad atrophy and those written before 1990. The search for "heel fat pad atrophy" resulted in 24 results. The search for "heel fat pad" resulted in 217 results. The third search, "treatment heel pad atrophy" resulted in 16 articles. The fourth search, "heel pain treatment" resulted in 1,764 articles. Lastly, the search "calcaneal pad atrophy obesity" resulted in 1 result. After applying the inclusion and exclusion criteria, 19 articles were available for review.

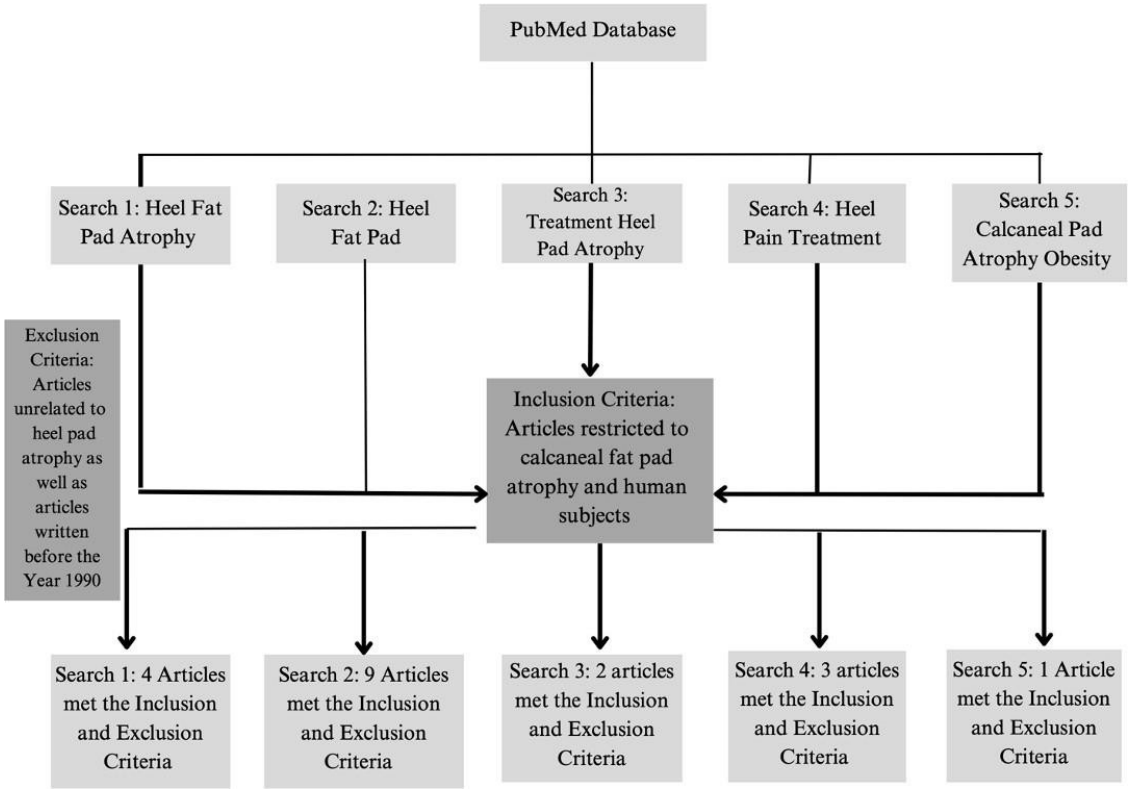


Figure 1: Articles yielded after the application of the inclusion and exclusion Criteria

RESULTS

Gait Cycle

Although many factors can affect the calcaneal fat pad, the presence of plantar heel pain is thought to have an association with the human gait cycle. The parameters for this mechanical cycle start and end when the heel contacts the floor, but the maximal amount of heel pain occurs in the stance phase, when the entire plantar aspect of the foot touches the floor (Alfaro-Santafé et al., 2021). This part of the cycle is also levying the most mechanical stress onto the foot, causing increased pronation, a reduction in the arch of the foot, and increased ankle dorsiflexion (Alfaro-Santafé et al., 2021). In an analysis completed by Aflaro-Santafe et

al., two groups of subjects - one with foot pain and one without - had their gait cycle studied as they stepped into stance phase to quantify and graph any pain they felt. These representations showed that when compared to the control group, the group with heel pain walked with a lesser physical force (Alfaro-Santafé et al., 2021).

Clinical Presentation

Heel pad atrophy is commonly seen with plantar fasciitis, however pain due to calcaneal fat pad atrophy is usually more diffuse and on the plantar aspect of the heel (Aldridge et al., 2006). Fat pad atrophy is also more common in patients who are elderly or obese (Aldridge et al., 2006). When compared to plantar fasciitis, heel pain due to calcaneal fat pad atrophy worsened with prolonged standing, pain at night, and pain on both heels as opposed to unilaterally (Yi et al., 2011). Patients older than 40 years also showed an increase in calcaneal fat pad atrophy (Yi et al., 2011).

Etiology*:*

Age/ Gender/ Race

In the study completed by Lopez et al., statistically significant differences were found between women and men in terms of weight and height, but factors such as BMI and fat pad density were found to have statistically insignificant differences. Due to the insignificant p value (P= 0.941) for the calcaneal fat pad denseness, the study found that gender did not determine whether a person would have heel pain (Lopez-Lopez et al., 2019). Within each gender, however, the study did find that heel pain was indicated based on the thickness of the heel pad. Both men and women in the group experiencing heel pain had a thinner pad when compared to the control group. Men in the control group had a calcaneal fat pad with a mean (M) of 8.58 mm and a standard deviation (SD) of 3.43mm while women had a M of 10.13mm with a SD of 1.78mm. With the group that experienced pain, the heel had a M of 7.37mm and a SD of 1.33 for men and a M of 7.09mm and SD of 1.44mm for women (Lopez-Lopez et al., 2019).

Calcaneal fat pad atrophy is a component of a broader term used to describe heel pain known as Heel Fat Pad Syndrome (HFPS). The primary criteria consists of the heel being less than 3 millimeters in density, but secondary criteria such as deviation in pain is also considered. In one of the studies reviewed by Chang et al., a statistical difference was found between races (HFPS was found more commonly in Hispanic/ Latino people), but no difference was found between the genders (Chang et al., 2022).

Rheumatoid Arthritis

11 patients with rheumatoid arthritis were compared to 8 controls to determine calcaneal fat pad atrophy. 20mg of fat was surgically removed from the heels of each patient and compared for compositional differences. Patients with rheumatoid arthritis were found to have heel fat pads containing increased saturated fatty acids and decreased unsaturated fatty acids when compared to controls. This compositional difference can affect the inherent qualities of the fat pad, making it more viscous in rheumatoid patients. The increase in viscosity reduces the ability of the calcaneal heel pad to dissipate the force put on the heel upon heel strike, increasing heel pain. Over time, this can break down the septal organization of the fat pad, resulting in atrophy (Resnick et al., 2016).

Diabetes Mellitus

It is well known that patients with diabetes mellitus can often develop neuropathy of the foot, leading to dangerous foot ulcers and potential amputations if their blood glucose

levels are not controlled. Kao et al., conducted a study on the feet of 16 cadavers from patients with and without diabetes, as well as 8 living diabetic patients and 8 controls. The study performed MRIs on each foot to examine the effect diabetes has on the composition of the calcaneal fat pad. The three images taken were spin lattice (T1), spin-spin (T2), and magnetization transfer (MT). All three of these measurements revealed a statistically significant difference between diabetic and non-diabetic feet. The increase in relaxation time of T1 in diabetic feet, when compared to controls, suggests an increase in water and a decrease in fat content within the heel pad (Kao et al., 1999). The increase in T2 revealed the opposite effect and the author notes that additional studies need to be conducted to clarify this difference. The MT activity was increased in diabetic patients, supporting previous research that states this measure is increased in diabetic patients with neuropathy (Kao et al., 1999). The increase can be due to the increased collagen in the fat pad, more availability of collagen due to degeneration of the fibrous septa, or increased water content in non-diabetic feet (Kao et al., 1999).

DISCUSSION

Treatment

Treatment for this condition includes insoles or heel cushions in the patients' shoes. In addition, low-dye taping has been seen to reduce heel pain by decreasing the peak plantar pressure of the hindfoot in patients with heel pad atrophy (Chae et al., 2018). Laser therapy and diathermy therapy has been successful when treating soccer players with a 57 +/- 37 days for return to play time (Saggini, 2018). Other conservative measures include off-loading, icing, and anti-inflammatory drugs such as NSAIDs (Choo et al., 2020).

The limitation of conservative treatment is that they only treat the symptoms of pain without fixing the root cause: more research is being done on how to stop the degradation of the fat pad itself, such as the effect of surgery. Surgical interventions for heel pad atrophy includes autologous fat grafting. When compared with other fillers such as liquid silicon or hyaluronic acid, fat is safer and more permanent, respectively (James et al., 2021). In addition, it is a relatively easy procedure, and the patient does not have a lot of self-maintenance. Studies have shown that this procedure ultimately increases dermal thickness of the heel, significantly reducing heel pain in patients who undergo the grafting both 6 months and 12 months after the completed procedure. This fat graft allows for a better foot function when compared to the control group, which had increased foot pain during that same time (James et al., 2021). Patients who had undergone the surgery had evidence of fat resorption yet surprisingly, they still stated that they had improvements with their heel pain. Although not certain, it is thought that this may be due to an area of the heel being less compressive after the procedure, even with the injected fat dispersion (James et al., 2021). Similar results were found in another study, although the sample size was much smaller. It was found that although the fat grafts returned to the original thickness a few months after the operation, functionality was improved up to the 24-month mark when the study was completed (Minteer et al., 2018).

Limitations to the study

One limitation of this subject is that there is not enough research nor a large enough sample size to conclude how long fat grafts can provide pain relief. Additionally, it

would benefit the study conducted by James et al. if the follow-up time was increased, so that the progress of the lipo-transplantation could be followed for many years in the future.

CONCLUSION

Calcaneal fat pad deterioration is the second most common cause of foot pain in adults worldwide. Current research suggests this degradation can be due to several different causes, such as obesity, diabetes mellitus and rheumatoid arthritis. Although there are many conservative measures that patients can use, they are cumbersome and time consuming. Due to this, patients may struggle with adhering to their treatment plan. Although more research needs to be done, early experiments show that fat grafts may be the better option. Not only do they fix the underlying pathology that causes pain, but it is easier for the patient to adhere to the post-operative instructions.

AUTHORS' CONTRIBUTION

Both authors contributed equally to the research paper.

STATEMENT OF COMPETING INTERESTS

Authors have no competing interests.

REFERENCES

1. Balius R, Bossy M, Pedret C, Porcar C, Valle X, Corominas H. Heel fat pad syndrome beyond acute plantar fascitis. Foot (Edinb). 2021;48:101829. doi:10.1016/j.foot.2021.101829
2. Yi TI, Lee GE, Seo IS, Huh WS, Yoon TH, Kim BR. Clinical characteristics of the causes of plantar heel pain. *Ann Rehabil Med*. 2011;35(4):507-513. doi:10.5535/arm.2011.35.4.507
3. Chang AH, Rasmussen SZ, Jensen AE, Sørensen T, Rathleff MS. What do we actually know about a common cause of plantar heel pain? A scoping review of heel fat pad syndrome. *J Foot Ankle Res*. 2022;15(1):60. Published 2022 Aug 16. doi:10.1186/s13047-022-00568-x
4. Saad A, Kho J, Almeer G, Azzopardi C, Botchu R. Lesions of the heel fat pad. *Br J Radiol*. 2021;94(1118):20200648. doi:10.1259/bjr.20200648
5. Allam AE, Chang KV. Plantar Heel Pain. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; June 5, 2022.
6. James IB, Gusenoff BR, Wang S, DiBernardo G, Minteer D, Gusenoff JA. A Step in the Right Direction: A Prospective Randomized, Controlled Crossover Trial of Autologous Fat Grafting for Rejuvenation of the Heel. *Aesthet Surg J*. 2021;41(7):NP959-NP972. doi:10.1093/asj/sjab095
7. Minteer DM, Gusenoff BR, Gusenoff JA. Fat Grafting for Pedal Fat Pad Atrophy in a 2-Year, Prospective, Randomized, Crossover, Single-Center Clinical Trial. Plast Reconstr Surg. 2018;142(6):862e-871e. doi:10.1097/PRS.0000000000005006
8. Salvioli S, Guidi M, Marcotulli G. The effectiveness of conservative, non-pharmacological treatment, of plantar heel pain: A systematic review with meta-analysis. Foot (Edinb). 2017;33:57-67. doi:10.1016/j.foot.2017.05.004
9. Chanda A, McClain S. Mechanical Modeling of Healthy and Diseased Calcaneal Fat Pad Surrogates. *Biomimetics (Basel)*. 2019;4(1):1. Published 2019 Jan 3. doi:10.3390/biomimetics4010001
10. Lopez-Lopez D, Becerro-de-Bengoa-Vallejo R, Losa-Iglesias ME, et al. Relationship Between Decreased Subcalcaneal Fat Pad Thickness and Plantar Heel Pain. A Case Control Study. *Pain Physician*. 2019;22(1):109-116.
11. Ozdemir H, Söyüncü Y, Ozgörgen M, Dabak K. Effects of changes in heel fat pad thickness and elasticity on heel pain. *J Am Podiatr Med Assoc*. 2004;94(1):47-52. doi:10.7547/87507315-94-1-47
12. Lareau CR, Sawyer GA, Wang JH, DiGiovanni CW. Plantar and medial heel pain: diagnosis and management. *J Am Acad Orthop Surg*. 2014;22(6):372-380. doi:10.5435/JAAOS-22-06-372
13. Choo YJ, Park CH, Chang MC. Rearfoot disorders and conservative treatment: a narrative review. *Ann Palliat Med*. 2020;9(5):3546-3552. doi:10.21037/apm-20-446
14. Alfaro-Santafé JV, Alfaro-Santafé J, Lanuza-Cerzócimo C, et al. Locally linear embedding and plantar pressure-time graph selection in heel pain classification:

An observational, case-control study. *J Biomech*. 2021;128:110784. doi:10.1016/j.jbiomech.2021.110784
15. Aldridge T. Diagnosing heel pain in adults [published correction appears in Am Fam Physician. 2006 Mar 1;73(5):776]. *Am Fam Physician*. 2004;70(2):332-338.
16. Resnick RB, Hudgins LC, Buschmann WR, Kummer FJ, Jahss MH. Analysis of the heel pad fat in rheumatoid arthritis. *Foot Ankle Int*. 1999;20(8):481-484. doi:10.1177/107110079902000803
17. Kao PF, Davis BL, Hardy PA. Characterization of the calcaneal fat pad in diabetic and non-diabetic patients using magnetic resonance imaging. *Magn Reson Imaging*. 1999;17(6):851-857. doi:10.1016/s0730-725x(99)00019-3
18. Chae YH, Kim JS, Kang Y, Kim HY, Yi TI. Clinical and Biomechanical Effects of Low-Dye Taping and Figure-8 Modification of Low-Dye Taping in Patients With Heel Pad Atrophy. *Ann Rehabil Med*. 2018;42(2):222-228. doi:10.5535/arm.2018.42.2.222
19. Saggini R, Migliorini M, Carmignano SM, Ancona E, Russo C, Bellomo RG. Inferior heel pain in soccer players: a retrospective study with a proposal for guidelines of treatment. *BMJ Open Sport Exerc Med*. 2018;4(1):e000085. Published 2018 Feb 7. doi:10.1136/bmjsem-2015-000085

Comparing treatment outcomes and subsequent sequelae for Rheumatoid Arthritis of the foot and ankle

Sruthi Kosuru, BS; Shivani Mahajan, BS; Jyoti Borate, BA; Srishti Ramthirthkar, MS; Tamara Pavlovic, BS

ABSTRACT

Introduction

Rheumatoid arthritis (RA) is an autoimmune multi-systemic disease characterized by inflammation of tissues lining joint cavities. Changes in innate and adaptive immunity lead to altered immunological production of cytokines and autoantibodies, which pathologically result in synoviocyte and osteoclast mediated cartilage and bone destruction. Periarticular and musculoskeletal manifestations, as seen on MRI and other imaging modalities, include synovitis, bone marrow edema, and bone erosions. If RA is not managed properly, it can cause chronic disability in the functionality and mobility of affected joints. The goal of this study is to assess how each treatment modality manages inflammation, reduces overall foot and ankle pain, enhances mobility, and overall improves the quality of life of those suffering from RA.

Study Design: Qualitative Systematic Review of Literature

Methods

A search query of "(Rheumatoid Arthritis) AND (foot pain) AND (therapy)" in PubMed yielded a total of 479 articles. The inclusion criteria factors of certain publication types (such as RCT, SR), publishing date within the last 5 years, and English language, yielded a total of 22 articles. Subsequently, with the exclusion criteria factors of relevance to RA, tangibility of results, and with additional manual filtering, a final total of 9 articles were utilized in this study.

Results

It was proven with statistical significance that the use of footwear interventions such as thin customizable insoles and soft custom foot orthoses resulted in immediate relief in walking-induced forefoot pain. It could not be statistically proven, however, that foot orthoses alleviate the overall burden of pain and disability in RA patients. Nonsurgical and nonpharmacological interventions such as physical exercise and psychosocial interventions aid in reducing the global impact burden of RA, though the extent of effectiveness is unknown. HA and PRP injections appeared to alleviate ankle pain in the short term, though statistical significance was weak due to small sample size and variability in patient population. Imaging modalities proved that biologics have the added benefits of not only reducing pain, but also enhancing function and preventing further joint destruction.

Discussion and Conclusion

There are a variety of treatments utilized in order to control the painful symptoms of RA of the foot and ankle, ranging from biological agents to foot orthoses to other physical footwear to non-pharmacological interventions. The majority of the publications included in the study utilized the Visual Analog Scale (VAS) for measuring pain, and the Foot Function Index (FFI) for measuring functional disability. There is a plethora of research discussing experimental and

novel treatment modalities for improving the quality of life for patients diagnosed with systemic RA; but very few focused specifically on the foot and ankle. While a few articles did statistically prove that a particular treatment modality has the potential to alleviate pain or improve function; there is scarce evidence to suggest one is superior at improving quality of life compared to the others, minus established biological agents.

Key Words: Rheumatoid Arthritis, foot and ankle, foot orthoses, biologics, intraarticular injections, insoles, non-pharmacological interventions, foot pain, foot function, quality of life

Level of evidence: 3

INTRODUCTION

Rheumatoid Arthritis (RA) is a predominantly autoimmune condition characterized by inflammatory changes of the synovial tissue lining joint cavities, and subsequent destruction of cartilage and bone.[1] It is marked by synovial hyperplasia, intense thickening of the synovial lining, which results primarily due to the invasion of macrophage-like cells and the marked proliferation of resident synovial fibroblasts.[1] Degree of this visible hyperplasia and disease activity status directly correlates with the severity of cartilage erosion and formation of an inflammatory pannus, which attaches to and invades nearby joint cartilage. Osteoclast activation that happens simultaneously erodes surrounding bone.[1]

Risk factors

The systemic manifestations of inflammatory cytokines, arachidonic acid metabolites, and rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) autoantibodies are high RA risk factors.[2] The rheumatoid factor is increased in people with genetic haplotypes VKA and SKR.[3] Production of the anti-CCP antibody is associated more with genetic haplotypes VKA, VRA, and LRA.[3] Another gene, protein tyrosine phosphatase N22 (*PTPN22*), has been indicated to increase the citrullination of proteins and cause hyperreactivity of T and B cells, which leads to the synovial inflammation seen in patients with RA.[2] Risk factors include a morbid body mass index, tobacco exposure, female gender, and the genetic haplotype HLA-DR beta, which is exacerbated by smoking.[3] Consequently, the development of comorbidities such as lung cancer and lymphoma are of serious concern.[6]

Foot and ankle pain

The incidence of developing foot and ankle pain in patients with preexisting RA is significantly high. Epidemiological studies point to serious foot pain in nearly 90% of patients with RA.[4] Previous studies suggest a prevalence rate of ~ 70% of foot joint arthritis, pain, and walking disability in patients with early stages of RA or arthralgia.[5] Pain is especially localized to areas of functional movement and can persist even when the disease is not clinically apparent. Therefore, it is crucial for health professionals to continually assess foot health while monitoring RA in a patient, especially in at risk joints of the forefoot, such as the metatarsophalangeal joint and other symmetric joints. The foot functioning index is a clinical instrument utilized for scoring foot pain, related disability, and activity limitation in patients with debilitating disease conditions.[5] This index can assess the risk for slower and unstable gait patterns, abnormal foot joint rotations and altered plantar pressure loading characteristics of the foot and ankle in patients with RA.[5] Health professionals should do a more comprehensive exam by inquiring about foot symptoms in every patient with RA and examine joint function in the foot and ankle in addition to joints of the hand to enhance rheumatological management of RA.

Treatment considerations

Chronic inflammation is a predominant etiology but also a concerning side effect of RA in the foot and ankle. Novel treatments of RA are now more focused on management of the synovial inflammation and vascularization.[8] NSAIDs are commonly used to manage RA symptoms, however they do not prevent progression of the disease. In contrast, conventional disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX), sulfasalazine (SSZ), and leflunomide have the capacity to slow disease progression by

suppressing the immune system.[4,14] If DMARDs are used early in the RA process, it can enable better long-term outcomes. Biologics, a special type of DMARDs, can further limit joint destruction because they block specific parts of the immune system which promote inflammation. Despite 90% of the respondents on biologics discussing foot pain with their rheumatologist, only 70% received adequate podiatry care.[4] A previous systematic review concludes that compared with DMARDs alone, biologics, in combination with DMARDs achieve a 50% reduction of joint destruction.[14] Patients receiving anti-TNF alpha biologic therapy are significantly more likely to be affected by foot pain, stiffness, swelling, and numbness in comparison to patients prescribed traditional DMARD therapies. Results of previous clinical trials with anti-TNF alpha drugs show dramatic reductions in visual analog scale (VAS) pain scores.[4] Counter-intuitively, studies have shown that a greater proportion of patients not on anti-TNF alpha therapy are receiving podiatric care compared to patients on anti-TNF alpha therapy due to more advanced foot impairment.[4]

For some RA affected feet and ankles, systemic therapies may pose an unnecessary risk in overriding immune regulation, compared to local therapies designed to alleviate symptoms. The use of conservative semi rigid foot orthotics is thought to stabilize the functional movements in joints of the foot and ankle, and therefore reduce the associated pain, compared to insoles.[9] However, the effectiveness in substantially reducing pain in joints of the foot and ankle, in addition to improving long term function, is disputable. Non-traditional methods such as exercise interventions are also being considered, with multicomponent and single component exercise regiments proving to alleviate the global impact of RA on an individual. The increasing usage of non-operative therapies such as systemic analgesics, or oral non-steroid anti-inflammatory drugs have potential undesirable side effects and can lose potency with repeated use.[15] Further research is required in order to help patients manage their symptoms without surgical intervention or to preserve the RA affected joint if future operative intervention becomes necessary.[15] This literature review aims to evaluate various RA treatments and their efficacy in minimizing inflammation and joint degradation in the foot and ankle.

METHODS

A preliminary search of "Rheumatoid arthritis therapy" on PubMed revealed 1691 results, with the majority of studies reporting results of immunological clinical trials. There were, however, a noticeable number of published articles discussing other therapeutic remedies for Rheumatoid Arthritis (RA) such as dietary modifications or exercise interventions. Since the question posed a comparison amongst therapies, all aforementioned results needed to be part of the final inclusion criteria. However, the vast majority of those studies were focusing on the wrist, neck, and hip joints rather than on the foot and ankle. The search query was therefore modified to be “(Rheumatoid Arthritis) AND (foot pain) AND (therapy)”, with the inclusion filter limit only allowing publications from the past 5 years. Once the inclusion and exclusion filters were applied, manual filtering eliminated two more articles because they were simply protocols, but were utilized for the Introduction section as a source for epidemiological statistics. One more article was eliminated because it was declared that the first author had a conflict of interest. An additional 4 articles not included in this search criteria were utilized as sources for the Introduction,

mainly for citing disease pathogenesis, and risk factors.

Preliminary searches of the Cochrane Library were also conducted. A simple query of "RA ankle" revealed 2 results, while another simple search query of "RA foot" revealed 36 results. However, all of these articles were entirely unusable, either because they were repeats of PubMed articles or because the trials were stopped midway or the authors failed to publish the results. One article was eliminated because the study was an experiment on arthritis-induced mouse models and the results could not be extrapolated to humans.

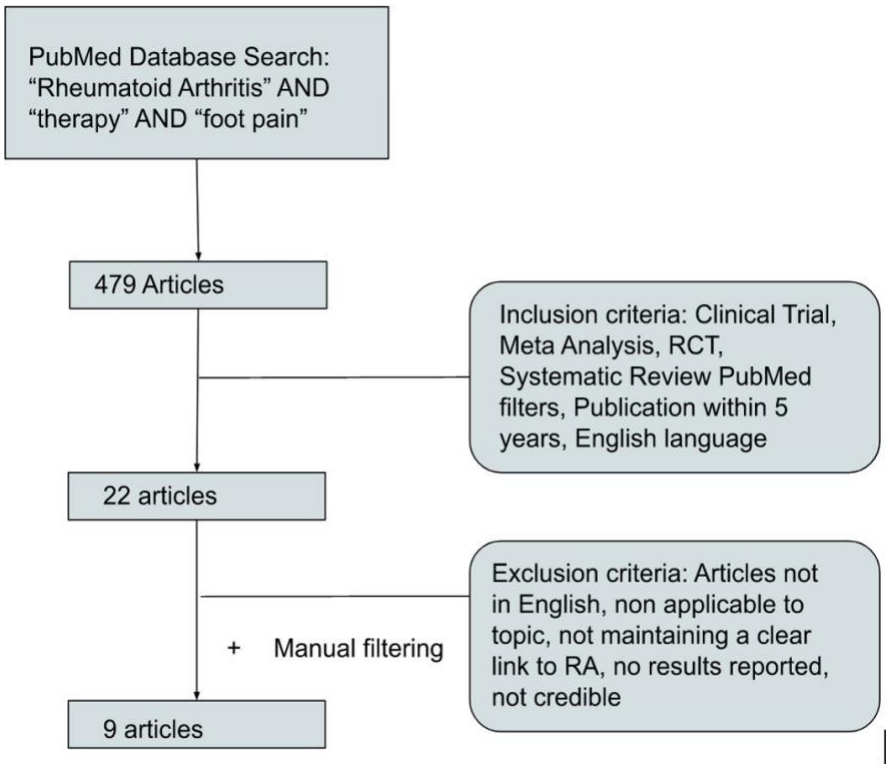


Figure 1: Articles yielded after the application of the inclusion and exclusion Criteria

RESULTS

Ramos-Peterson et al. conducted a systematic review of RCTs and observational studies that assessed the use of biologics in the feet of patients with RA. Individual RCTs conducted by Van Vollenhoven et al., Huizinga et al., and Van Herwaarden et al. revealed similar but positive findings that biologics will lessen the extent of RA progression as evidenced by X-ray imaging. Van Herwaarden et al. conducted a RCT that assessed the efficacy of biologics and dose reduction vs usual care without dose reduction on 180 total patients with RA. The biologics group showed significantly better global assessment of foot health as measured by the DAS28 metric and health assessment disability index at 18 months. In regards to foot outcomes, the biologics group also presented with shorter lived flares and minimal radiological

progression. Huizinga et al. conducted a RCT in 2015 that assessed the efficacy of methotrexate + tocilizumab combination therapy vs tocilizumab + placebo on 556 total patients with active RA. The tocilizumab group showed significantly better global assessment of foot health as measured by the DAS28 metric and RA Quality of Life index post 2 years, with even 50.4% achieving remission. Conversely, the addition of biologics to conventional DMARD methotrexate treatment resulted in minimal further progression of structural joint damage. Van Vollenhoven et al. conducted a RCT in 2012 that assessed the efficacy of conventional DMARD treatment vs biologics on 487 patients with RA whose treatment with methotrexate failed. The biologics group showed significantly lesser radiological disease progression as measured by the DAS28 metric and health assessment disability index at 24 months. However, it is important to note here that the initial response to the different therapies was indistinguishable.[14]

Santos et al. conducted a systematic review of RCTs and observational studies to determine the effectiveness of non-pharmacological and non-surgical interventions on disease impacting domains of pain, function and fatigue. The interventions include multicomponent exercise, single exercise, psychosocial, hydrotherapy and balneotherapy, and custom orthoses of the foot. Cramp et al., Rongen-van Dartel et al., Baillet et al. 2012, Baillet et al. 2016 all conducted quantitative RCTs on the effects of multicomponent and single exercise interventions. Baillet et al. 2012 and Baillet et al. 2016 demonstrated that there was a positive effect in lessening pain and improving functional disability (n=545). Cramp et al. showcased a small positive effect in terms of improving fatigue, while Rongen-van Dartel et al. concurred this, but emphasized that this was only beneficial in the short term (n=628). Al-Qubaeissy et al., Verhagen et al. demonstrated that hydrotherapy and balneotherapy produced an insufficient effect for pain compared to usual care, exercise, mudpacks, and relaxation therapy (n=998). No significant conclusions could be made in regards to the effect of hydrotherapy for improving functional disability. Knittle et al. illustrated that psychosocial interventions had a small positive effect on pain improvement (n=1316) and functional disability (n=1180). Cramp et al. illustrated that psychosocial interventions had a small positive effect on improving fatigue (n=1556). Hennessey et al. showcased that custom orthoses of the foot had a moderate effect on improving pain (n=340), and a small positive effect on improving functional disability (n=220).[13]

Wang et al. conducted a RCT to determine whether hyaluronic acid injections (n=24) into RA affected feet and ankles can improve foot function and reduce synovial hypervascularization compared to lidocaine injections (n=20). The injection site was determined partially based on patient assessment of pain and tenderness, but also determination of active synovitis under ultrasound imaging. The effects were qualified through utilizing color doppler ultrasound (CDUS), visual analog scale (VAS), and FFI scores (subscales are pain, functional limitation, and disability) at baseline, four weeks, and twelve weeks. Hyaluronic acid injections significantly improved VAS score, FFI_{pain}, FFI_{total} at 4 weeks, and decreased CDUS values at 4 weeks ($p = 0.005$) and 12 weeks ($p < 0.001$) compared to baseline. Since the result at 12 weeks is much more significant in comparison, it was theorized that hyaluronic acid injections mediated pain relief through a cumulative effect. The lidocaine control

achieved a 20% reduction response in CDUS values; compared to the hyaluronic acid variable which achieved a 54% reduction response. However, the magnitude of reduction was the same for both groups and the reduction of CDUS values had no correlation with clinical pain reduction or functional improvement.

Synovial hypertrophy was evaluated in a semiquantitative manner utilizing the Leeds Score, with 0 representing none, 1 representing mild, 2 representing moderate, and 3 representing severe.[8] Among the participants responding to hyaluronic acid injections, 80% had a high initial vascularity assessment of Leeds Scores 2 and 3. This initially suggested that hyaluronic acid had the potential to reduce active synovitis, however, the extent to which this is effective needs to be confirmed with further testing.[8] Clinically, HA injections are promising for patients who do not respond to simple analgesics or are not fit for surgery. However, there is uncertainty as to which patients, based on age or arthritis severity, would benefit the most and required dosage.[15]

Vannabouathong et al. conducted a systematic review to evaluate whether the efficacy of IA treatment modalities such as corticosteroids (CS), hyaluronic acid (HA), platelet rich plasma (PRP), and mesenchymal cells (MSC) which are more commonly used to treat knee arthritic pain applies to ankle arthritis as well. The clinical outcomes of pain, joint function, stiffness, quality of life, and disease-specific indices such as swelling were recorded; in addition to adverse side effects, patient satisfaction, and tolerability outcomes. Furtado et al (98 patients) and Lopes et al (54 patients) both found positive responses to CS therapy with triamcinolone hexacetonide in individuals with ankle RA, with regard to both pain and swelling up to 4 weeks postinjection. A trial on 100 ankle OA patients treated with betamethasone (a maximum of 3 weekly injections or until all symptoms disappeared) found just 35% of patients had improvement in their symptoms, however positive outcomes for CS injections were found in patients without grade V disease (totally disabled). Bossert et al found that 68% of patients treated with a combination of HA plus mannitol were “very satisfied” or “satisfied” and 94% of patients had “very good” or “good” tolerability with the injection. RCTs that utilized a 5-injection regimen of Hyalgan, demonstrated that HA injections improved pain, function, and stiffness relative to placebo up to 26 weeks postinjection, with the maximum effect at 6 months, as per the self-administered ankle osteoarthritis scale (AOS) score. In contrast, Schmid et al. concluded that CS injections may only be useful for short term ankle arthritis, maximum effect being up until 8 weeks.[15] Fukawa et al and Repetto et al (20 patients each) reported that VAS pain when administering PRP changed from 59.7 to 42.4mm (P= .02) at 24 weeks and from 7.8 to 2.6mm (P=0.001) at an average follow up of 17.7 months, respectively. Repetto et al also found that Foot and Ankle Disability Index (FADI) scores also significantly improved from 59.2 to 80.2 points (P=0.001) and that 80% of their subjects deemed themselves either “very satisfied” or “satisfied” at their final follow up.[15]

Tenten-Diepenmaat et al. conducted a systematic review in which they aimed to compare various types of foot orthoses (FO), which differ on grounds of materials used, functionality and modifications applied. The effectiveness of these various types of FOs were analyzed by looking at the primary outcomes on foot function and foot pain, secondarily the paper looked at physical functioning, quality of life, compliance,

adverse effects, overall costs, and patient satisfaction. By applying pertinent research parameters, a literature search was conducted and 10 total articles were selected to be a part of the literature review. Data was meta-analyzed and when this couldn't be done, qualitative data analysis was performed. Pooled scores pointed to a medium, but statistically significant, immediate reduction of forefoot plantar pressure-time integral, while looking at 28 study participants. Similarly, forefoot plantar peak pressure was also studied in looking at soft FOs but wasn't statistically significant. Pooled scores also showed a small intermediate effect in favor of FOs with metatarsal bars for reduction of forefoot plantar pressure but were deemed insignficiant within this study; reduction in plantar pressure vs. pressure time interval yielded P = 0.58 and marking reduction in plantar pressure vs. peak pressure yielded P = 0.30. These pooled scores showed no benefit in comparison between soft FOs and semi-rigid FOs in regards to foot pain. Other parameters of comparison, such as cost effectiveness and patient satisfaction were inconclusive as most studies mostly looked at immediate effects and didn't conduct the respective studies for long-term.[9]

Frecklington et al. in a literature review focused on the effectiveness of footwear on foot pain, function, and ability to reduce impairment for RA patients. Articles selected to be analyzed were selected by inclusion criteria and that led to the inclusion of 11 articles for this review. Footwear interventions studied in this paper included off-the-shelf footwear, therapeutic footwear and therapeutic footwear with foot orthoses. Articles were grouped in regards to foot pain, patient-reported outcomes, plantar pressure and temporal-spatial parameters. Significant between group reductions in foot pain was seen when using newer therapeutic footwear (d: 1.08 - 1.24; large effect) , and extra-depth footwear with semi-rigid orthoses group (d: 0.45; medium effect). One listed cross-sectional study also reported a significant reduction in rearfoot and forefoot peak plantar pressure (PPP) when using athletic footwear. While this study also examined gout and first MTP osteoarthritis, there were many more supporting articles that looked at study participants with RA. Overall, many patients reported that most efficient forms of footwear intervention were associated with extra-depth footwear and cushion to allow for increased toe box volume. Cushioned midsoles offer a significant reduction of forefoot plantar pressure in RA patients.[10]

Reina-Bueno et al. conducted a randomized controlled clinical trial to test the effect of custom-made foot orthoses in comparison to placebo foot insoles in RA patients. There was a group of 53 patients selected for the trial and split into two groups for placebo vs. custom orthoses. There was a statistically significant difference between the groups of P=0.048 proving that the custom-made orthoses provided better pain relief in RA patients. RA patients are more prone to increased plantar pressure and structural problems such as hallux valgus, rearfoot valgus and subluxation of metatarsophalangeal joints. Custom-made orthoses were designed to tackle these deformities and pain. Group A orthoses were made of polypropylene layer phenolic foam molds while Group B received the placebo foot insoles. The procedure called for participants to wear foot orthoses assigned for a minimum eight hours per day all week for three months. This was a blinded research model and measurements were taken on days 0,30, 60 and 90. Variables discussed in the study were pain, functionality, disability and quality of life. The results table reflected that pain level on

VAS scale went down in Group A (custom orthoses) compared to Group B (placebo). However, there wasn't a significant difference in foot function, disability or quality of life. Overall, the study proved that customized foot orthoses resulted in reduction of pain in RA patients.[11]

Gijon-Nogueron et al. performed a systematic review and meta-analysis on the effectiveness of foot orthoses in patients with RA related to disability and pain. Of the initial 118 studies considered 5 were included in the final systemic review and meta-analysis amounting to 301 participants. Data used to measure the effectiveness of foot orthosis included the visual analogue scale (VAS) measured pain and the Questionnaire of Foot Function index (FFI) measured pain, disability and activity limitation. The studies results were divided into two groups, those obtained in long-term (>6 months) follow up and short-term (≤ 6 months) follow up. The studies in the short term group found improved foot pain outcomes in patients with foot orthoses but there was no statistically significant difference between the intervention group and control groups. In the long term studies one study recorded no significant difference between control and intervention group: the other study did observe significant improvements in foot pain at the end of follow up, their results corresponded to AUC analyses, once adjusted the results obtained were not statistically significant. When analyzing for disability the short term follow up group found no statistical significance between intervention and control groups. The long term follow up group found no statistical significance when analyzing for disability although the meta-analysis detected a slight difference from intervention and control groups. Analysis of the articles selected for the study found that there was no significant difference in outcomes when using a foot orthosis, another insole, or a placebo. The lack of significant impact can be due to the small sample sizes of the studies being reviewed or in the limited sensitivity of the FFI questionnaire to detect differences.[7]

Linberg et al. conducted a randomized control study to investigate the immediate effects of thin easily customizable insoles on pain and walking ability in patients with RA who have forefoot pain and to determine if they were using the insoles 1 year later. The study included 21 subjects recruited from an outpatient clinic and inpatient ward of a hospital for rheumatic disease. Inclusion criteria included a definite diagnosis of RA, ≥18 years of age, foot pain on walking, and pain in at least one forefoot when assessed for affliction of the MTP joints using the Ganseln test. The insole used was a 4-mm flat insole of a malleable plastic material with a textile material on the upper side, it was customized to provide support for the transverse and longitudinal arches of the foot. Patients' functional level was classified into functional classes I-IV according to the American college of Rheumatology 1991 classification of functional status. The foot function Index (FFI) was used to determine foot pain and disability. Walking ability was assessed by the 6 minute walking test (6MWT), foot pain was assessed after walking with and without insoles by a 10-cm visual analogue scale (VAS). Patients' satisfaction with insoles after 1 year was assessed by a standardized questionnaire. The study found a statistically significant reduction in foot pain for the group using insoles during the 6MWT. Walking distance was increased in patients using insoles during the 6MWT but it was not statistically significant. 90% patients continued using the insoles after the initial test in a 1 year follow up. Results show an immediate forefoot pain relief when walking using these insoles and

that these insoles can be used to relieve forefoot pain in patients not severely affected by RA.[12]

DISCUSSION

Many of the studies cited in this literature review utilized the same measuring variables. Pain was primarily measured by the Visual Analog Scale (VAS) for pain, fatigue was measured by Multidimensional Assessment of Fatigue among others, and functional disability was measured by Health Assessment Questionnaire and Foot Function Index (FFI).[13,14] The outcome variable of FFI also included three subscales of FFI_{pain}, $FFI_{disability}$, $FFI_{functional\ limitation}$.[8] The level of disease activity as measured by the DAS28 metric has cutoff values of 2.6 for remission, 3.2 for low, 5.1 for moderate, and 5.1+ for high.[8]

Ramos-Peterson et al. also asserted secondary findings by Tada et al. and Kubota et al. that biologics are not a risk factor for post operative surgical site infection (SSI) or delayed wound healing. The exception is that Huizinga et al. revealed the potential for serious adverse effects and infections is reduced significantly in the methotrexate + tocilizumab group compared to patients who are being treated with biologics alone.[14] This data was measured by the DAS28 metric and is significant because of previous assumptions that DMARDs negatively alter cytokine pathways that are necessary for repair mechanisms. This review also underlined the previous understanding that RA is more common in women than in men at a 3:1 ratio due to differences in comorbidities and hormonal differences between the sexes.

Multicomponent exercise and single exercise were proven to reduce the overall global burden of RA, as measured by the RA Impact of Disease and global Quality of Life metrics, while also lessening pain, lessening fatigue and improving function.[13] Psychosocial interventions and custom orthoses were proven to lessen pain and improve function.[13] However, this study demonstrated procedural bias since the non-pharmacological interventions were performed in a non-standardized manner at non-standardized intervals, mostly dependent on patient preferences. It is also important to note that this systematic review included studies that are not primarily focused on foot pathology. The cited articles also failed to mention the effects of RA on the disease impact domains of sleep, coping, emotional well-being and physical well-being.

Despite conventional treatments such as DMARDs and corticosteroids being established as the standard for RA treatment, research and resources are being devoted towards uncovering new methods. Due to the prevalence of corticosteroid side effects, hyaluronic acid injections have emerged as an alternative anti-inflammatory therapy. The mechanism of action of hyaluronic acid is thought to be desensitization of the overactive nociceptive nerves, which are characteristic in inflamed areas. Similarly, lidocaine is thought to act by diluting inflammatory mediators throughout the body.[8]

Previous research conducted by Goto et al. cited that five consecutive hyaluronic acid injections to RA affected knees improves pain upon ambulation by suppressing PGE2 inflammatory mediator levels in synovial fluid. Saito et al. in an observational cohort study, compared hyaluronic acid to steroids and stated that the former is preferable. Wang et al. preliminarily compared the effectiveness of lidocaine and hyaluronic

acid injections in RA ankles and feet. The relative control and experimental groups did not differ significantly at baseline, with the exception of age. This could have resulted in a confounding bias, but it is unknown how and to what extent. Other limitations included not having a placebo group receiving saline injections for global efficacy comparison, small sample sizes, and measurement bias of the color doppler signals. Hyaluronic acid injections were shown to improve RA affected foot function in the short term and pain reduction, though further testing is warranted to truly confirm this result based on these limitations.

The modalities of CS, PRP, MSC, and HA injections have different benefits and limitations due to different mechanisms of action, and aside from hyaluronic acid, there is currently limited high quality clinical evidence to base treatment recommendations on. Moreover, there are currently no trials comparing one injection modality to another. The evidence on CS, PRP, and MSC is even less well defined than research on HA. For example, Vannabouathog et al. only reviewed one low-quality trial on MSC therapy done by Emadedin et al, which evaluated 18 OA patients treated with MSCs, but only six of the patients had ankle OA.[15] Furthermore, no trials were evaluated on MSCs therapy for RA as there is a lack of research currently being done on this modality. It is important to note that out of the 27 studies regarding intra-articular injections, the study population that was predominantly studied was ankle OA patients (22 studies), whereas limited trials with RA patients were studied as clinical research in this patient population has not been conducted.

The studies that investigated arthritic ankles were limited to just CS and HA injections. Despite current evidence consisting of low quality trials of small sample sizes, the majority of the 27 studies suggested that IA injections may be effective in improving clinical outcomes in ankle arthritis as well as have limited safety concerns. Previous systematic reviews have not included trials examining PRP or MSC therapy as they are relatively new treatment modalities. More high-quality, randomized trials with standard outcome reporting is needed for these therapies, ideally with a comparable control group – especially in RA patient populations.

Articles included in our literature review that studied the efficiency of orthoses in reducing foot complications in RA patients overall pointed to improvement in the quality of life. However, the level of significance and the impact that each type of orthotic had on foot pain and functionality differed tremendously. Tenten et al. pointed to immediate improvement upon the administration of soft orthoses rather than semi-rigid orthoses, but within the same paper pointed to the pooled scores being insignificant when comparing the effect of treatment by soft vs. semi-rigid orthoses.[9] These findings may be due to the already small effect that orthoses have in preventing the progression of foot problems in late stage RA patients, making it even harder to differentiate the effectiveness of the various types of orthoses compared.[9] Interestingly, articles that were analyzed in the literature review by Frecklington et al. provided contradicting results in terms of soft vs. semi-rigid orthoses.[10] The majority of studies from this literature review pointed to significant improvement in treatment groups with semi-rigid orthoses, which completely opposes the findings discussed by Tenten et al.

Gijon-Nogueron et al. found that orthosis did reduce foot pain in patients with RA but there was no statistical significance. This is due to the limited sample size in the analyzed studies and limited sensitivity of the FFI questionnaire used to collect data. Other limitations include the different materials used for the orthosis and the variation of total time per day use of the orthosis in the studies analyzed.[7] Limitations visible in Reina-Bueno et al.'s study mainly dealt with an inconsistent experimental design in terms of the participants chosen. Randomized groups had an unequal female to male ratio, with females making up a staggering 80% of the sample size.[11]

The study conducted by Linberg et al. evaluated the effect of thin, easily customizable orthotics on pain. A limitation to this study is that the patients were aware of when the insoles were being used or not this could have impacted their subjective scoring of pain and exertion after the 6MWT. Another limitation would be the 6MWT could not have been a long enough period of time for the patients to notice a significant difference in pain and walking ability. Future studies should include prefabricated thin insoles vs placebo to mitigate the patients bias, a more challenging walking test should be conducted rather than the 6MWT, and a larger sample size of a population with varying degrees of severity of RA.

Ultimately, the study designs that assessed the validity of orthoses as a treatment for foot pain and mobility problems in RA patients all had similar drawbacks in attaining results. Many articles looked at immediate results based on a limited sample size but failed to follow the participants for a longer period of time to truly gauge the difference in lifestyle after following the treatment regimen. Hence, any findings that deducted one type of orthoses were more efficient in minimizing foot complications merely based on immediate effects are automatically insignificant. Whilst comparing the progression of RA of participants in these orthoses' studies, it was deduced that participants studied by Linberg et al. were not severely affected by RA which makes findings not generalizable to a more severely affected patient population. Thus, future studies that aim to compare different orthoses should keep all other variables that are of no interest constant, so the validity of their findings are maximized. A systematic review solely based on randomized controlled studies between comparable ingroups will provide much more applicable, and reproducible significant findings.

One limitation with the Rheumatoid Arthritis (RA) search query was that all pharmacological or biological treatments of RA of the foot and ankle were not being included. This could be because the systematic effects of such treatments no longer limit the scope to a single region of the body. Since >90% of patients with systemic RA report instances of foot pain, it becomes nearly impossible to isolate patients with solely RA of the foot and ankle. This is plausibly a reason why certain articles cited in this review concentrate more on systemic arthritis. The conclusions specific to the foot and ankle in these cases are inferred and deduced, compared to being experimentally proven.[13,14]

CONCLUSION

Management of Rheumatoid Arthritis (RA) is multifaceted, where the patient can elect to improve overall foot function through a range of pharmacological and non-pharmacological interventions. Systemic biologics, the more traditional

modality of management, have been proven to be beneficial for RA associated pain relief, functional improvement, and to prevent any further structural damage. Different injection agents such as hyaluronic acid have also been shown to improve pain and foot function in the short term.[8] However, this is not considered a first line alternative, since there is limited evidence proving its ability to reduce synovial hypertrophy, which is a predominant etiology in RA affected joints. Previous studies have shown PRP injections to be effective for OA individuals, and weak evidence shows that it may also be effective in ankle RA.[15] On the other hand, footwear interventions were also proven to immediately reduce forefoot plantar pressure when utilizing soft foot orthotics, as compared to semi-rigid orthotics.[9] Additionally, thin customizable insoles provided immediate relief from weightbearing-induced forefoot pain.[12] Findings also show reduced pain in RA patients with custom-made foot orthoses compared to insoles; though improvements in overall foot functionality, disability and quality of life remain questionable.[11]

Clinical remission of RA is achieved when three separate inflammatory indicators are within normal limits. These include lessening the number of painful and swollen joints, lessening the acute phase reactant levels in the bloodstream, and measurement of Patient Global Assessment (PGA).[13] However, the disease impact of RA may still be felt even during the remission phase. As RA becomes a more prevalent disease in our society, the treatment modalities that are being utilized in clinical practice are gaining focus. As proven with this literature review, many of the evidentiary claims from RA research are by articles that have proven biases in study design, which casts doubt on the results. More RCTs and strong evidence based studies need to be performed in order to definitively establish a gold standard treatment that specifically targets foot and ankle pain and functional disability in RA affected individuals.

AUTHOR'S CONTRIBUTIONS

All five authors contributed equally to the creation of this literature review.

STATEMENTS OF COMPETING INTERESTS

All of the authors declare that they have no associated competing interests.

REFERENCES

1. Scherer HU, Häupl T, Burmester GR. The etiology of rheumatoid arthritis. *J Autoimmun*. 2020;110:102400. doi:10.1016/j.jaut.2019.102400 (external - Introduction only)
2. DiBaise M, Kohn S. Diagnosing and managing patients with rheumatoid arthritis. *JAAPA*. 2021;34(5):27-34. doi:10.1097/01.JAA.0000742944.34 230.87 (external - Introduction only)
3. Zhao M, Mauer L, Sayles H, et al. HLA-DRB1 Haplotypes, Shared Epitope, and Disease Outcomes in US Veterans with Rheumatoid Arthritis. *J Rheumatol*. 2019;46(7):685-693. doi:10.3899/jrheum.180724 (external - Introduction only)
4. Otter SJ, Lucas K, Springett K, et al. Comparison of foot pain and foot care among rheumatoid arthritis patients taking and not taking anti-TNFα therapy: an epidemiological study. *Rheumatol Int*. 2011;31(11):1515-1519.

doi:10.1007/s00296-010-1700-2 (external - Introduction only)
5. Gallagher KS, Godwin J, Hendry GJ, Steultjens M, Woodburn J. A protocol for a randomised controlled trial of prefabricated versus customised foot orthoses for people with rheumatoid arthritis: the FOCOS RA trial [Foot Orthoses - Customised v Off-the-Shelf in Rheumatoid Arthritis]. *J Foot Ankle Res*. 2018;11:24. Published 2018 May 31. doi:10.1186/s13047-018-0272-3 (external - Introduction only)
6. De Cock D, Hyrich K. Malignancy and rheumatoid arthritis: Epidemiology, risk factors and management. *Best Pract Res Clin Rheumatol*. 2018;32(6):869-886. doi:10.1016/j.berh.2019.03.011 (external - Introduction only)
7. Gijon-Nogueron G, Ramos-Petersen L, Ortega-Avila AB, Morales-Asencio JM, Garcia-Mayor S. Effectiveness of foot orthoses in patients with rheumatoid arthritis related to disability and pain: a systematic review and meta-analysis. *Qual Life Res*. 2018;27(12):3059-3069. doi:10.1007/s11136-018-1913-5
8. Wang CC, Lee SH, Lin HY, et al. Short-term effect of ultrasound-guided low-molecular-weight hyaluronic acid injection on clinical outcomes and imaging changes in patients with rheumatoid arthritis of the ankle and foot joints. A randomized controlled pilot trial. *Mod Rheumatol*. 2017;27(6):973-980. doi:10.1080/14397595.2016.127049
9. Tenten-Diepenmaat M, Dekker J, Heymans MW, Roorda LD, Vliet Vlieland TPM, van der Leeden M. Systematic review on the comparative effectiveness of foot orthoses in patients with rheumatoid arthritis. *J Foot Ankle Res*. 2019;12:32. Published 2019 Jun 13. doi:10.1186/s13047-019-0338-x
10. Frecklington M, Dalbeth N, McNair P, et al. Footwear interventions for foot pain, function, impairment and disability for people with foot and ankle arthritis: A literature review. *Semin Arthritis Rheum*. 2018;47(6):814-824. doi:10.1016/j.semarthrit.2017.10.017
11. Reina-Bueno M, Vázquez-Bautista MDC, Pérez-García S, Rosende-Bautista C, Sáez-Díaz A, Munuera-Martínez PV. Effectiveness of custom-made foot orthoses in patients with rheumatoid arthritis: a randomized controlled trial. *Clin Rehabil*. 2019;33(4):661-669. doi:10.1177/0269215518819118
12. Linberg BH, Mengshoel AM. Effect of a thin customized insole on pain and walking ability in rheumatoid arthritis: A randomized study. *Musculoskeletal Care*. 2018;16(1):32-38. doi:10.1002/msc.1199
13. Santos EJF, Duarte C, Marques A, et al. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis: an umbrella review. *JBI Database System Rev Implement Rep*. 2019;17(7):1494-1531. doi:10.11124/JBISRIR-D-18-00020
14. Ramos-Petersen L, Nester CJ, Reinoso-Cobo A, Nieto-Gil P, Ortega-Avila AB, Gijon-Nogueron G. A Systematic Review to Identify the Effects of Biologics in the Feet of Patients with Rheumatoid

Arthritis. *Medicina (Kaunas)*. 2020;57(1):23. Published 2020 Dec 29. doi:10.3390/medicina57010023

15. Vannabouathong C, Del Fabbro G, Sales B, et al. Intra-articular Injections in the Treatment of Symptoms from Ankle Arthritis: A Systematic Review. *Foot Ankle Int*. 2018;39(10):1141-1150. doi:10.1177/1071100718779375

Combined Anticoagulant and Antiplatelet Therapy on Peripheral Arterial Diseases: A Literature Review

Biao Zhang, MS

ABSTRACT

Introduction

Peripheral arterial disease (PAD) is defined as an atherosclerotic arterial disease that reduces blood flow to the affected limb by stenosis or occlusion of the arteries. Patients with PAD experience intermittent claudication and limb ischemia. Critical limb ischemia occurs when blood flow reduction is severe, leading to rest pain and tissue damage, putting patients at risk of limb amputation. The management of PAD varies depending on its severity and symptoms, and the current primary treatment involves aspirin. However, this therapy still leaves a residual risk of ischemia and bleeding. Therefore, there is a need for optimal antithrombotic therapy. The combination of rivaroxaban, an anticoagulant, and aspirin plays a crucial role in PAD treatment. This review aims to assess the effectiveness and safety of combined anticoagulant and antiplatelet therapy for patients with PAD

Study Design: Systematic Review of Literature

Methods

A PubMed database search was performed for this literature review. The following queries were entered "(((peripheral arterial disease[MeSH Terms]) AND (lower extremity[MeSH Terms])) AND (anticoagulant[MeSH Terms])) AND (Platelet Aggregation Inhibitor[MeSH Terms])". The search result yielded a total of 35 articles. After using inclusion and exclusion criteria, this resulted in a total of four articles applicable for review.

Results

The studies consistently demonstrated that rivaroxaban plus aspirin significantly reduced the risk of adverse cardiovascular and limb events compared to aspirin alone. Additionally, this combination therapy was found to reduce both arterial and venous thrombotic events compared to aspirin alone. Furthermore, it was observed that the addition of rivaroxaban plus aspirin reduces the risk of adverse cardiovascular and limb events regardless of short-term clopidogrel use.

Discussion and Conclusion

Rivaroxaban alone did not demonstrate a significant reduction in major adverse cardiovascular events. Therefore, the combination of rivaroxaban and aspirin appears to be a more effective treatment option for PAD patients at higher risk of cardiovascular events. However, since this combination therapy is relatively new, further long-term studies are needed to enhance treatment selection and improve care for patients with symptomatic peripheral arterial disease.

Keywords: Peripheral arterial disease, PAD, limb ischemia, revascularization, anticoagulant, antiplatelet, rivaroxaban, aspirin

Level of Evidence: 4

INTRODUCTION

Background

In the 21st century, peripheral arterial disease (PAD) has become a global problem.[1] There are estimated 200 million people living with peripheral arterial disease and its incidence is increasing.[1] Peripheral arterial disease is defined as an atherosclerotic arterial disease that reduces blood flow to the affected limb by stenosis or occlusion of the arteries.[2] Many patients with PAD experience intermittent claudication and limb ischemia.[2] Critical limb ischemia occurs when the reduction in blood flow is so severe that it causes pain at rest or tissue loss (ulceration or gangrene), and patients are at high risk of limb amputation and premature death.[2] PAD is also associated with a high risk of vascular complications such as myocardial infarction, stroke, and even cardiovascular-caused death.[2,3] Although the underlying mechanism of atherosclerosis is similar to coronary artery disease, PAD is increasingly clear to be a distinct disease characterized by high levels of risk of causing serious adverse effects in the limbs.[4] Treatment of PAD varies depending on the severity and symptoms of the disease.[5] Treatment options for PAD include lifestyle changes, reduction in cardiovascular risk factors, pharmacotherapy, endovascular intervention, and revascularization.[5] In addition to exercise and smoking cessation, antiplatelet therapy, anticoagulation therapy, and statin therapy can be used to treat patients with symptomatic PAD.5 Main treatment for patients with peripheral arterial disease includes the use of a single antiplatelet agent aspirin daily to prevent major adverse cardiovascular complications.[5] However, the remaining ischemic risk of single antiplatelet therapy persists along with the risk of bleeding.[6] Therefore, optimal antithrombotic therapy is needed. Recent attention has focused on the combination therapy of anticoagulant plus antiplatelet. However, not all anticoagulation therapies have been shown to be superior to single antiplatelet therapy on PAD. In a study, warfarin plus aspirin combination therapy does not show a reduction in major adverse cardiovascular events, but does show an increased risk of life-threatening bleeding.[7] Furthermore, another study with dual antiplatelet therapy does not show consistent superiority to single antiplatelet therapy in reducing adverse cardiovascular and limb events.[8] On the contrary, the clinical trial of peripheral arterial disease in Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS clinical trial) shows that low-dose rivaroxaban together with aspirin helps patients with PAD with complications such as cardiovascular death, myocardial infarction, stroke, acute limb ischemia and amputation compared to aspirin alone.[9] Furthermore, three studies use data from the Vascular Outcome Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral arterial Disease (VOYAGER PAD) clinical trial prove similar results.[10,11,12]. Therefore, an overview of combined rivaroxaban plus aspirin therapy is provided here.

Objective

The purpose of this review is to evaluate the efficacy and safety of using combined anticoagulant rivaroxaban and antiplatelet aspirin therapy in the treatment of patients with PAD.

METHODS

A PubMed database search was performed for this literature review. The following

queries was entered "(((peripheral arterial disease [MeSH Terms]) AND (lower extremity[MeSH Terms])) AND (anticoagulant[MeSH Terms])) AND (Platelet Aggregation Inhibitor[MeSH Terms])". The search result yielded a total of 35 articles. The article search was further filtered by applying inclusion criteria and exclusion criteria. Inclusion criteria consisted of randomized control trials, clinical trials, and human subjects. Exclusion criteria consisted of non-English articles and articles not specific for anticoagulant plus antiplatelet treatment for peripheral arterial disease patients. Two articles were written by the same author with the same clinical trial method and similar results, therefore, only one article was selected. Therefore, a total of four articles were selected for review.

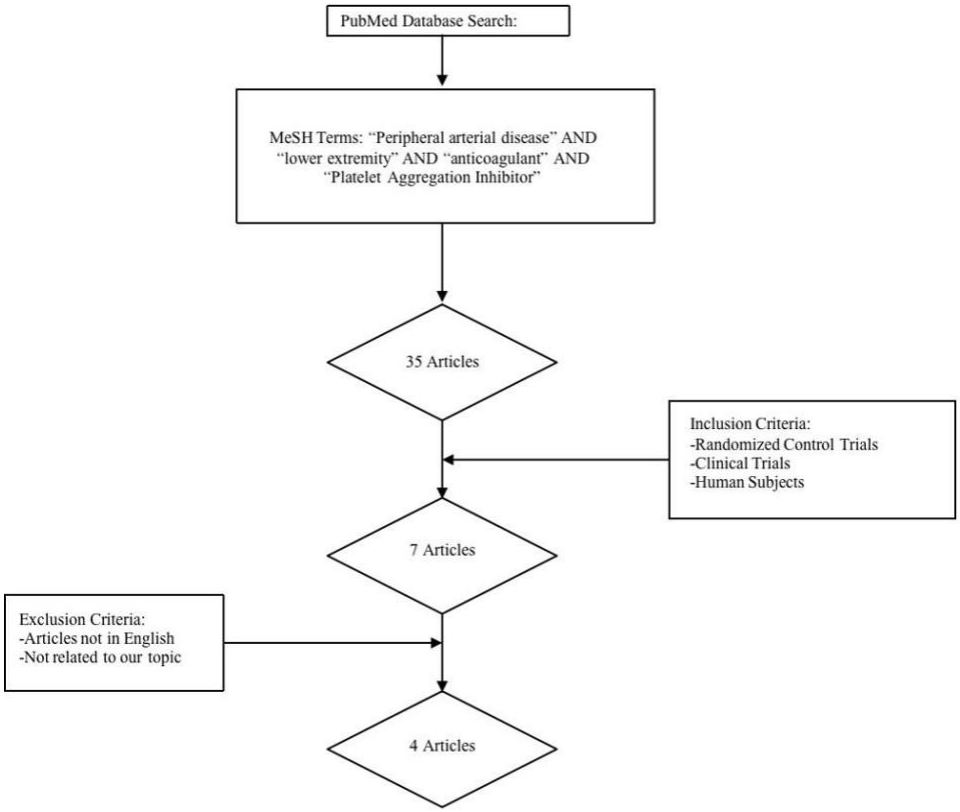


Figure 1.Article Search with Inclusion and Exclusion Criteria

RESULTS

Bonaca et al. conducted a study using data from Vascular Outcomes Study of ASA Along With Rivaroxaban in Endovascular or Surgical Limb Revascularization for Peripheral arterial Disease (VOYAGER PAD) clinical trial to assess combination therapy of rivaroxaban and aspirin compared to placebo and aspirin among patients with lower extremity peripheral arterial disease

(PAD) undergoing revascularization.[10] Patients were selected with the following criteria: at least 50 years of age and peripheral arterial disease of the lower extremity, including symptoms, anatomical evidence and hemodynamic evidence. Patients were excluded if they underwent revascularization for asymptomatic PAD, mild claudication without functional limitation, or major ischemic ulcers or gangrene at the index leg. A total of 6564 patients were randomized for 28 months in 34 countries. The results were classified into efficacy and safety outcomes. The primary efficacy outcome consisted of acute limb ischemia, major amputation for vascular causes, myocardial infarction, ischemic stroke, or death from cardiovascular cause. The principal safety outcome was severe bleeding. The primary efficacy outcome occurred in 508 patients in the rivaroxaban treatment group and 584 in the control group. Kaplan-Meier estimates of incidence at 3 years were 17.3% for rivaroxaban group and 19.9% for control group (hazard ratio=0.85, p=0.009). It showed that rivaroxaban group at any individual time during this randomized trial was 25% less likely to experience any primary efficacy outcome than placebo group. Thrombolysis in Myocardial Infarction (TIMI) major bleeding occurred in 62 patients in the rivaroxaban group and 44 patients in the placebo group (hazard ratio=1.43, p=0.07). International Society on Thrombosis and Haemostasis (ISTH) major bleeding occurred in 140 patients in the rivaroxaban group, compared to 100 patients in the placebo group (hazard ratio=1.42, p=0.007). This showed that the incidence of major bleeding in rivaroxaban group was higher only using the ISTH classification, and not statistically significant in TIMI classification. Overall, in patients with peripheral arterial disease who had undergone lower extremity revascularization, rivaroxaban at a dose of 2.5 mg twice daily plus aspirin was associated with a significantly lower risk of primary efficacy outcomes than aspirin alone.

Berkowitz et al. assessed the total burden of thrombotic plaque in the arterial and venous after lower extremity revascularization for symptomatic peripheral arterial disease and the effectiveness of anticoagulation in conjunction with antiplatelet therapy using data from the VOYAGER PAD clinical trial.[11] They found that rivaroxaban plus aspirin was associated with a lower first and total thrombotic events compared to aspirin alone. Rivaroxaban reduced the first arterial and venous thrombotic events by 24% (hazard ratio=0.76,p<0.0001), and for an absolute risk reduction (ARR) of 1.7 events per 100 patient-years. They also found that rivaroxaban reduced the total rate of arterial and venous thrombotic events by 23%(hazard ratio=0.77, p=0.0005), for an ARR of 2.4 events per 100 patient-years. Additionally, this article showed by using combined therapy of rivaroxaban with aspirin, 4.8 first thrombotic events and 6.1 total thrombotic events per 100 patients would be prevented during 3 years of clinical trial.

Hiatt et al. conducted a study aimed at evaluating whether rivaroxaban plus aspirin reduces the risk of adverse cardiovascular and limb events and the addition of concomitant clopidogrel modified the risk-benefit relationship of rivaroxaban plus aspirin.[12] The primary focus of this research article was to investigate the impact of clopidogrel, an antiplatelet drug commonly administered alongside aspirin after endovascular revascularization. The study aimed to assess whether the addition of clopidogrel modified the efficacy and safety outcomes of rivaroxaban plus aspirin, a

combination therapy that had not been previously explored in this specific context. The treatment group was randomly selected with patients who were administered clopidogrel at the time of randomization. The safety of clopidogrel was explored by adding study groups of short-term exposure (less than 30 days) and long-term exposure (>30 days). Patients were prohibited from taking any additional antithrombotic therapy other than clopidogrel with study drug (rivaroxaban and aspirin), including anticoagulants, doses of aspirin >100 mg daily, vorapaxar, ticagrelor, prasugrel, or cilostazol. The efficacy of rivaroxaban with aspirin compared to placebo was consistent regardless of the background use of clopidogrel. Acute limb ischemia was significantly reduced regardless of clopidogrel use in the treatment of rivaroxaban plus aspirin. For safety concerns, they found that rivaroxaban was associated with more TIMI major bleeding regardless of background clopidogrel. However, for the long-term use of clopidogrel with rivaroxaban plus aspirin treatment, there was an increased bleeding risk with clopidogrel(>30days) using ISTH classification. Overall, clopidogrel did not modify the benefit or risk of bleeding in this treatment, and rivaroxaban plus aspirin reduced adverse cardiovascular and limb events regardless of clopidogrel.

Anand et al. studied whether rivaroxaban given twice a day when used with aspirin or without aspirin was more effective than aspirin alone in reducing major adverse cardiovascular events and major adverse limb events in patients with peripheral arterial disease using Cardiovascular Outcomes for People Using Anticoagulation Strategies trial (COMPASS trial).[9] In this 21-month study, 6048 participants with symptomatic PAD and 1422 patients with coronary arterial disease who had an ankle-brachial index less than 0.90 were added to a total of 7470 participants under the category of PAD patients. They were randomized into 3 groups, 2492 assigned low-dose rivaroxaban plus aspirin, 2474 assigned to rivaroxaban alone and 2504 assigned to aspirin alone. The results were classified into primary efficacy and safety outcomes. The primary efficacy result consisted of cardiovascular events and limb events, and the safety outcome was major bleeding in different organs. The primary outcome of cardiovascular death, myocardial infarction, or stroke occurred in 126 patients with peripheral arterial disease who received rivaroxaban plus aspirin and in 174 who received aspirin alone. This showed that rivaroxaban plus aspirin was superior to aspirin alone by a reduction of 28% of adverse cardiovascular incidences (hazard ratio=0.72, p=0.0047). However, the primary efficacy outcome in the rivaroxaban alone group was not significantly lower than that observed in the aspirin alone group (p=0.19) for the incidences of adverse cardiovascular events. For the primary outcome of adverse limb events, there were significantly lower incidences in the low-dose rivaroxaban plus aspirin group compared to the aspirin alone group by 46% reduction (hazard ratio=0.54, p=0.0054). Similar results were found in rivaroxaban alone group compared to aspirin alone group with 37% reduction. Furthermore, they stated that there were fewer major amputations leading to a 31% reduction in risk with rivaroxaban plus aspirin versus aspirin alone (p=0.0003). For safety outcomes, the authors found that major bleeding occurred in 77 patients who had rivaroxaban plus aspirin, 79 patients who had rivaroxaban alone, and 48 patients who had aspirin alone. This showed that there was an increase in major bleeding with the use of rivaroxaban. However, there were no differences in fatal or non-fatal intracranial

hemorrhages or symptomatic bleeding to a critical organ between any of the treatment groups, and the most common site of bleeding for all groups was gastrointestinal. Overall, the low-dose rivaroxaban taken twice a day plus aspirin once a day reduced major adverse cardiovascular and limb events compared to aspirin alone. Rivaroxaban alone did not show a statistically significant reduction in major adverse cardiovascular events compared to aspirin alone but reduced major adverse limb events and increased major bleeding. Therefore, they estimated that the net clinical benefit favored the use of low-dose rivaroxaban plus aspirin. They also recommended the combination therapy of low-dose rivaroxaban with aspirin to replace aspirin alone as standard care in patients with stable PAD who are not at high risk for bleeding.

Article	Study Design	Trial Population	Study Objective	Study Results and Conclusion
Bonaca MP, Bauersachs RM, Anand SS, et al. (2020)[10]	Randomized Controlled Trial (based on VOYAGER PAD trial)	Group 1=3286 were assigned to receive rivaroxaban and aspirin Group 2=3278 were assigned to receive placebo and aspirin	Primary efficacy objective: Test whether rivaroxaban and aspirin reduce the risk of adverse cardiovascular and limb events in PAD patients. Primary safety objective: Test whether rivaroxaban and aspirin increase the risk of major bleeding	Rivaroxaban with aspirin reduced the risk of primary efficacy outcome compared to aspirin alone. (p=0.009) But it increased the risk of major bleeding compared to aspirin alone with ISTH classification. (p=0.007)
Berkowitz SD, Bauersachs RM, Szarek M, et al. (2022)[11]	Randomized Controlled Trial (based on VOYAGER PAD trial)	Group 1=3286 were assigned to receive rivaroxaban and aspirin Group 2=3278 were assigned to receive placebo and aspirin	Assess total arterial and venous thrombotic burden after lower extremity revascularization for symptomatic PAD and effect of anticoagulation plus antiplatelet therapy.	Rivaroxaban plus aspirin reduced the total arterial and venous thrombotic events by 23% compared to aspirin alone ((hazard ratio=0.77, p=0.0005)
Hiatt WR, Bonaca MP, Patel MR, et al. (2020)[12]	Clinical Trial (based on VOYAGER PAD trial)	Group 1=1658 were assigned to receive rivaroxaban and aspirin Group 2=1655 were assigned to receive placebo and aspirin	Evaluate if rivaroxaban plus aspirin reducing the risk of adverse cardiovascular and limb events and the addition of concomitant clopidogrel modify the risk-benefit of rivaroxaban plus aspirin	Rivaroxaban plus aspirin reduced risk of adverse cardiovascular and limb events regardless of clopidogrel use. But longer duration of clopidogrel use was associated with increased bleeding

Anand SS, Bosch J, et al. (2018)[9]	Randomized Controlled Trial (based on COMPASS trial)	Group 1=2492 receive rivaroxaban and aspirin Group 2=2474 receive rivaroxaban alone Group 3=2504 receive aspirin alone	Determine whether rivaroxaban given with aspirin or without aspirin, was more effective than aspirin alone in reducing major adverse cardiovascular events and major adverse limb events in PAD patients	Low-dose rivaroxaban plus aspirin reduced major adverse cardiovascular and limb events when compared with aspirin alone. Major bleeding was increased, but fatal or critical organ bleeding was not.

DISCUSSION

Revascularization was one of the surgical treatment options for PAD patients with lifestyle-limiting claudication who responded poorly to other therapies.[5] The studies used VOYAGER PAD clinical trials focused on PAD patients who underwent lower extremity revascularization and showed that patients with PAD were at increased risk of developing major adverse cardiovascular and limb events after revascularization. Revascularization of patients with intermittent claudication associated with an increasing progression to chronic limb-threatening ischemia and amputation.[10,13] Patients with a history of revascularization were at high risk of subsequent vascular complications, particularly acute limb ischemia, with a risk estimated 4 times higher than in patients who had never undergone revascularization. This contradicted the purpose of performing revascularization surgery in PAD patients in the first place. Therefore, revascularization treatment for PAD patients would need more clinical research to show its efficacy and safety, and our healthcare providers must be aware of the risk and benefit of providing this treatment option. Combined therapy with rivaroxaban and aspirin could be an alternative treatment option for those who may need to undergo revascularization. However, this would require more data to support the hypothesis that this replacement therapy would benefit these patients.

In studies using VOYAGER PAD clinical trials, there were 80% of patients taking statin therapy, 63% took angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and 51% were taking clopidogrel. Although the impact on the efficacy and safety of rivaroxaban plus aspirin with the concomitant use of clopidogrel was determined by Hiatt et al., the influence on the efficacy and safety of rivaroxaban plus aspirin with the use of statin therapy and ACE inhibitor was not studied. Statin therapy and ACE inhibitors might also have contributed to the results. A more in-depth study focused on rivaroxaban plus aspirin therapy under the background use of statin and ACE inhibitors is necessary to determine a conclusion about how the statin and ACE inhibitor might interact with rivaroxaban plus aspirin therapy.

The use of hazard ratio for time-to-event analysis to determine the relative risk of using rivaroxaban compared to placebo was a good way to analyze data from clinical trials. Because it considers the occurrence of events over time, allowing for the assessment of event rates and the comparison of risks between different groups, taking into account varying follow-up durations. Understanding the reduction in adverse events using these ratios allows for a quantitative assessment of the treatment's efficacy. These studies utilized these ratios to quantify the

magnitude of risk reduction and compare it between treatment groups, providing a more meaningful interpretation of the treatment's benefits and potential harm. However, the hazard ratio only showed the probability of an event occurring during any given time during the duration of the trial, and it could not express the reduction of events at the end of the study. Berkowitz et al. showed relative/absolute risk in its analysis. Therefore, it would be better for the other three articles to include relative/absolute risk in their analysis to allow comparison. However, in general, all articles showed a reduction in adverse cardiovascular and limb events using rivaroxaban and aspirin with statistical significance hazard ratios.

The anticoagulant drug, rivaroxaban, is metabolized by cytochrome P450 3A4 (CYP3A4). It is necessary to be aware of possible drug interactions with potent inhibitors of CYP3A4, including clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, verapamil, goldenseal and grapefruit. If drug interactions result in decreased metabolism of rivaroxaban, it can lead to drug retention and potential drug toxicity, such as excessive bleeding due to the prolonged retention of the anticoagulant in the body.

In this review, only the study by Anand et al. examined the use of rivaroxaban as a standalone treatment to assess its efficacy in reducing cardiovascular and limb complications in PAD patients, independent of aspirin. Furthermore, only their population selection included all PAD patients with and without previous revascularization. Therefore, their approach was more accurate in answering the question of whether rivaroxaban plus aspirin would reduce the incidence of any adverse cardiovascular and limb events in patients with PAD. This study also recommended replacing the current main treatment of aspirin alone with combined rivaroxaban plus aspirin. Moreover, they concluded that rivaroxaban alone did not significantly reduce adverse cardiovascular events compared to aspirin alone but reduced major adverse limb events and increased major bleeding. Should PAD patients with a history of previous adverse limb events or at risk of adverse limb events consider using rivaroxaban alone without aspirin? I think it will be better for these types of patients to receive combined therapy with rivaroxaban plus aspirin only if they are not at risk for major bleeding. As stated above, PAD is also associated with a high risk of vascular complications, and many risk factors for serious cardiovascular and limb events overlap. In addition, it is difficult to predict that this patient will not have any adverse cardiovascular events. Therefore,if the treatment plan outweighs the risk, a better treatment selection plays a crucial role in providing better care to patients. Furthermore, this review only studied the anticoagulant rivaroxaban and antiplatelet aspirin. More different combinations of anticoagulant and antiplatelet therapy are needed to determine the optimal treatment for patients with PAD.

Combined anticoagulant and antiplatelet therapy in the treatment of patients with PAD holds significance for podiatric medicine and podiatrists. As part of the multidisciplinary approach to managing PAD, podiatrists play a crucial role in diagnosing and treating foot-related complications associated with the disease. By staying informed about the latest treatment options, such as combined anticoagulant and antiplatelet therapy, podiatrists can collaborate effectively with other healthcare providers, including vascular specialists, in the comprehensive care of PAD patients. This knowledge

allows podiatrists to offer appropriate recommendations, monitor patients' response to treatment, and provide optimal foot care to improve outcomes and quality of life for individuals with PAD.

CONCLUSION

All studies show a significant reduction in adverse cardiovascular and adverse limb events such as cardiovascular death, myocardial infarction, stroke, acute limb ischemia, and major amputations in combination therapy of rivaroxaban plus aspirin compared to aspirin alone. Although previous studies found that rivaroxaban treatment was associated with increased major bleeding, there was no excess of fatal bleeding, intracranial bleeding or bleeding in critical organs with rivaroxaban plus aspirin treatment and there was a clinical benefit favoring the use of rivaroxaban plus aspirin. Unlike combination therapy with rivaroxaban plus aspirin, rivaroxaban alone did not significantly reduce major adverse cardiovascular events. Therefore, for PAD patients at risk of adverse cardiovascular events, rivaroxaban plus aspirin may be a better treatment option. An optimal alternative treatment for PAD patients was evident using rivaroxaban and aspirin. Since rivaroxaban plus aspirin is relatively new as a combination of anticoagulant and antiplatelet therapy, further and long-term research will help decision-making with treatment selection and ultimately provide better care for patients with symptomatic peripheral arterial disease.

STATEMENT OF COMPETING INTERESTS

One author contributed to this literature review. The author drafted and reviewed the final manuscript.

REFERENCES

1. Fowkes FG, Rudan D, Rudan I, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. Lancet 2013;382: 1329–40.

2. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ. 2018 Feb 1;360:j5842. doi: 10.1136/bmj.j5842. PMID: 29419394.

3. Kim M, Yang YS, Ko YG, Choi M. Major Adverse Events in Patients with Peripheral Artery Disease after Endovascular Revascularization: A Retrospective Study. J Clin Med. 2022 May 1;11(9):2547. doi: 10.3390/jcm11092547. PMID: 35566674; PMCID: PMC9102344.

4. Bonaca MP, Scirica BM, Creager MA, et al. Vorapaxar in patients with peripheral artery disease: results from TRA2{degrees}P-TIMI 50. Circulation. 2013 Apr 9;127(14):1522-9, 1529e1-6. doi: 10.1161/CIRCULATIONAHA.112.000679. Epub 2013 Mar 15. PMID: 23501976.

5. Firnhaber JM, Powell CS. Lower Extremity Peripheral Artery Disease: Diagnosis and Treatment. Am Fam Physician. 2019 Mar 15;99(6):362-369. Erratum in: Am Fam Physician. 2019 Jul 15;100(2):74. PMID: 30874413.

6. Gurbel PA, Tantry US. Combination antithrombotic therapies. Circulation. 2010 Feb 2;121(4):569-83. doi: 10.1161/CIRCULATIONAHA.109.853085. PMID: 20124137.

7. Warfarin Antiplatelet Vascular Evaluation Trial Investigators; Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007 Jul 19;357(3):217-27. doi: 10.1056/NEJMoa065959. PMID: 17634457.

8. Bhatt DL, Fox KA, Hacke W, et al.; CHARISMA Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006 Apr 20;354(16):1706-17. doi: 10.1056/NEJMoa060989. Epub 2006 Mar 12. PMID: 16531616.

9. Anand SS, Bosch J, Eikelboom JW, et al.; COMPASS Investigators. Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet. 2018 Jan 20;391(10117):219-229. doi: 10.1016/S0140-6736(17)32409-1. Epub 2017 Nov 10. PMID: 29132880.

10. Bonaca MP, Bauersachs RM, Anand SS, et al. Rivaroxaban in Peripheral Artery Disease after Revascularization. N Engl J Med. 2020 May 21;382(21):1994-2004. doi: 10.1056/NEJMoa2000052. Epub 2020 Mar 28. PMID: 32222135.

11. Berkowitz SD, Bauersachs RM, Szarek M, et al. Prevention of arterial and venous thrombotic events in symptomatic peripheral arterial disease patients after lower extremity revascularization in the VOYAGER PAD trial: Dual anticoagulant/antiplatelet regimen vs antiplatelet therapy alone. J Thromb Haemost. 2022 May;20(5):1193-1205. doi: 10.1111/jth.15673. Epub 2022 Mar 7. PMID: 35170216; PMCID: PMC9314576.

12. Hiatt WR, Bonaca MP, Patel MR, et al. Rivaroxaban and Aspirin in Peripheral Artery Disease Lower Extremity Revascularization: Impact of Concomitant Clopidogrel on Efficacy and Safety. Circulation. 2020 Dec 8;142(23):2219-2230. doi: 10.1161/CIRCULATIONAHA.120.050465. Epub 2020 Nov 3. PMID: 33138628.

13. Madabhushi V, Davenport D, Jones S, et al. Revascularization of intermittent claudicants leads to more chronic limb-threatening ischemia and higher amputation rates. J Vasc Surg. 2021

Sep;74(3):771-779. doi: 10.1016/j.jvs.2021.02.045. Epub 2021 Mar 26. PMID: 33775749.

Differences in Surgical Outcomes for Tarsal Coalition Based on Interposition Used: A Systematic Review of the Literature

Jacques Blondet, BS; Ahra Cho, MS; Kai Higuchi, BS; Sahil Mapkar, BS

ABSTRACT

Coalitions of the foot can lead to numerous pathologies such as flatfoot, recurrent sprains, limited range of motion, and pain. There are various types of tarsal coalitions, such as talocalcaneal, calcaneonavicular, and talonavicular coalition, with the latter two being the most common. Surgical treatments involve resection of the coalition and insertion of an interposition to prevent recurrence. Three commonly used interposition materials include fat grafts, bone wax, and muscle tendons. A total of 17 relevant articles from PubMed were identified and systematically reviewed to evaluate the surgical efficacy of interpositions for tarsal coalitions. We found that silicone sheet interpositions may be more suitable for talocalcaneal but not for cuboid-navicular coalitions, and extensor digitorum brevis tendon interpositions may be associated with higher complication and coalition recurrence rate in calcaneonavicular coalitions compared to fat graft and bone wax.

INTRODUCTION

Diagnosis

Congenital tarsal coalitions usually occur during development due to the failure of mesenchyme to segment properly, leading to the fusion of two tarsal bones. They have recently been linked to an autosomal dominant inherited disorder with a point mutation at Pro250Arg in the fibroblast growth factor 3 receptor (*FGF3R*) gene.[1] Usually, coalitions do not become symptomatic until the age of 10-16 years with activity-induced pain.[2] In order to determine which bones have fused in a patient's foot, imaging is conducted from the anteroposterior, lateral, 45° internal oblique, and Harris Beath heel views during weight bearing.[3] However, if the disease is in early stages, radiography may fail to detect the coalition due to fibrous or cartilaginous involvement and MRI must be utilized. This divides coalitions into three categories: synostosis (bone), synchondrosis (cartilage), and syndesmosis (fibrous tissue).[4]

Conservative Treatments

Conservative treatments for symptomatic tarsal coalitions include non-steroidal anti-inflammatory medications, orthotics, cast immobilization, and lifestyle changes.[7] A study on the outcomes of nonoperative treatments for tarsal coalitions has identified short leg casts, splints, orthoses, ankle support such as lace-up and brace, and physical therapy as treatments that could effectively prevent surgery.[7] In general, conservative measures have been reported to relieve symptoms in 30% of patients.[8]

Surgical Procedures

When conservative treatments have failed, surgical interventions are recommended.[1] A traditional approach to treat calcaneonavicular coalition is the open technique, which entails excision of the coalition and insertion of interposition to minimize the recurrence of coalition.[1 4 9] Although it is less common, in some surgeries for tarsal coalitions, interposition may not be used, especially in the case of arthroscopic approach to coalition resection as opposed to standard open techniques.[6 10 11] Commonly used types of interposition are muscle tendon, fat, and bone wax.[6] Some studies reported uses of less commonly used interpositions such as silicone sheet,[9] pediculated flap of a tibialis posterior tendon sheath,[12] lateral supramalleolar adipofascial flap,[13] juvenile hyaline cartilage.[14] Despite the many available options for interposition, there have not been enough studies to derive a conclusion on the effectiveness or postoperative complications of each interposition used. In addition to the standard open technique, a relatively newer technique, endoscopic/arthroscopic resection with no interposition, was introduced to correct calcaneonavicular (CNC) and talocalcaneal (TCC) in goals of lower morbidity rate and faster recovery but studies to evaluate its effectiveness is limited.[10]

METHODS

A literature search was conducted via the PubMed database using the search terms, "*((talocalcaneal coalition) OR (coalition) OR (tarsal coalition) OR (calcaneonavicular coalition)) AND ((interposition) OR (fat graft) OR (bone wax) OR (excision)) AND ((outcome) OR (treatment))*" which yielded 112 articles. Inclusion Criteria were applied to articles on human species printed in English with full-text availability through interlibrary loan through the New York College of Podiatric Medicine, and

published in 2012-2022, yielding 39 articles. The exclusion criteria were applied to articles not written in English, not focused on tarsal coalition, with no specification of interposition used, published prior to 2012, and secondary sources, such as systematic reviews and literature reviews. After applying the inclusion criteria, 39 articles were identified. Following the exclusion criteria, a total of 17 unique articles were selected for this systematic review .

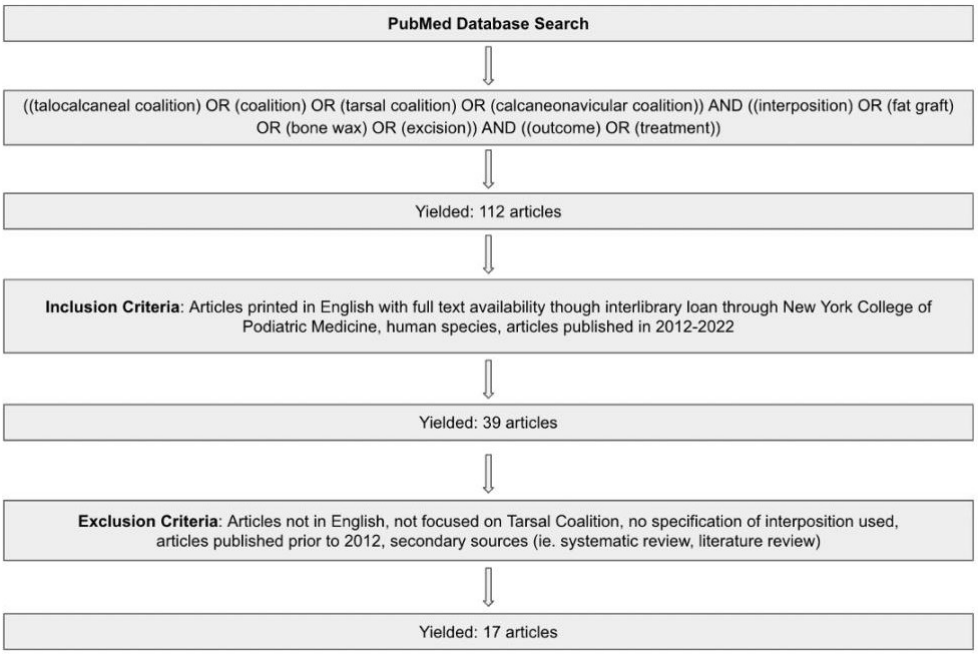


Figure 1. PubMed articles remaining after the application of inclusion and exclusion criteria.

RESULTS

Talo-Calcaneal					
Interposition	**Author**	**Level of Clinical Evidence**	**#Patient (#Feet)**	**Follow Up Period**	**Outcome (Recurrence / Complication)**
Fat Graft	Rocchi, 2020	Level IV, Case Report	1 (1)	60 months	No recurrence or complication. Increased subtalar motion to near-normal level.
	Slullitel , 2017	Level IV, Case Reports and Series	1 (2)	24 months	No recurrence or complication. Increased AOFAS Score (pre-op: 45, post-op: 92).

					Decreased VAS pain score (pre-op 10, post-op: 0).
	Kehoe, 2021	Level N/A, Case Report	2 (2)	12 months	No indication of recurrence or complication; Improved Patient-reported outcome measures (PROMs).
	Bhat, 2017	Level N/A, Case Report	1 (2)	14 months	No indication of recurrence or complication; AOFAS hindfoot score: 93 bilaterally.
Frozen Fascia Lata Allograft	Di Gennaro, 2020	Level N/A, Retrospective Study	21 (34)	36+ months	No indication of recurrence. No complication. Increase in AOFAS score (pre-op: 71, post-op: 94).
Pediculated Flap of Tibialis Posterior Tendon Sheath	Hubert, 2018	Level IV, Case Series	10 (12)	12-128 months (Mean: 57.2 months)	1 patient (10%) reported activity-related hindfoot pain at 12-month follow-up. No recurrence or complication. Increase in average AOFAS score (pre-op: 62.9, post-op: 95.8). Decrease in average VAS score (pre-op: 7.3, post-op:0.3). Increase in frontal plane motion (eversion/inversion) (pre-op: 0/0, post-op: 10/30).
Silicone Sheet	Krief, 2016	Level IV, Case Report and Series	3 (3)	12/53/80 months	No recurrence or complication. All resumed sports activity at 6 months. Mean VAS score: 0. Mean AOFAS Score: 100.
Juvenile Hyaline Cartilaginous Allograft	Tower, 2015	Level IV, Retrospective Study	3 (4)	41-47 months	No indication of recurrence or complication; Improved subtalar joint motion. Decreased pain; Engage in Physical Activities.

None	Jagodzinski, 2013	Level N/A, Retrospective Study	8 (9)	12-66 months	3 cases of complication (scar sensitivity, posterior tibial nerve damage, degenerative changes). No indication of recurrence. Generally increased Sports Athlete Foot and Ankle Score. Generally reduced VAS score.
Cubo-Navicular					
Interposition	**Author**	**Level of Clinical Evidence**	**#Patient (#Feet)**	**Follow Up Period**	**Outcome (Recurrence / Complication)**
Adipose Graft	Sarage, 2021	Level IV, Case Report and Series	4 (4)	N/A	Mid foot pain in a patient with a past medical history of L5 radiculopathy. and concurrent osteopenia and tarso-metatarsal arthritis. 2 patients able to engage in sports activity after 8-10 weeks from operative intervention.
Adipose Autograft with Amniotic Membrane Allograft	Ehredt, 2020	Level IV, Case Report	1 (1)	24 months	No recurrence or complication. Ambulating without pain. Increase in range of motion of midfoot in sagittal, frontal, transverse planes.
Silicone Sheet	Krief, 2016	Level IV, Case Report and Series	1 (1)	15 months	Occasional activity-related pain and pain at rest. No recurrence. AOFAS score: 74; VAS score: 4.
Navicular-Medial Cuneiform					
Interposition	**Author**	**Level of Clinical Evidence**	**#Patient (#Feet)**	**Follow-Up Period**	**Outcome (Recurrence / Complication)**

Free Fat Graft	Malone (2016)	Level IV, Case Report	1 (2)	24 months	No indication of recurrence or complication. Pain-free & resumed running track.
Calcaneo-Navicular					
Interposition	**Author**	**Level of Clinical Evidence**	**#Patient (#Feet)**	**Follow Up Period**	**Outcome (Recurrence / Complication)**
Fat Graft	Masquijo, 2017	Level III, therapeutic	19 (23)	12-78 months (mean: 35 months)	Recurrence of CN Coalition in 1 patient (4%) 3 Complications (1 infection, 2 cases of wound dehiscence). Improved VAS score (pre-op: 7, post-op: 0.5). Improved AOFAS score (pre-op: 59, post-op: 98).
Bone Wax	Masquijo, 2017	Level III, therapeutic	14 (18)	12-78 months (mean: 35 months)	Recurrence of CN Coalition in 1 feet (6%). No indication of complication. Improved VAS score (pre-op: 7, post-op: 0). Improved AOFAS score (pre-op: 50, post-op: 98).
Extensor Digitorum Brevis (EDB)	Masquijo, 2017	Level III, therapeutic	15 (15)	12-78 months (mean: 35 months)	Recurrence of CN Coalition in 6 feet (40%). Development of Pain with Ambulation in 5 feet (33%). Improved VAS score (pre-op: 7, post-op: 1.7). Mild improvement in AOFAS score (pre-op: 48, post-op: 78).
	Angelis, 2022	Level N/A, Case Series	13 (13)	12-48 months (mean: 27.2 months)	1 patient (7.69%) has a reformation of the CN coalition. 2 patients (15.38%) experienced infection after the procedure.

					AOFAS score ranging from 53-100 (mean: 90.84).
Lateral Supramalleolar Adipofascial Flap	Okada, 2013	Level IV, Case Report	1 (1)	32 months	No recurrence; No indication of complication. Increase in Range of Motion in sagittal plane motion (DF/PF) (pre-op: 15/40, post-op: 20/45) and frontal plane motion (Inversion/Eversion) (Pre-op: 10/5, Post-op: 20/15).
Lateral Cuneo-Cuboid					
Interposition	**Author**	**Level of Clinical Evidence**	**#Patient (#Feet)**	**Follow Up Period**	**Outcome (Recurrence / Complication)**
Bone Wax	Imai, 2016	Level IV, Case Report	1 (1)	24 months	No indication of recurrence or complication. Unrestricted weight-bearing activities. Painless ambulation.

Parameters for Successful Operative Intervention

Besides recurrence and complications, parameters used to define success in surgical intervention among the studies included the American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Score, a 10-point Visual Analog Scale (VAS), Foot and Ankle Disability Index (FADI), Oxford Ankle Foot Questionnaire (OAFQ), University of California Los Angeles (UCLA) Activity Score, Patient Reported Outcomes Measurement Information System (PROMIS), HSS Pedi-FABS, Foot Function index, Manual Muscle Testing, and Sports Athlete Foot and Ankle Score (SAFAS). Commonly used parameters for successful operative interventions were AOFAS (7 articles)[2, 5, 9, 12, 15-17] and VAS scores (5 articles).[2, 9, 11, 12, 15] AOFAS score was scored on a 100-point scale, where below 70 points was poor, 70-80 was fair, 80-90 was good, and 90-100 was excellent. It was used to assess pain (40 points), function (50 points), and alignment (10 points). VAS scores rated the pain level with 0 indicating no pain, and 10 indicating severe pain.

Bone Wax

In a study by Masquijo et al., out of 56 participants with CNC, 18 received bone wax, with one resulting in reossification.[2] The mean postoperative AOFAS score in the bone wax group of the study was 98 points, which was a 43.5-point increase from mean preoperative scores. Another case report by Imai et al. also used a bone wax interposition on a 60-year-old patient but with a cuneocuboid coalition (CCC).[21] There

were no complications after a 6-month follow-up with the patient, demonstrating the ability to walk without pain.

Fat Graft

In the study by Masquijo et al., out of 56 participants with CNC in the study, 23 received a fat graft for interposition. One of those participants had a form of reossification after a 24-month follow-up.[2] There were three reported complications, but these complications came from the graft harvesting process where there was wound dehiscence in the buttocks. Within the 23 participants, there was a mean increase of 37 points of their AOFAS score, with the postoperative mean being 98. In a case study of a TCC by Bhat et al., one patient received a fat graft bilaterally and after a 14-month follow-up, it was noted that there was no reossification nor complications with a postoperative AOFAS score of 93.[16] This outcome is similarly reflected on another case study by Kehoe and Scher where they operated on a single patient with a TCC demonstrating no reossification or complication after a 12-month follow-up.[20] A case report by Rocchi and Mubarak discussed the importance of treating the underlying TCC to treat the complication, which was a ganglion cyst in this case.[22] A patient with reduced subtalar motion and a ganglion cyst in her ankle was diagnosed with posterior TCC. A resection of the coalition was completed, and a buttock fat graft was inserted for the interposition. The surgery managed the ganglion cyst through aspiration and drainage. At the follow-up after five years, the patient had an increase in the subtalar joint and a reduction in foot pain. No complication nor recurrence of coalition or ganglion cyst was observed.

Ehredt et al. used subcutaneous fat from sinus tarsi wrapped in amniotic membrane allograft as interposition for a patient who underwent resection of the cuboid-navicular coalition (CbNC).[18] There was no complication nor recurrence at the 24-month follow-up. The patient had an increased range of motion in all cardinal planes (transverse, frontal, sagittal) and had no pain in ambulation.

In a case report by Slullitel et al., they had operated on a patient who had bilateral cuneocuboid coalitions (CnCbC) that required excision after the failure of prior conservative treatment.[15] After excision, they covered the edges of the bone surface with bone wax but used a fat graft taken from a previous anterolateral incision of the same patient. The 24-month follow-up yielded no evidence of reossification or complications. The study also noted a postoperative increase in AOFAS score from 45 to 92.

Three patients with activity-related midfoot pain and one patient with trauma-related midfoot pain were surgically treated for fibrous CbNC with an adipose graft from the anterior lower leg.[23] Two of the three patients with activity-related midfoot pain were able to engage in sports activity after 8-10 weeks from operative intervention. The patient who came in for trauma-related midfoot pain also had a past medical history of L5 radiculopathy and concurrent osteopenia and tarsometatarsal arthritis. He complained of reduced but mild midfoot pain postoperatively. Lastly, there was no indication of follow-up for the third patient who came in for activity-related midfoot pain.

In a case report by Malone and Raney, a regimen for a bilateral case of rare navicular-medial cuneiform coalition (NMCC) was discussed.[24] The patient suffered from medial foot pain, which resolved after a 24-month follow-up after being treated with excision of coalition and interposition of free fat that was taken anterior to the Achilles tendon.

A use of lateral supramalleolar adipofascial flap as interposition in the resection of CNC was mentioned in a case report by Okada and Saito.[13] After the resection of the coalition, an adipofascial flap was inserted, and the patient was followed up for 32 months. There was no recurrence of the coalition, and complications did not occur. In fact, increases in the range of motion in the sagittal plane (dorsiflexion/plantarflexion) and frontal plane (inversion/eversion) were noted. Sagittal plane motion improved from 15 (DF)/ 40 (PF) to 20 (DF)/ 45 (PF), and frontal plane motion improved from 10 (inversion)/ 5 (eversion) to 20 (inversion)/ 15 (eversion).

Tendon Graft

Out of 56 participants in the study by Masquijo et al., 15 received a tendon interposition, specifically with extensor digitorum brevis (EDB).[2] Six of those participants had radiographic confirmation of reossification after a 37-month follow-up, and five of those with reossification also developed symptoms. Within the 15 participants in the EDB group, there was a mean increase of 35 points in their AOFAS score (postoperative mean: 75). A similar study by Angelis et al. had 13 participants with CNC who were also treated with EDB interposition. In this group, two cases of post-operative infections and one case of reossification were noted. The postoperative AOFAS score ranged from 53-100, with an average score of 90.84.[5]

A pediculated flap of tibialis posterior tendon sheath was used to treat medial TCC in 10 children with ages ranging from 10-18 years, making a total of 12 coalition cases (6 fibro-osseous, six fibro-cartilaginous).[12] All TCCs were classified as Downy Type IIA (juvenile without secondary arthritis), and all children had a past medical history of activity-related hindfoot pain and subtalar joint stiffness. After the resection of the coalition and insertion of the pediculated flap, patients were checked up for recurrence or complication over a follow-up period ranging from 12-128 months (mean: 57.2 months). At the follow-up, no recurrence or complication was observed, and all patients reported significantly improved activity levels. However, one patient (10%) reported persistence of pain in the hindfoot related to activity 12 months after the operative intervention. The tibialis posterior muscle in all operated legs exhibited function in full strength with the Manual Muscle Testing (Noreau and Vachon) (MMT Score: 5). Patients all had an improvement in the subtalar joint range of motion (pre-op inversion/eversion: 0/0 degree, post-op inversion/eversion: 10/30 degrees). The pain level among the patients was significantly reduced (VAS pre-op mean: 7.3, post-op mean: 0.3). AOFAS ankle-hindfoot score also improved significantly (pre-op mean: 62.9, post-op mean: 95.8).[12]

A retrospective cohort study by Di Gennaro et al. discussed the operative treatment of 21 children (12 males, 9 females) with ages ranging from 10-15 years, making a total case of 34 TCC with rigid flatfoot. In the study, frozen fascia lata allograft was used for interposition, and the patients were followed for at least three years after the operative intervention, averaging 4.7 years. Di Gennaro et al. noted a significant improvement in the AOFAS ankle-hindfoot score (pre-op mean: 71, post-op mean: 94).[19]

Miscellaneous (Silicone, Hyaline Cartilage)

Silicone Sheet

A sterile reinforced silicone sheet was used in a study by Krief et al. The study had four patients, two males, and two females. All patients had congenital tarsal coalitions (1 Talocalcaneal Synchondrosis, 2 Talocalcaneal Synostosis, and 1

Cuboid-Navicular Synostosis) classified under Downey Type IIA, meaning that no patient had secondary arthritis. All patients had a past medical history of multiple ankle pseudo-traumas and midfoot pain from activity/sports.[9] After the coalition resection was completed and the silicone sheet was inserted as interposition, the patients were followed up over the course of at least 12 months (12-80 months). In the follow-up, no recurrence was observed. All patients were able to resume sports activities at 6 months, except for the patient with cuboid-navicular synostosis (25%), who complained of occasional pain after running. Three talocalcaneal patients scored excellent (mean AOFAS score: 100) and the cuboid-navicular synostosis patient scored fair (AOFAS score: 74) in the post-operative AOFAS ankle-hindfoot score.[9] Substantial improvement in pain was observed in all patients (mean VAS score: 1).

Hyaline cartilage

Hyaline cartilaginous allograft material was harvested from donors of less than 13 years of age and was used on three patients in this case series by Tower et al. Among the three patients, two were female, and one was male. All had talocalcaneal middle facet coalitions, and after resection of the coalition and insertion of juvenile hyaline cartilaginous allograft interposition, there was a follow-up for an average of 43 months, with none showing any bony regrowth or complications.[14] All patients had an increased range of motion and increased participation in activities with the decreased association of pain.

No Interposition

Eight patients with middle facet talocalcaneal coalitions (two osseous, six fibrous) were treated without an interposition after an arthroscopic resection in a study by Jagodzinski et al. After a 39-month follow-up, three complications were reported: 1) scar sensitivity and suture reaction at a portal site, which resolved following oral antibiotics and wound management, 2) numbness of the entire medial ray due to posterior tibial nerve damage, and 3) joint degeneration, which warranted subsequent arthroscopic subtalar fusion.[11] While the posterior tibial nerve damage was recovered at one-year post-operation without intervention, loss of sensation was only recovered after undergoing cable-grafting using the patient's sural nerve. Even with the complications, there was an overall postoperative improvement in SAFAS and pain measures within the cohort.[11]

Interposition used vs. Coalition Type

Summarized in **Table 1.** is the list of grafts used per coalition type among 17 studies reviewed in this study. For TCC, the interposition used were fat graft,[22 15 20 16] frozen fascia lata allograft,[19] a pediculated flap of tibialis tendon sheath,[12] silicone sheet,[9] and Juvenile hyaline cartilaginous allograft.[14] Interpositions used for CbNC were adipose graft,[23] adipose autograft with amniotic membrane allograft,[18] and silicone sheet.[9] For CNC, fat graft,[2] bone wax,[2] extensor digitorum brevis,[2 13] and lateral supramalleolar adipofascial flap[13] were used. Free fat grafts[24] were used for NMCC, and bone wax[21] was used for lateral cuneo-cuboid coalition.

DISCUSSION

Interpositions vs. None

Many of the studies argue that the use of interpositions plays a role in the success rate of tarsal coalition resections. For example, a study by Hollander et al. compared the success rates of both TCC and CNC depending on the presence of an interposition.[25] The results showed that TCC interpositions increased the success rate by

about 4% and CNC interpositions by 12%. Success in this article was defined as when a good or excellent result was achieved at follow-up using AOFAS or Foot and Ankle Ability Measure (FAAM) score above 80. Another study by Krief et al. compared recurrence rates based on the presence of interposition and the type of interposition used. A study that did not use interposition for a CNC found as much as a 66% recurrence rate, whereas those that used interposition had a maximum of 22% with the use of EDB for the same type of coalition.[9] These papers are in favor of the use of interpositions and demonstrate their effectiveness through cases.

On the other hand, a study by Jagodzinski et al. argues that the resection of coalitions can be successful without the use of interpositions. They go on to cite a study done in 1992 by Kumar et al. that reported an 88.9% satisfactory rate in patients that underwent resection with no interposition used. They believe that there is no need for any type of interposition after resection to prevent recurrence and advocate for the use of early movement with oral NSAIDs to inhibit bone healing.[26]

In the same study, five out of the eight patients that underwent arthroscopic resection without interpositions had no complications. However, the other three patients (37.5%) had varying complications ranging from scar sensitivity, joint degeneration, and posterior tibial nerve damage.[11] We found that open or posterior approach arthroscopic resection can introduce posterior tibial nerve damage in a coalition that extended one-fourth away along the surface of the posterior facet of the subtalar joint.[11] In the case of a TCC, a direct arthrodesis rather than a posteromedial approach may be desirable to reduce the risk of posterior tibial nerve damage, especially if the resection may leave less than three-fourths of the posterior facet. While differences in surgical techniques may play a confounding role, the direct relationship between disuse of interposition in the arthroscopic approach and complication/recurrence was brought into question.

Since many of the articles have advocated for the use of interpositions and have shown through cases and statistics, it is safe to assume that interpositions do increase the rate of successful resections as well as decrease the rate of coalition recurrence and complications.

Recurrence and Complications

No complications were reported following TCC interposed with fat grafts,[16] [15] frozen fascia lata,[19] and pediculated flap of tibialis tendon sheath.[12] However, Hubert et al. favored pediculated flap for its well-maintained blood supply, which may have prevented complications by reducing the risk of necrosis seen in fat graft interpositions.[12] [13] Okada et al., also suggests the use of interpositions other than fat graft in the case of CNC due to its lack of vascular source.[13] Fat autograft harvested from the posterior crease of the buttocks raised the risk of wound dehiscence as a complication.[2] [14] In addition to wound dehiscence, Tower et al. claim the advantage of juvenile hyaline cartilage allograft use over autografts for its reduction in the risk of donor site morbidity.[14]

Although the risk of wound dehiscence and donor site morbidity may be reduced, as with all allografts, there is a risk of host rejection, which can be minimized with thorough preoperative screening.[14] In addition to the risk of host rejection, Hubert et al. further mentioned the possible risk of postoperative delamination or infectious disease transmission associated with the use of allografts.[12]

In CbNC with silicone sheet interposition, one patient (25%) had occasional pain at rest

and when running despite preservation of EDB, sural nerve, and peroneal tendons.[9] On the contrary, three other patients who had silicone sheet interposition for TCC resection were successful with no pain (mean VAS: 0) and excellent AOFAS scores (mean: 100). This suggests that the silicone sheet may not be fit for CbNC but very effective for TCC. However, this assumption cannot be made without more sample sizes using silicone sheets as interposition for each type of coalition. Although not mentioned in the study by Hubert et al. added that a possible complication of silicone sheet interposition is postoperative infection from the colonization of microorganisms.[12]

In CNC with fat graft, bone wax, and EDB graft, recurrence of coalitions was present in all three groups. Fat grafts were associated with recurrence of coalitions without symptomatic pain (1 patient, 4%), superficial infection at the surgical site (1 patient, 4%), and superficial wound dehiscence in the posterior crease of the buttocks where the fat graft was harvested (2 patients, 9%). The use of bone wax was also associated with the recurrence of coalitions (1 patient, 6%) without symptomatic pain. Although no complications with bone wax interpositions were found in the study by Masquijo et al., chronic inflammation and an increase in the risk of infection due to decreased bacterial clearance in cancellous bones were listed as possible complications.[2]

Complications of EDB grafting for calcaneonavicular coalition included recurrence of coalitions (6 feet, 40%) and symptomatic pain with ambulation as observed prior to operation (5 feet, 33%), three of which were treated with conservative treatment and two of which required surgical revision.[2] Although all three types of interpositions (fat graft, bone wax, EDB) resulted in coalition recurrence, it should be mentioned that recurrence occurred at a much higher rate among the EDB interposition group (40% vs. 4% in the fat graft group vs. 6% in the bone wax group). Other complications of using EDB interposition for CNC resection included early lateral wound infection (2 patients, 15%) and recurrence with pain and mild to moderate functional limitations (1 patient, 8%).[5] With these two studies mentioning a relatively high rate of recurrence and complication with the use of EDB as interposition for CNC, it may be worthwhile to re-examine the risk of using such interposition for this type of coalition.

This finding is concurrent with a review by Klammer et al., which stated that CNC resection is usually accompanied by fat graft or bone wax interposition,[6] possibly indicating that EDB interposition for CNC had been associated with higher incidences of coalition recurrence and complications. Additionally, Okada et al. mentioned that EDB may not be suitable for interposition after the resection of CNC due to its insufficient size to fill the bone spaces.[13] A high rate of wound dehiscence from an increase in dead space at the wound site after EDB transfer has been previously reported for CNC coalitions.[27]

Limitations of the Study

Due to the small number of studies included in this systematic review, there are some limitations in deriving a comprehensive conclusion. Firstly, with the studies having a variety of levels of evidence between each paper, along with the fact that the papers consist of mostly lower levels of evidence, there is less reliability in drawing interpretation from their outcomes. In total, 14 studies were either case series, case studies, or case reports. Therefore, they are simply reporting coalitions and their interposition without sufficient information on preoperative or postoperative variables. Additionally, simplification of coalition

types may accidentally undermine the clinically significant differences in surgical outcomes of interposition use, which could impose an issue with reliability and validity. For example, studies by Hubert, Bhat, Masquijo, Imai, Krief, differentiated the osseous and non-osseous coalition, but in **Table 1.,** fibrous and osseous coalitions are not differentiated for the sake of conciseness. Problems with reliability also stem from the fact that follow-up periods between patients varied from 12 to 128 months between and within studies. The measure of reossification is completely dependent on the length of time a follow-up is conducted, and those that were followed up within only a 12-month span could miss any future problem. Issues in validity stem from the fact that some studies did not measure outcomes in any objective measure, and those that did only measured after the surgery. This occurred mostly with the AOFAS, which was most used to measure postoperative improvement after resection. However, almost half of the studies that used AOFAS did not measure preoperative scores and could not be compared with the postoperative score. In summary, there were small sample sizes, intragraft variations, differences in surgical technique, and low levels of evidence between the studies that were taken. In a future study, a larger sample size with a standardized method of comparing interposition type and the surgical outcome would be ideal.

CONCLUSION

In conclusion, our findings aligned with the current understanding of the crucial role of interpositions in preventing coalition recurrence. We found that silicone sheet interpositions may be more suitable for TCC but not for CbNC, and EDB tendon interpositions may be associated with higher complication and coalition recurrence rate in CNC compared to fat graft and bone wax. Additionally, we identified that the most common complications associated with interpositions were pain, infection, wound dehiscence, chronic inflammation, and reossification. Further studies are needed to confirm our findings and to determine the optimal interposition for each coalition type to maximize surgical outcomes .

REFERENCES

1. Soni JF, Valenza W, Matsunaga C. Tarsal coalition. *Curr Opin Pediatr*. 2020;32(1):93-99. doi: 10.1097/MOP.0000000000000858.
2. Masquijo J, Allende V, Torres-Gomez A, Dobbs MB. Fat graft and bone wax interposition provides better functional outcomes and lower reossification rates than extensor digitorum brevis after calcaneonavicular coalition resection. *J Pediatr Orthop*. 2017;37(7):e427-e431. doi: 10.1097/BPO.0000000000001061.
3. Murphy JS, Mubarak SJ. Talocalcaneal coalitions. *Foot Ankle Clin*. 2015;20(4):681-691. doi: S1083-7515(15)00078-9 [pii].
4. Bonasia DE, Phisitkul P, Amendola A. Endoscopic coalition resection. *Foot Ankle Clin*. 2015;20(1):81-91. doi: S1083-7515(14)00113-2 [pii].
5. Angelis S, Myrgiotis D, Apostolopoulos AP, et al. Surgical removal of bone bridge and interposition of the extensor digitorum brevis in the treatment of calcaneonavicular coalition in pediatric patients: A case series, short review, and commentary. *J Long Term Eff Med Implants*. 2022;32(4):27-37. doi: 10.1615/JLongTermEffMedImplants.2022042255.
6. Klammer G, Espinosa N, Iselin LD. Coalitions of the tarsal bones. *Foot Ankle Clin*. 2018;23(3):435-449. doi: S1083-7515(18)30040-8 [pii].

7. Shirley E, Gheorghe R, Neal KM. Results of nonoperative treatment for symptomatic tarsal coalitions. *Cureus*. 2018;10(7):e2944. doi: 10.7759/cureus.2944.
8. Jayakumar S, Cowell HR. Rigid flatfoot. *Clin Orthop Relat Res*. 1977;(122)(122):77-84.
9. Krief E, Ferraz L, Appy-Fedida B, et al. Tarsal coalitions: Preliminary results after operative excision and silicone sheet interposition in children. *J Foot Ankle Surg*. 2016;55(6):1264-1270. doi: S1067-2516(15)00109-X [pii].
10. Corin B, Laumonerie P, Zrounba V, Langlais T, De Gauzy JS, Accadbled F. Resection of calcaneonavicular coalition: Arthroscopic or open approach? *J Child Orthop*. 2022;16(2):136-140. doi: 10.1177/18632521221087170.
11. Jagodzinski NA, Hughes A, Davis NP, Butler M, Winson IG, Parsons SW. Arthroscopic resection of talocalcaneal coalitions--a bicentre case series of a new technique. *Foot Ankle Surg*. 2013;19(2):125-130. doi: S1268-7731(13)00025-8 [pii].
12. Hubert J, Hawellek T, Beil FT, et al. Resection of medial talocalcaneal coalition with interposition of a pediculated flap of tibialis posterior tendon sheath. *Foot Ankle Int*. 2018;39(8):935-941. doi: 10.1177/1071100718768257.
13. Okada M, Saito H. Resection interposition arthroplasty of calcaneonavicular coalition using a lateral supramalleolar adipofascial flap: Case report. *J Pediatr Orthop B*. 2013;22(3):252-254. doi: 10.1097/BPB.0b013e328353a1c1.
14. Tower DE, Wood RW, Vaardahl MD. Talocalcaneal joint middle facet coalition resection with interposition of a juvenile hyaline cartilage graft. *J Foot Ankle Surg*. 2015;54(6):1178-1182. doi: 10.1053/j.jfas.2015.02.016.
15. Slullitel PAI, Tripodi ML, Bosio ST, Puigdevall M, Maenza R. Massive osteochondral lesion of the talus in a skeletally immature patient associated with a tarsal coalition and valgus hindfoot. *J Foot Ankle Surg*. 2017;56(6):1257-1262. doi: S1067-2516(17)30276-4 [pii].
16. Bhat AK, Madi S, Mane PP, Acharya A. Bilateral tarsal tunnel syndrome attributed to bilateral fibrous tarsal coalition and symmetrical hypertrophy of the sustentaculum tali. *BMJ Case Rep*. 2017;2017:10.1136/bcr-220087. doi: bcr-2017-220087 [pii].
17. Di Gennaro GL, Stallone S, Olivotto E, et al. Operative versus nonoperative treatment in children with painful rigid flatfoot and talocalcaneal coalition. *BMC Musculoskelet Disord*. 2020;21(1):185-5. doi: 10.1186/s12891-020-03213-5 [doi].
18. Ehredt DJ, Zulauf EE, Kim HM, Connors J. Cryopreserved amniotic membrane and autogenous adipose tissue as an interpositional spacer after resection of a cubonavicular coalition: A case report and review of the literature. *J Foot Ankle Surg*. 2020;59(1):173-177. doi: S1067-2516(19)30234-0 [pii].
19. Di Gennaro GL, Stallone S, Olivotto E, et al. Operative versus nonoperative treatment in children with painful rigid flatfoot and talocalcaneal coalition. *BMC Musculoskelet Disord*. 2020;21(1). doi: 10.1186/s12891-020-03213-5.
20. Kehoe CM, Scher DM. Sustentaculum tali fracture adjacent to talocalcaneal tarsal coalitions: A report of 2 cases. *JBJS Case Connect*. 2021;11(1):e20.00360. doi: 10.2106/JBJS.CC.20.00360 [doi].
21. Imai K, Ikoma K, Kido M, et al. Nonosseous tarsal coalition of the lateral cuneocuboid joint: A case report. *J Foot Ankle Surg*. 2016;55(5):1072-1075. doi: 10.1053/j.jfas.2015.07.008.
22. Rocchi V, Mubarak S. Ankle ganglion associated with tarsal coalition: A case

report with a 5-year follow-up. *JBJS Case Connect*. 2020;10(3):e2000090. doi: 10.2106/JBJS.CC.20.00090.
23. Sarage AL, Gambardella GV, Fullem B, Saxena A, Caminear DS. Cuboid-navicular tarsal coalition: Report of a small case series with description of a surgical approach for resection. *J Foot Ankle Surg*. 2012;51(6):783-786. doi: 10.1053/j.jfas.2012.07.003.
24. Malone JB, Raney EM. Bilateral navicular-medial cuneiform synostosis manifesting as medial foot pain: A case report and review of the literature. *J Pediatr Orthop B*. 2016;25(2):138-141. doi: 10.1097/BPB.0000000000000235.
25. Hollander JJ, Dusoswa QF, Dahmen J, Sullivan N, Kerkhoffs GMMJ, Stufkens SAS. 8 out of 10 patients do well after surgery for tarsal coalitions: A systematic review on 1284 coalitions. *Foot Ankle Surg*. 2022;28(7):1110-1119. doi: S1268-7731(22)00059-5 [pii].
26. Kumar SJ, Guille JT, Lee MS, Couto JC. Osseous and non-osseous coalition of the middle facet of the talocalcaneal joint. *J Bone Joint Surg Am*. 1992;74(4):529-535.
27. Cohen BE, Davis WH, Anderson RB. Success of calcaneonavicular coalition resection in the adult population. *Foot Ankle Int*. 1996;17(9):569-572. doi: 10.1177/107110079601700912.

Evaluating the Efficacy of L-Arginine and Glutamine on Wound Healing: A literature Review

Muhammad Umair Husain, MPH; Tuba Azam, BS; Naila Habeeb, MS

ABSTRACT

Introduction

The process of wound healing requires a series of orchestrated steps that must occur in an optimal environment. Through various cascades of biological mechanisms, this process can be divided broadly into the inflammatory, proliferative, and maturation or remodeling phases. Proper nutrition is essential for carrying out these phases, each of which has its own unique requirement of substances. Arginine, a crucial amino acid in wound healing, plays a pivotal role in modulating immune functions, including inflammation – the first step in the wound healing cascade. Immune functions are responsible for protection of the body against harmful pathogens, many of which can alter the prognosis of wound healing. Glutamine is a non-essential amino acid, which has properties that promote tissue repair via cell proliferation and collagen involvement. Hence, the properties of Glutamine are vital for the success of the maturation or remodeling phase of wound healing. In combination, both these amino acids are necessary in the biological processes involved in healing a wound. The purpose of this literature review is to evaluate the efficacy of nutritional supplementation with arginine and glutamine on wound healing.

Study Design: Systematic Literature Review

Methods

A Pubmed search was done using the query, "wound healing"[MeSH Terms] AND "glutamine"[MeSH Terms] AND "arginine"[MeSH Terms]. The search yielded 19 articles and, after implementation of exclusion criteria of articles older than 10 years and inclusion criteria of randomized control trials, meta-analysis, and systematic reviews, our query produced 4 articles.

Results

The 4 articles that were used for this literature review yielded similar results. While oral supplementation with glutamine and arginine are theoretically beneficial and showed some angiogenetic properties, there was insufficient evidence to make the claim that there is a positive correlation between wound healing and supplementation with arginine and glutamine.

Conclusion

The overall evidence for the supplementation of amino acids was inconclusive when used to enhance wound healing in diabetic patients. However, supplementation of glutamine and arginine in some studies was shown to aid in wound healing as well as decrease mortality and duration of hospital stays. As this remains a novel area with inconclusive data, further research needs to be conducted in order to target objective measures as well as a greater sample size.

Keywords: Amino acids, wound healing, arginine, glutamine

Level of Evidence: 4

INTRODUCTION

The epidermis and dermis of the skin provide structural support and serve as a protective barrier against pathogens, chemicals, ultraviolet radiation, and various other external factors that cause damage. However, when damaged, a series of complex physiological reactions takes place in an effort to revitalize new tissue. An injury to living tissue caused by a cut or other trauma-related impact is referred to as a wound. Wound healing can be broken up into four dynamic phases referred to as hemostasis, inflammatory, proliferative, and remodeling. For proper healing, all four phases must occur in sequence and within a reasonable margin of time. The first phase of wound healing is hemostasis, which occurs within seconds to minutes of the initial trauma. In this phase, blood starts to coagulate in an attempt to protect the open area and prevent further blood loss. Blood vessels constrict and restrict blood flow to the area. Platelets form a clot and reinforce the platelet plug as fibrin begins to mesh. Pro-coagulant and prothrombin transform the liquid blood to a gel and keep the cells localized to the injured area. The second inflammatory stage begins with the release of pro-inflammatory cytokines and growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF).[4] Immune cells such as neutrophils, macrophages and lymphocytes flood the area creating swelling, heat, pain, and redness. The proliferative phase generally overlaps with the inflammatory phase as fibroblasts multiply to promote collagen formation, capillary growth, as well as production of glycosaminoglycan and proteoglycans which are essential components of the extracellular matrix. Capillary growth is imperative during this phase as it allows for granulation tissue to be made and for the site to receive an adequate supply of oxygen and nutrients.[4] The final remodeling phase is when collagen fibers cross-link to decrease thickness and strength the area of the wound. Even with complete recovery of the wound, tensile strength is not that of normal, unwounded skin.[7]

Arginine and glutamine are two amino acids that are crucial in the process of wound healing. These two conditionally essential amino acids are involved in the biological processes that occur after trauma to the skin and leading to the formation of a wound.[5] Arginine is an essential amino acid derived from dietary intake, recycled from body protein breakdown or de novo synthesis in the kidneys. During conditions of stress, when the body is in a catabolic state, arginine becomes essential as it plays a role in metabolic, immune, and reparative responses.[5] Arginine is the only substrate for nitric oxide syntheses, which is critical for vasodilation
and sustenance of equilibrium in the system. Arginine release is also stimulated upon inflammation with cell damage and cell death. Arginase I is expressed in collagenase granules and is systemically released with activation of an immune response.[5] Arginine deficiency can lead to a disruption of these cellular functions, which is why supplementation for these deficiencies is essential in wound healing.

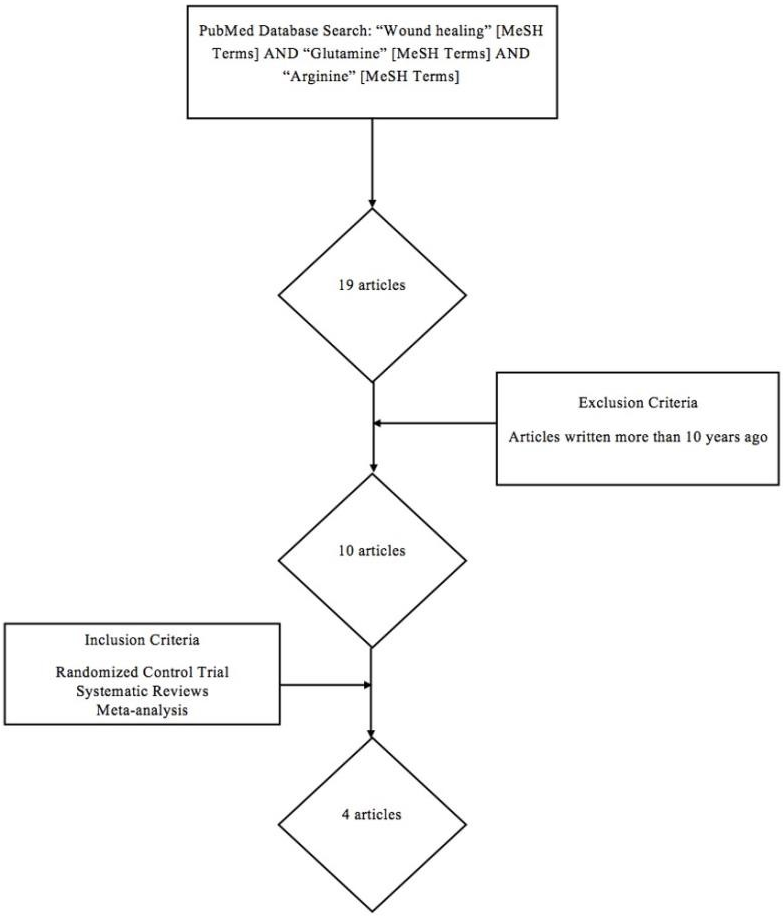
Glutamine can be synthesized in the body and is one of the most abundant in the body. It is also a precursor for nicotinamide adenine dinucleotide (NAD), glutathione, and other amino acids, such as arginine.[1] Glutamine serves as the primary source of energy for cells that are rapidly dividing, such as those of the new skin around a healing wound. Like arginine, Glutamine becomes essential during catabolic states and there is a strong correlation between low levels of glutamine and an increased rate of

mortality for critically ill patients. This can be due to the role glutamine plays in tissue repair and collagen synthesis.[3] The stages of wound healing are complex and any impediment in phases can lead to the worsening of infection. Many factors can impede the process causing delays in wound healing.

This article will review one of the pertinent factors that disrupt effective wound healing: lack of proper nutrition, specifically of arginine and glutamine. Injuries and infections can cause protein loss, which worsens wound conditions and impedes healing time.[1] With cases of severe injury and wound, metabolic demand in the body increases, thereby increasing the patients' daily nutritional needs. Specific cell processes, including those needed for cell proliferation and protein synthesis, are enhanced, leading to increased nutritional demand.[6] The supply of energy the body obtains from the daily intake of carbohydrates, proteins, and fats is essential for cellular proliferation and the promotion of several immune cell functions. With the positive impact of nutritional supplements in promoting the biological process of wound healing, it is imperative for patients with nutritional scarcity to be counseled on the advantages of supplements. Glutamine and arginine have similar characteristics and play a major role in metabolic processes, such as cellular proliferation and stimulating collagen synthesis, which ultimately can help the wound healing process. This review analyzes the effects of arginine and glutamine administration on the wound healing process.

METHODS

A literature search was performed utilizing the PubMed database. The search was conducted with the query “wound healing”[MeSH Terms] AND “glutamine”[MeSH Terms] AND “arginine”[MeSH Terms]; which yielded 19 articles, after which inclusion and exclusion criteria were applied. The exclusion criteria was set to exclude any articles not published within the past 10 years, which brought the search yield to 10 articles. The inclusion filter consisted of randomized controlled trials, systematic reviews, meta-analysis, bringing the final count to 4 articles for utilization in the literature review.



RESULTS

To study the effect of oral nutritional supplementation on wound healing for patients with diabetic foot ulcers, Armstrong et al conducted a multinational double-blind study that spanned the US, Europe, and Taiwan, including a total of 270 subjects following their wound healing process for a duration of 16 weeks. At the end of the 16-week study, the study concluded that there was no statistically significant difference in the primary and secondary outcomes of total wound healing of those who received oral supplementation compared to a control group, which did not receive oral supplementation. In addition, there was no clinically significant difference in the PT, PTT, INR, or other blood coagulation variables. Subjects with an albumin level of ≤ 40 g/l, indicating malnutrition, were shown to heal better by week 16 in the group supplemented with arginine, glutamine and β-hydroxy-β-methylbutyrate as opposed to the control subjects. Albumin can be directly correlated with injury, infection and inflammatory response. However, in this study, albumin levels remained unchanged indicating that the improvement was credited to other mechanisms.[3]

In the systematic review performed by Lopez et al., 5 studies focused on arginine and 39 studies on glutamine. Arginine supplementation was shown to increase collagen deposition in these studies. There was also increased collagen synthesis measured via hydroxyproline deposition and

T-cell-mediated immune function. In regards to glutamine supplementation, nitrogen balance was significantly increased in 11 studies, suggesting enhanced protein synthesis in those patients. Two studies indicated a lower infection rate and significantly improved wound healing time compared to the control group. Glutamine supplementation displayed a significant decrease in the length of hospitalization in 21 studies. Meta-analysis of 11 studies indicated that patient mortality rates decreased in glutamine-supplemented groups as compared to control.[2]

Moore et al., collected and analyzed relevant studies, including randomized controlled trials to assess whether or not additional nutritional supplementation could enhance the healing of foot ulcers in the diabetic population. Nine studies were identified from 2004 to 2019 involving 629 participants. These studies utilized the following supplements: magnesium oxide, protein drink with added vitamins, arginine, glutamine, and β-hydroxy-β-methyl butyrate supplement, zinc sulfate, vitamin D, and omega 3-fatty acids. Findings from the studies were inconclusive on the effectiveness of extra supplementation in healing foot ulcers.[9]

Wong et. Al. examined a total of thirty-four patients with pressure ulcers with twelve patients in the experimental group and fourteen patients in the placebo group. The study showed no significant differences between the anthropometric, biochemical, demographic, and nutritional parameters studied at baseline. There was also no change seen in body weight and muscle mass measurements. Wound area measurements showed a pattern of reduction in perimeter and depth for both groups after the two-week mark. The placebo group showed a 37.5% decrease in wound area, while the experiment group saw a 27.5% decrease. On the Pressure Ulcer Scale for Healing (PUSH), the experimental group showed improvement within one week of taking beta-hydroxy beta-methylbutyrate, arginine, and glutamine supplementation.[8]

DISCUSSION

Glutamine and arginine have implications in wound healing, so it was surprising to find that research done by Armstrong et al. reported that there was no significant difference when it came to oral supplementation to enhance diabetic wound healing.[3] This was the first prospective randomized control trial conducted aimed at addressing the effect of oral nutritional supplementation on wound healing specifically for the diabetic population. Wound healing has many intricate aspects to it, and any number of factors can have a wide range of impacts on the entire process of wound healing. When it comes to wound healing, one big factor that plays a role is impaired blood flow; decreased blood perfusion to the wound causes oxygen deficiency, as well as nutrient deficiency. Nutrient access is imperative for wound healing and as nutrients are transported via blood, nutrient access is limited if there is impaired blood flow. In addition to the poor limb perfusion commonly seen in the diabetic population, many diabetic patients may also have sedentary lifestyles, lack proper podiatric care, have unhealthy diets, and take numerous medications. These medications can affect metabolism, which in turn may lead to poor nutrient utilization. Impaired utilization of nutrients has the same effect of malnutrition. These factors complicate both research and assessment of wound healing, as there are many independent variables, each of which can have a wide range of effects on proper wound healing.

Lopez et al. utilized the understanding that glutamine and arginine, as essential amino acids, are required for proper wound healing based on the mechanism of action in the different stages of healing. This was an area that had not been explored before, especially in relation to arginine. The authors discovered that arginine supplementation caused an increase in hydroxyproline levels, which is indicative of greater collagen formation. Glutamine supplementation was also shown to be associated with shorter hospital stays, improved nitrogen retention, and lower levels of proinflammatory cytokines. The authors did point out that the method by which glutamine was administered, as well as the dose, could impact the results of the studies, as it was not standard. Additionally, due to glutamine's role as a neurotransmitter, it may also have played a positive role in the overall well-being of the patients.[2]

Moore et al. explored whether supplementation of nutrients or special diets were beneficial in treating diabetic patients with foot ulcers. Primary objective measurements of ulcer healing included time to complete healing, percent change in ulcer dimensions, the proportion of ulcers healed, and healing rate. Secondary factors were also considered such as cost of intervention, quality of life, adverse events, length of hospital stay, development of new foot ulcers, amputation rate, surgical interventions, and osteomyelitis incidence. Findings from the studies did not show significant results and the certainty of the evidence was low.[9]

Wong et. al compared the healing rate of pressure ulcers in patients who were given supplements with a mixture of important amino acids used in the wound healing process.[8] To adequately assess the features of the pressure ulcers, a specific scale was used to determine the success of the specialized supplementation. This assessment included the onset and duration of the ulcer, wound location and area, estimated change in the proportion of viable and non-viable tissue, wound depth, wound bed and periwound appearance, and wound exudate type and amount.[8] Many studies have been conducted that show the positive effects of arginine and glutamine on the wound healing process. However, this was the first study conducted in an acute setting with an Asian cohort of patients who were given the supplement containing beta-hydroxy beta-methylbutyrate, arginine, and glutamine. This study did not see an increase in wound healing with the given supplement. Although there was a decrease in the wound area, the decrease was shown at a faster rate in the placebo group than in the experimental group..[8] To properly assess the wound healing success, PUSH scores were used to validate the viable tissues. PUSH scores improved in the experimental patients who took the supplement indicating that the wound healing rate increased. Within the first week of supplementation, the proportion of viable tissue increased by 28%.[8] Patients in the study previously had low C-reactive protein levels and prealbumin levels due to the infected wound causing inflammation and malnutrition, respectively. Increased intake of arginine and glutamine can prove to be beneficial to malnourished patients given an adequate increase in caloric intake which was not examined in this study due to the requirements. The experimental group and placebo group had no significant difference in caloric intake which was likely due to the hospital setting itself which led to fasting for procedures in some cases. The use of three nutrients, beta-hydroxy beta-methylbutyrate, arginine, and glutamine, makes it unclear which played a critical part in wound healing.[8] Other factors like supervision and compliance could have also led to the

increase in wound healing not linked to the supplementation given to the two distinct groups.

CONCLUSION

Oral supplementation with arginine, glutamine, and β-hydroxy-β-methylbutyrate did not have an enhancing effect on wound healing within the diabetic population with those individuals who have a normal albumin level. However, there is some implication of enhanced diabetic wound healing with oral supplementation for patients who have poor limb perfusion, low levels of albumin, or both.[3] Nutritional supplementation with arginine and glutamine showed a positive impact on wound healing as well as secondary factors related to healing such as mortality and lower hospitalization duration.[2] Overall, there is very low-certainty evidence as to whether there is a difference in healing, amputation, or death with nutritional supplementation. More research needs to be conducted focusing on objective measures of ulcer healing with a high subject population. There is insufficient data currently to support or reject the hypothesis that nutritional intervention can accelerate the treatment of foot ulcers in individuals with diabetes.[9]

No key changes in wound size were noticed with the supplementation of beta-hydroxy beta-methylbutyrate, arginine, and glutamine. Tissue viability, as well as general conditions of the wound may improve with constant use of supplements with glutamine and arginine.[8] There are still many factors that need to be considered in future research to assess if there is an effect of oral nutrition on diabetic wound healing and to what extent. There seems to be a positive correlation with the supplementation of these amino acids, however, this is still a novel area that requires more studies and data.

AUTHORS' CONTRIBUTION

All authors contributed equally to the topic conception, evaluation of available articles, and writing of this literature review. All authors have reviewed this draft of the literature review for submission.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

REFERENCES

1. Morris CR, Hamilton-Reeves J, Martindale RG, Sarav M, Ochoa Gautier JB. Acquired amino acid deficiencies: A focus on arginine and glutamine. *Nutrition in Clinical Practice*. 2017;32(1_suppl). doi:10.1177/0884533617691250

2. Arribas-López E, Zand N, Ojo O, Snowden MJ, Kochhar T. The effect of amino acids on wound healing: A systematic review and meta-analysis on arginine and glutamine. *Nutrients*. 2021;13(8). doi:10.3390/nu13082498

3. Armstrong DG, Hanft JR, Driver VR, et al. Effect of oral nutritional supplementation on wound healing in diabetic foot ulcers: A prospective randomized controlled trial. *Diabetic Medicine*. 2014;31(9):1069-1077. doi:10.1111/dme.12509

4. S. Guo, L.A. DiPietro. Factors Affecting Wound Healing. *Nutrition in Clinical Practice.* 2010 Mar; 89(3): 219–229. doi: 10.1177/0022034509359125

5. Suzuki K, Birnbaum Z. Current Perspectives On Nutrition And Wound Healing. HMP Global Learning Network. https://www.hmpgloballearningnetwork.com/site/podiatry/current-perspectives-nutrition-and-wound-healing. Published May 2017. Accessed November 30, 2022.

6. Curreri N, Johnson D, Khan K. Crucial Considerations In Diabetic Foot Ulceration And Nutrition. Hmpgloballearningnetwork. https://www.hmpgloballearningnetwork.com/site/podiatry/diabetes-watch/crucial-considerations-diabetic-foot-ulceration-and-nutrition. Published September 2021. Accessed November 30, 2022.

7. Velnar, T., Bailey, T., & Smrkolj, V. The Wound Healing Process: An overview of the cellular and molecular mechanisms. *Journal of International Medical Research*, 2009;37(5):1528-42 doi: 10.1177/147323000903700531

8. Wong, A., Chew, A., Wang, C., Ong, L., Zhang, S., & Young, S. (2014). The use of a specialised amino acid mixture for pressure ulcers: A placebo-controlled trial. *Journal of Wound Care*, *23*(5), 259–269. doi: 10.12968/jowc.2014.23.5.259

9. Moore, Z. E., Corcoran, M. A., & Patton, D. (2020). Nutritional interventions for treating foot ulcers in people with diabetes. The Cochrane database of systematic reviews, 7(7), CD011378. https://doi.org/10.1002/14651858.CD011378.pub2

Evaluating the Implication of Copper Nanoparticles in Diabetic Wound Healing: A literature review

Ronald Baraga Delannoy, BS; Muhammad Umair Husain, MPH

ABSTRACT

Introduction

Copper is an essential micronutrient involved in angiogenesis, and induction of vascular endothelial growth factor. In patients with diabetes there has been shown to be deficient angiogenesis in their wound healing. A common delivery method of copper in diabetic wounds is by copper nanoparticles. Copper nanoparticles have been commonly used as antibacterial and antiviral treatments. This paper presents a review of literature from the past ten years regarding copper nanoparticles and diabetic wound healing. This literature review will assess the efficacy of implementation of copper nanoparticles in diabetic wound care.

Study Design: Systematic Literature Review

Methods

A Pubmed search with "Copper nanoparticles" [MeSH Terms] AND "Diabetic wound healing" [MeSH Terms] was conducted which produced 7 results. After implementing exclusion criteria of articles published more than 10 years ago and inclusion criteria of English language and articles relevant to our review, a total of 6 articles were used.

Results

All 6 of the articles in our literature review demonstrated that copper nanoparticles are beneficial for wound healing. None of the articles stated that there was a neutral or negative relationship between wound healing and copper. Articles either discussed the angiogentic properties, antimicrobial properties, or both. Vijayakumar et al. explored how to further enhance copper nanoparticles to increase its stabilization and make it more efficient in diabetic wound healing.

Conclusion

Our literature review concluded that there is indeed an implication for utilization of copper nanoparticles in wound healing. Copper nanoparticles promote angiogenesis while having anti-microbial properties, two properties that decrease the timeline of wound repair.

Keywords: Copper nanoparticles, wound healing, diabetic wound healing

Level of Evidence: 4

INTRODUCTION

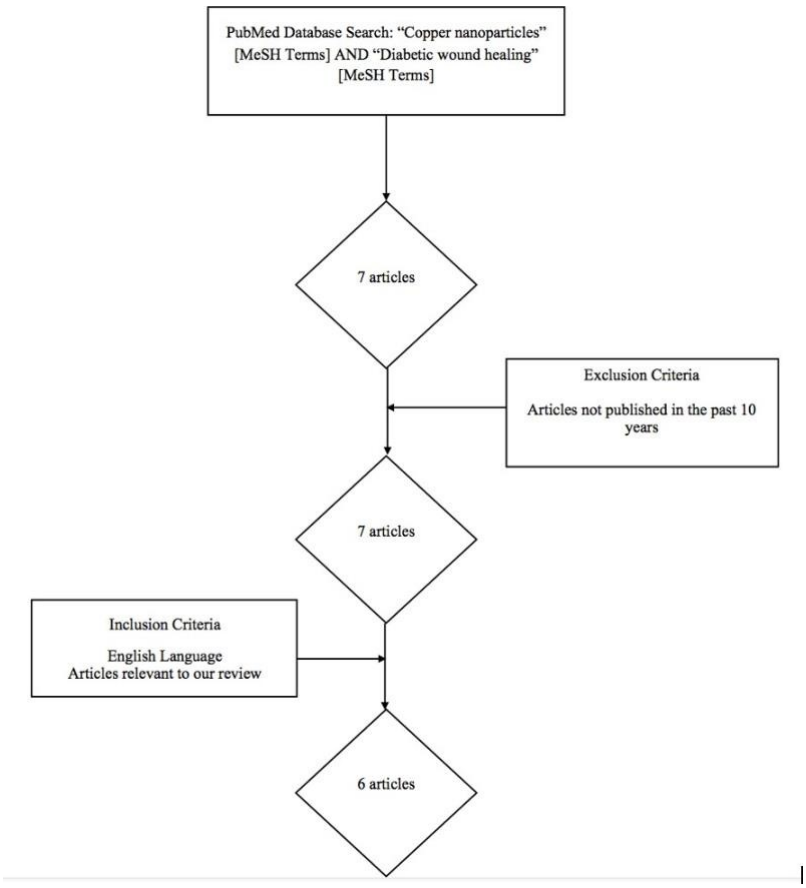
Diabetic wound care is both a complicated and expensive situation in medicine today. The average annual cost per patient with a diabetic foot ulcer is 8,659 USD.[1] Additionally, the total medical cost of managing diabetic wound disease is between 9 and 13 billion dollars[1]. Not only are diabetic foot ulcers an expensive problem, but they are also a dangerous one for patients as 85%[1] of diabetic amputations are associated with a foot ulcer. This is a prevalent issue as nearly 1 in 10 people are diabetics which equates to about 37.3 million people in the United States. As many as 1 in 3 Americans are prediabetic. This means that these people have an elevated blood sugar, but not enough to classify them with Type 2 diabetes. However, according to the American Diabetes Organization, up to 70% of people with prediabetes will progress to having Type 2 diabetes.[2] This is significant because in 2019, 96 million adults over the age of 18 were diagnosed with prediabetes. According to the University of Michigan, 15% of diabetic patients will develop a foot ulcer at some point. This means that nearly four million people every year will have an amputation that is associated with a foot ulcer.

In a study done by the NIH, they found that for diabetic patients many processes associated with inflammation and healing were suppressed in the healing of their foot ulcers compared to non-diabetic patients.[3] Lack of healing of diabetic foot ulcers can in part be attributed to the lack of blood supply that a diabetic patient may experience in their extremities. Chronic high blood sugar can cause damage to the vessels and nerves of the foot. Copper has been shown to promote factors that stimulate blood vessel growth such as Vascular Endothelial Growth Factor (VEGF) and also hypoxia-inducible factor 1 (HIF-1).[4] In cancer therapies, it is noted that copper chelating agents are utilized to suppress tumor growth via inhibition of neovascularization of tumors; thus it can be asserted that copper ion agents have an imperative role when it comes to the neovascularization of tissues. In a study done it showed that copper levels, along with other micronutrients, were significantly decreased in diabetic patients with foot ulcers, compared to diabetic patients without foot ulcers.[5]

Treating chronic foot ulcers as well as other wounds on the lower extremity become a challenge when there is an implication that the patient is a diabetic. Previous research has been conducted to investigate whether or not supplementing diabetic wound management with copper has any implications in improved or accelerated wound healing. This literature review serves to assess whether or not there is a correlation between wound healing and copper nanoparticles, and assessing whether it is an efficacious strategy to implement when treating patients who are diabetic.

METHODS

A literature search was conducted using the PubMed database. The search was conducted with the query “Copper nanoparticles” [MeSH Terms] AND “Diabetic wound healing” [MeSH Terms]; which yielded seven articles, after which inclusion and exclusion criteria were applied. The exclusion criteria was intended to exclude any articles not published within the past ten years, which brought the search yield to seven articles. The inclusion filter consisted of articles in English, as well as articles that were relevant to the scope of our literature review, which resulted in a final six articles for utilization in this literature review.



RESULTS

The study "Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair" found that sustained release of copper into a wound site increased both antibacterial and angiogenic factors. The way they did this was by creating injectable dual-network silica-based nanocomposite hydrogel scaffolds. This scaffold includes a network that has bioactive glass-nanoparticles that contain copper (BGNC). The goal of the scaffold is that it would close the wound, absorb the extravasate, have antibacterial properties, increase angiogenesis and promote healing of the wound. The scaffold was tested with and without the BGNC which contains the copper. It was found that the BGNCs increased the swelling ability of the scaffold in a significant manner. There was also an increase in the weight loss rate of the scaffold which is the rate of degeneration. By incorporating the BGNCs, it was observed that there was sustained release of copper in the scaffold because the BGNCs could decrease the rate of its release. This is what lead to the increase in the antibacterial and angiogenic activity. Another observation was that the copper in the BGNC likely had a strong ionic bond with sodium alginate (ALG). This helped the self-healing ability of the hydrogel. This can also be attributed to the fact that the addition of the BGNC to

the scaffold caused the storage modulus the scaffold to be more stable which also contributed to the increase in self-healing. There was also increased compressive strength of the scaffold with the addition of the BGNC. Also, the study found that the scaffolds with low concentration of the BGNC could increase the interaction between the nanoparticle and ALG, but a high amount of BGN would cause a decrease in the mechanical properties of the scaffold. In order to asses the antibacterial properties of the scaffold the study looked at the effect of copper in the scaffold. They looked at both Staphylococcus Aureus (Gram positive) and Escherichia Coli (Gram-negative). The intrinsic scaffold without the scaffold showed no antibacterial properties against these colonies. However after a three hour incubation with a copper containing scaffold, the results should that the number of surviving colonies was almost 0%. Another biochemical process that was assessed was with cell proliferation. The scaffold that contained copper showed to have enhanced cell proliferation compared to the scaffold that didn't and also the cooper containing scaffold demonstrated increased angiogenic properties. However it was noted that the angiogenic activity could be due to the bioactive glass. The study also assessed wound healing with the copper scaffold. They found that the wounds with the copper scaffold healed much quicker than the non-copper compared at days 7, 14, and 21. There was a newly-formed epidermis over the wound by day 21 with the copper scaffold. The healing of the wound was tested with H&E staining. The study demonstrated that the wound area was smaller in the copper containing scaffold compared to the non-copper. Both the copper and non-copper scaffolds had granulation tissue and epidermis proliferation, however the non-copper scaffold did not show as much regenerated tissue in the control group. There also seemed to be more skin appendage-like structures in the wounds with the copper scaffold indicating that the wound may have less scar tissue. The copper containing scaffold also showed the highest level of blood volume compared to the non-copper containing scaffold showing there was better angiogenesis in the copper scaffold compared to the non-copper scaffold. To find the newly-formed and mature vessels, CD31 and alpha-SMA immunofluorescence staining was done respectively. In addition in the wounds without copper, VEGF-A protein level had almost no expression, while it was increased in the copper group. The same effect was seen with VEGF-B and HIF-α. There was also increased amount of blood vessels in the copper containing groups compared to the ones that did not have copper.

In a literature review conducted by Vijayakumar et al, one of the studies they included evaluated wound healing effects on mice of a chitosan based copper nanocomposite. The study yielded the results that the rats that were treated with the composite solution, experienced a "towering significance in the contracture of the wound".[6] If the utilization was beneficial for mice and aided in the wound contracture and wound healing due to its antibacterial properties and/or efficacy of wound healing, then it would serve as a beneficial practice when it comes to diabetic wound healing as well. The purpose of using chitosan with the copper nanocomposite was to stabilize the copper aspect of the nanocomposite. In the study "Copper Metal-Organic Framework Nanoparticles Stabilized with Folic Acid Improve Wound Healing in Diabetes" by Xiao et al, they used Folic acid instead of something like chitosan, to stabilize the copper-based metal-organic framework nanoparticle (HKUST-1), calling it F-HKUST-1. HKUST-1 was prone to rapid

degradation in a protein solution, so the folic acid was added to yield stability for the nano-particle. After further stabilization of HKUST-1 to F-HKUST-1, there was angiogenesis, re-epithelialization, increased collagen deposition, and increased wound closure rates. Using diabetic mice they assessed wound healing and the results of their experiment yielded that "the time for 50% of the wound area to close was 14 days for F-HKUST-1 vs 19 days for wounds treated with PBS, folic acid, and HKUST-1, demonstrating the acceleration of wound closure due to folic-acid-stabilized HKUST-1".[11] Thus one can deduce that further stabilization of copper nanoparticles to better control release of copper serves to enhance the angiogenic and healing capacity of diabetic wounds.

Li, S et al observed four hydrogels and their implications in wound healing. One with just Sodium Alginate (SA). SA with DFO (SA-DFO), SA with copper (SA-Cu), and DFO was mixed with SA-Cu (SA-DFO/Cu). The study found that these four hydrogels did not have a difference in the water content and swelling ratios. They all contained a swelling ratio of about 3600% and about 97% water. The gelling time was longest in the SA-Cu compared to the other hydrogels and the SA-DFO and SA-DFO/Cu were shortened. Human umbilical venous endothelial cells (HUVEC) were shown to proliferate best in response to a concentration of 2 μg/mL Cu-NP. This concentration also had the most clear effect of tube formation promotion on human umbilical venous endothelial cells. The study also found there to be antibacterial activity of the Cu-NPs showing them to be effective against E. Coli and S. Aureus. There was seen to be a significant decrease in the E. Coli and S. Aureus colonies in the SA-Cu and SA-DFO/Cu groups compared to the SA group without copper. The study also found that DFO and Cu-NP could work together to promote proliferation, migration, and tube formation of HUVECs. The study found that all of the hydrogels had more than an 85% cell viability without a significant difference between groups. Also there was minimal cytotoxic effects. The SA-DFO/Cu group showed the most significant promotion of migration compared to the other groups and also had the most clear effect of tube formation promotion on HUVECs. The SA-DFO/Cu group demonstrated the quickest wound healing with significant reduction after ten days, while the other groups were significantly reduced after fourteen days. SA-DFO, SA-Cu, and SA-DFO/Cu all showed quicker re-epithelization compared to the negative control and SA group, while the SA-DFO/Cu showed the most dramatic effect. The inflammatory response was reduced in all of the hydrogels, but was most reduced in the SA-DFO/Cu group. There was more collagen deposition in the SA-DFO, SA-Cu, and SA-DFO/Cu groups compared to the SA group. The SA-DFO/Cu group had the most compact and largest collagen arrangement. The SA-DFO/Cu group had the highest density of microvessels as measured by CD31 for new vessels and α-SMA for mature vessels, and also had the highest HIF-1α and VEGF expression.

Sankar et al conducted research in which they tested the effects of copper oxide nanoparticles on Wilstar albino rats; the variables they were observing included inhibition of pathogenic bacterial growth and the secondary effect that had on wound healing. To observe the inhbition activity of the nanoparticles they tested them on 5 agar dishes, each of which was contaminated with Shigella dysenteriae, Staphylococcus aureus, Salmonella typhimurium, Klebsiella penumoniae, and Escherichia coli. The zones of inhibition that resulted from treatment with copper oxide nanoparticles

were 9 mm for Shigella dysenteriae, 7 mm for Staphylococcus aureus, 5 mm for Salmonella typhimurium, 4 mm for Klebsiella pneumoniae, and 6 mm for Escherichia coli. This proves that the nanoparticles had antibacterial activity. Furthermore to test wound healing implication of copper, Sankar et al performed an experiment on 6 Wilstar albino rats. All the mice were given a 2 cm full thickness excision wound. 3 mice in the treatment group were given green synthesized copper oxide nanoparticles applied topically for a duration of 12 days, while the 3 mice in the control group were given saline. "On the 4th day onwards copper oxide nanoparticles treated group revealed distinguished wound closure, reduced wound size and it was enhanced on upcoming treatment days as compared with control group. At the end of experiment day, the copper oxide nanoparticles treated wound showed 93 % of closure whereas control wound showed only 80% of closure".[8] The group that had been treated with the copper oxide nanoparticles had more macrophages, fibroblasts, and collagen fibers and the group that was given the saline control had loose connective tissue and a lesser amount of collagen and fibroblasts. "The copper oxide nanoparticles boosted formation of new blood capillaries and re-epithelialization process in the wound tissue".[8] The copper in this study proved its effect of antibacterial activity as well as angiogenesis activity.

In the study "Electrospun Micropatterned Nanocomposites Incorporated With Cu2S Nanoflowers for Skin Tumor Therapy and Wound Healing" used a nanocomposite PLA/PCL to incorporate the copper. The polymers were named based on the weight percentage of copper content in the polymer ranging from 0, 10,30, 40, 50. The 30% was named for example 30CS-PLA/PCL. This study used a mouse model to analyze the polymers. The healing of the wound was observed over 12 days. The results were that the 30CS-PLA/PCL group had a significantly higher wound healing rate than the control and 0CS-PLA/PCL groups. However there was no difference in the early stage which was on days 2,4, and 6. It was at eight days when the 30CS-PLAPCL group showed a significant difference. The revascularization was observed by looking at CD31 expression. It was found that the 30CS-PLA/PCL group had more blood vascular networks and CD31 positive vessels compared to the control and 0CS-PLA/PCL groups. This showed that there was more capillary formation in the 30CS-PLA/PCL group.

DISCUSSION

It was found in the electrospun nanocomposite study that the 30CS-PLA/PCL membranes increased the rate of migration of endothelial cells compared to the 0CS-PLA/PCL membrane without Cu2S particles. This supports previous studies that demonstrated copper ions stimulate migration and proliferation of endothelial cells. A finding was that the copper concentration needed for stimulation of hypoxia-inducible factor (HIF-1α) and vascular endothelial growth factor (VEGF) was less in this study compared to previous studies done. Overall this paper found that the nanocomposites "indicated the enhanced regenerative efficacy of Cu2S-loaded membranes, which makes them more suitable and safer for healing the cutaneous wounds resulting from surgery excision of tumor tissues".[10] Going forward, further research needs to be done regarding comparing the effectiveness of the nanoparticles in different hemoglobin A1C ranges and assessing different Cu2S concentrations to see which nanocomposites work best for the severity of diabetes in the

patient in which the wound is being treated. A limitation of this study is that they did not mention how costly implementation of this treatment would be for diabetic wounds.

In the study by Li et al. "Calcium ion cross-linked sodium alginate hydrogels containing deferoxamine and copper nanoparticles for diabetic wound healing", there was found to be an increase of microvessels in the hydrogel Sa-DRO/Cu which is significant since an obstacle in diabetic wound healing is the reduced ability to do angiogenesis and fight off infection, which was also shown by SA-Cu and SA-DFO/Cu groups to be effective against S. Aureus and E.Coli. This study found that the hydrogels worked in vitro for its antibacterial properties and in vitro showed increased angiogenesis and decreasing inflammation. There was also an additional protective capacity of the hydrogels in that they covered the wound. The swelling property of the hydrogels discussed earlier showed "It was beneficial for wound healing because the hydrogel could absorb and retain wound exudates, which would promote proliferation of fibroblast and migration of keratinocyte".[7] A limitation of this study is that long term use of this treatment was not assessed for its toxicity because it was mentioned that the study demonstrated "that DFO and Cu-NPs synergistically improved the proliferation, migration, and tube formation of HUVECs in a concentration-dependent manner in vitro"[7] but they did not address potential systemic effects or long term effects this treatment could have locally or systemically. When it comes to the utilization of copper nanoparticles in diabetic wound healing, one of the intended purposes is due to its antibacterial properties specifically to E. Coli and Staph Aureus, but other pathogens as well. Vijayakumar et al found in their research that one of the studies reported that there was an increased wound healing rate due to the copper itself. A copper based metal-organic nanoparticle, when used, degrades in protein solution, which causes the copper ion to dissociate and decrease toxicity in addition to hasten wound healing. It was also found that when copper undergoes rapid oxidation and agglomeration, it becomes an issue, so it is suggestive to use biocompatible stabilizers such as chitosan so that the stability of the copper nanoparticle can be controlled.[6] Sankar et al stated that metal nanoparticles are "highly virulent to pathogenic microorganisms"[8] and additionally have angiogenic properties. Even in their research there was greater epithelialization as well as new blood capillary formation, all which again proves that copper nanoparticles entails a pro healing ability. The rats that they used in their experiment and the agar they used for testing the effectiveness against the different pathogens, all showed a positive correlation for copper both being antimicrobial and angiogenic.

The study "Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair" they found that the hydrogel scaffold had "robust antibacterial activity and angiogenesis capacity for treating diabetic wound".[9] There was also shown to be increased collagen deposition and remodeling. However, further research should be done in looking at the specific effect copper has in the development of skin appendages and the role this could have in both diabetic and non diabetic wound healing as it pertains to scar tissue formation and the remodeling of collagen, which may tie into the increased collagen deposition and remodeling discussed earlier. In the study a limitation was that they never went into which specific skin appendages were enhanced, which makes it hard to interpret

the result because the skin appendages have a wide range of functions.

CONCLUSION

In the studies that were analyzed it was found that copper nanoparticles had a positive correlation with promoting angiogenesis in diabetic wounds. In addition, it was also found that copper nanoparticles had the potential of having antibacterial properties which is important in diabetic wound healing because in diabetic patients they tend to have decreased angiogenesis and also have immunodeficiencies. While some research asserted that copper-nanoparticles on their alone were not stable enough, they still saw a positive trend in enhanced wound healing. Whether stabilization of the copper nanoparticles was done via chitosan or folic acid, copper nanoparticles do have an implication for wound healing. They do so by being antimicrobial agents as well as angiogenic agents. Our literature review has implicated that when treating diabetic wounds, using copper will have a beneficial effect, and the more stable the composition of the copper nanoparticle, the better the results. Future research should analyze the effectiveness of copper nanoparticles against Pseudomonas Aeruginosa infections because they are a common gram negative infection in many diabetic wounds. The studies analyzed in this paper looked at the effect of S. Aureus and E. Coli among a multitude of other pathogens. Further research can also be geared towards identifying the best possible organic agent that can be used to offer the best stabilization for the copper ions.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to all parts of this literature review from research to writing and editing. All authors have reviewed this draft of the literature review for submission

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

REFERENCES:

1. Raghav A, Khan ZA, Labala RK, Ahmad J, Noor S, Mishra BK. Financial burden of diabetic foot ulcers to world: a progressive topic to discuss always. Ther Adv Endocrinol Metab. 2018 Jan;9(1):29-31. doi: 10.1177/2042018817744513. Epub 2017 Dec 12. PMID: 29344337; PMCID: PMC5761954.
2. Tabák AG, Herder C, Rathmann W, Brunner EJ, Kivimäki M. Prediabetes: a high-risk state for diabetes development. Lancet. 2012 Jun 16;379(9833):2279-90. doi: 10.1016/S0140-6736(12)60283-9. Epub 2012 Jun 9. PMID: 22683128; PMCID: PMC3891203.
3. Poor immune response impairs diabetic wound healing [Internet]. National Institutes of Health. U.S. Department of Health and Human Services; 2020 [cited 2022Dec9]. Available from: https://www.nih.gov/news-events/nih-research-matters/poor-immune-response-impairs-diabetic-wound-healing
4. Tanaka A, Kaneto H, Miyatsuka T, Yamamoto K, Yoshiuchi K, Yamasaki Y, Shimomura I, Matsuoka TA, Matsuhisa M. Role of copper ion in the pathogenesis of type 2 diabetes. Endocr J. 2009;56(5):699-706. doi: 10.1507/endocrj.k09e-051. Epub 2009 May 20. PMID: 19461160.
5. Yadav C, Srikantiah RM, Manjrekar P, Shenoy MT, Chaudhury D. Assessment of Mineral Pathophysiology in Patients with

Diabetic Foot Ulcer. Biol Trace Elem Res. 2020 Jun;195(2):366-372. doi: 10.1007/s12011-019-01868-3. Epub 2019 Aug 21. PMID: 31435884.
6. Vijayakumar V, Samal SK, Mohanty S, Nayak SK. Recent advancements in biopolymer and metal nanoparticle-based materials in diabetic wound healing management. Int J Biol Macromol. 2019 Feb 1;122:137-148. doi: 10.1016/j.ijbiomac.2018.10.120. Epub 2018 Oct 18. PMID: 30342131.
7. Li S, Wang X, Chen J, Guo J, Yuan M, Wan G, Yan C, Li W, Machens HG, Rinkevich Y, Yang X, Song H, Chen Z. Calcium ion cross-linked sodium alginate hydrogels containing deferoxamine and copper nanoparticles for diabetic wound healing. Int J Biol Macromol. 2022 Mar 31;202:657-670. doi: 10.1016/j.ijbiomac.2022.01.080. Epub 2022 Jan 20. PMID: 35066024.
8. Sankar R, Baskaran A, Shivashangari KS, Ravikumar V. Inhibition of pathogenic bacterial growth on excision wound by green synthesized copper oxide nanoparticles leads to accelerated wound healing activity in Wistar Albino rats. J Mater Sci Mater Med. 2015 Jul;26(7):214. doi: 10.1007/s10856-015-5543-y. Epub 2015 Jul 21. PMID: 26194977.
9. Li Y, Xu T, Tu Z, Dai W, Xue Y, Tang C, Gao W, Mao C, Lei B, Lin C. Bioactive antibacterial silica-based nanocomposites hydrogel scaffolds with high angiogenesis for promoting diabetic wound healing and skin repair. Theranostics. 2020 Mar 31;10(11):4929-4943. doi: 10.7150/thno.41839. Erratum in: Theranostics. 2022 May 28;12(10):4599-4600. PMID: 32308759; PMCID: PMC7163448.
10. Wang X, Lv F, Li T, Han Y, Yi Z, Liu M, Chang J, Wu C. Electrospun Micropatterned Nanocomposites Incorporated with Cu2S Nanoflowers for Skin Tumor Therapy and Wound Healing. ACS Nano. 2017 Nov 28;11(11):11337-11349. doi: 10.1021/acsnano.7b05858. Epub 2017 Oct 26. Erratum in: ACS Nano. 2019 Mar 26;13(3):3740. PMID: 29059516.
11. Xiao J, Zhu Y, Huddleston S, Li P, Xiao B, Farha OK, Ameer GA. Copper Metal-Organic Framework Nanoparticles Stabilized with Folic Acid Improve Wound Healing in Diabetes. ACS Nano. 2018 Feb 27;12(2):1023-1032. doi: 10.1021/acsnano.7b01850. Epub 2018 Feb 12. PMID: 29406741.

Efficacy of Foot and Ankle Orthoses in the Treatment of Gait Abnormalities in Children with Neurological Deficits: a Systematic Review

Noran Abo-Donia, BS and Jo-Yu Fang, BS

ABSTRACT

Introduction

Ankle-foot orthoses (AFOs) are commonly a treatment prescribed to patients with cerebral palsy (CP) to correct their gait pattern and reduce the spasticity in their lower limbs. Cerebral palsy is a clinical description of the features shared by children who have experienced some sort of brain injury during periods of development. CP is not just one disease, rather it is a group of diseases mainly characterized by physical and movement impairments (Graham et al., 2016). The objective of this paper is to conduct a systematic review in analyzing current existing literature that compares the general effects of AFOs on gait in children with CP.

Study Design

Systematic Review of Literature

Methods

Journal articles were retrieved from the Journal of the American Academy of Orthopaedic Surgeons, ScienceDirect, and PubMed between 2007 and 2019. Adult participants, non-AFO, and comparison of orthoses were excluded from the search.

Results

The search was narrowed down to 8 articles including case studies, prospective studies, and systematic reviews.

Discussion and Conclusion

Based on these publications the consensus was reached that, overall, wearing AFOs showed improvements in the gait patterns of patients with CP, in comparison to barefoot or shoe-wearing conditions. In fact, different types of AFOs have their corresponding strengths in correcting distinct elements of the gait pattern, including stride length, energy expenditure, speed in walking, and gross motor function. In conclusion, this systematic review proved that AFOs are beneficial for children with CP in naturalizing their gait and correcting it to reduce energy expenditure while walking. Since AFOs across the studies were described differently and were not named consistently, it was somewhat difficult to know the exact effect of each type of AFO.

Keywords: Cerebral Palsy, Ankle-Foot Orthoses, Diagnosis, Treatment, Lower Extremity

INTRODUCTION

Cerebral palsy (CP) is a group of disorders that affect a person's ability to maintain balance and conduct movements. It is mostly seen in children and may accompany other symptoms such as intellectual disability; issues with hearing, vision, or speech; seizures; spinal problems; or joint issues (Yang and Wuthoff, 2022). With most of the CP cases being spastic cerebral palsy, meaning patients' muscles are stiff and can result in different awkward movements or paralysis, additional support such as braces and ankle-foot orthoses (AFOs) are often used as treatments to support these patients in their physical activities (Davids et al., 2007). Patients can be classified depending on the severity of their mobility limitation with the Gross Motor Function Classification System, with GMFCS levels I and II being able to walk without assistance, and GMFCS levels III, IV, and V requiring assistive devices such as walkers or a wheelchair (Palisano et al., 1997). Although CP is not a progressive disease, the disuse of muscles and lack of physical activity can ultimately lead to further problems in adulthood (Booth et al., 2018).

Dystonia and spasticity are two common phenomena seen in CP patients (Graham, 2016). Dystonia movement is characterized by muscular spasms and abnormal movement and interferes with voluntary movements (Albanese et al., 2013), whereas spasticity is defined as an abnormal increase in muscle tone or stiffness of the muscles (Kim et al., 2003). From gait analysis, CP patients can display hyperactivity of the soleus muscle when the feet are loaded and in mid-stance, which would be compensated by hyperextension of the knee and decreased forward progression of the tibia. In contrast, soleus weakness would result in flexion and knee progressing forward during loading and in mid-stance. On the other hand, hyperactivity of the gastrocnemius muscle causes hyperextension in the heel rise phase, and it may also block knee extension during terminal stance and/or pre-swing (Graham, 2016). Therefore, assessing patients' weakness in gait is essential in providing assistance in helping them ambulate stably. [1] The goal for most pediatric patients with cerebral palsy is to be able to independently walk before school age. Various therapeutic approaches are being implemented, such as improving walking ability, muscle strength exercises, functional electrical stimulation, cardiopulmonary endurance exercises, task-oriented gait training, proprioceptive neuromuscular facilitation, and neurodevelopmental treatments (Rosenbaum et al, 2007). From podiatric medicine's point of view, prescribed ankle-foot orthoses (AFOs) are a common treatment in managing children with cerebral palsy. Prescribed AFOs are also complementary to other medical interventions such as physical therapy and/or orthopedic management (Wright and DiBello, 2017). Current works of literature, specifically, those named in journals such as *Prosthetics and Orthotics International* and *Annals of Physical and Rehabilitation Medicine*, have reviewed the effectiveness of various types AFOs on CP patients' gait parameters (step length, ankle kinematics, and gait speed) and found that improvement of specific gait parameters can be achieved with different types of AFOs (Lintanf et al., 2018). In an original research report published by the *International Society for Prosthetics and Orthotics*, the effects of AFOs on gait patterns in children with cerebral palsy were investigated using a statistical parametric mapping. Researchers classified the gait patterns of the participants using the Gross Motor Function Classification System (GMFCS) and assigned the AFOs accordingly. The AFOs used included bilateral, unilateral, ventral,

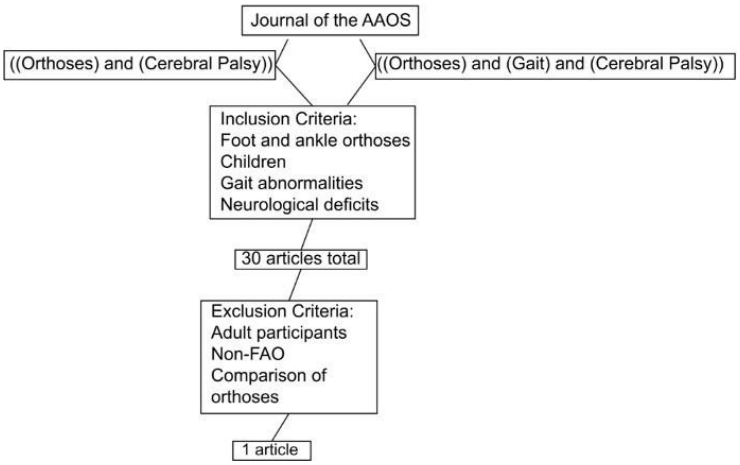
and dorsal (Dobler et al., 2023). Additionally, the results of barefoot walking and walking with shoes and AFOs were compared. The main goal of this study was to prove that it is important for researchers to distinguish the different gait patterns that are seen in participants and how AFOs may or may not be beneficial for these patients' specific gait abnormalities. Researchers found that when they did not distinguish the gait patterns in participants, there was an improvement in overall gait habits (increased walking speed, increased step length, increased ankle dorsiflexion, more controlled power generation at the ankle joint), this corresponded to older findings (Dobler et al., 2023). However, when identifying the different gait patterns seen in participants and comparing the effects of the AFOs, researchers found that not all components of gait were improved, contrary to previous reports. AFOs improved ankle equinus but did not correct the excessive knee flexion seen in patients with hyperextension (Dobler et al, 2023). These findings are crucial to research studies about the effects of AFOs on gait patterns in pediatric cerebral palsy patients because previous generalizations about their effects may be misleading. AFOs may be beneficial to participants, but their gait patterns should be identified prior to prescribing an orthosis in order to maximize the benefits and provide improvements in all aspects.

Due to the variety of types and materials of prescribed AFOs, a general consensus has not yet been reached by current studies on which types of AFOs are beneficial in achieving the goal of walking independently and increasing patients' quality of life. Thus, the primary aim of this systematic review is to analyze existing studies on the different types of AFOs and their effectiveness on the gait parameters of children with spastic cerebral palsy.

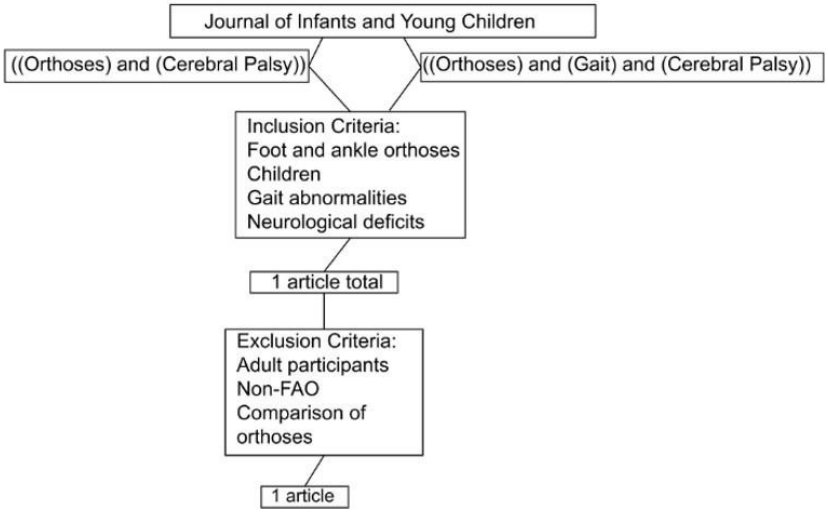
METHODS

PubMed search was conducted using MeSH terms in many databases including the Journal of the AAOS (American Academy of Orthopaedic Surgeons), ScienceDirect, PubMed, and the Journal of Infants and Young Children. The terms included "((Orthoses) and (Cerebral Palsy))", "((Orthoses) and (Gait) and (Cerebral Palsy))", "((Orthoses) and (Gait) and (Children) and (Cerebral Palsy))". The inclusion criteria included studies related to foot and ankle orthoses, patients who are children, and gait abnormalities in patients with neurological deficits. The exclusion criteria included studies with adult participants, orthoses not related to the foot and ankle (i.e. spinal orthoses), and studies focused on comparing different orthoses. Some filters that were applied to the search include: "Articles", "Review Articles", "Research Articles", "Full-Text Available", "All Dates", and "All Article Access Types". For the Journal of the AAOS, inclusion criteria yielded 30 articles and exclusion criteria yielded 1 article. For the Journal of Infants and Young Children, inclusion criteria yielded 1 article and exclusion criteria yielded 1 article. For ScienceDirect, inclusion criteria yielded 35 articles and exclusion criteria yielded 3 articles. For PubMed, exclusion criteria yielded 17 articles and inclusion criteria yielded 4 articles. For background information on the pathomechanics of cerebral palsy spasticity and gait patterns, an article from the *Physical Therapy and Rehabilitation Journal* was referenced. The results from each database are summarized in **Figure 1** below.

Journal of the AAOS



Journal of Infants and Young Children



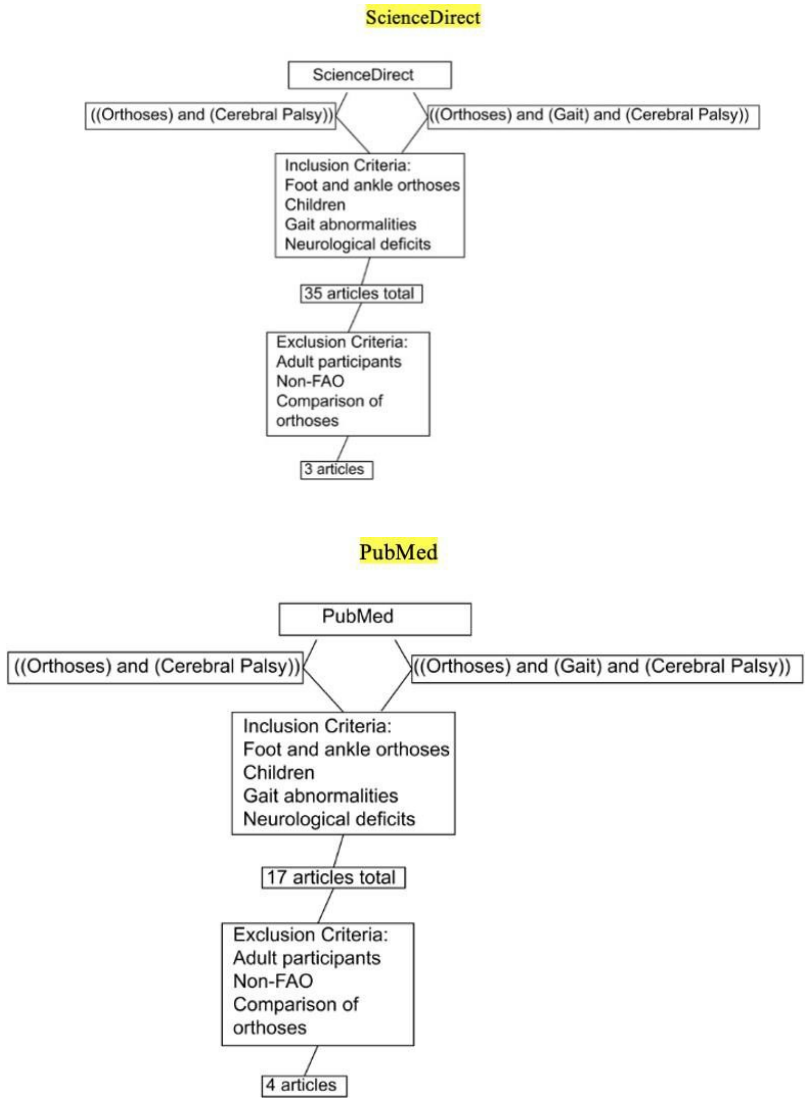


Figure 1: Methods for selecting studies

DISCUSSION

The importance of intervention in managing the symptoms of cerebral palsy

Manifestations of CP include limitations in movement, postural abnormalities, weakness, hypertonic (spastic) muscles, and disturbances in sensation and perception. Cerebral palsy may be classified into different levels based on the severity of the symptoms. However, a common feature shared by these different classifications is that there is no absolute cure (Graham et al., 2016). For this reason, intervention plays a major role in managing the symptoms experienced by CP patients and can improve their overall quality of life if implemented early.

The major symptoms that are targeted by new and improved technology are motor function and gait abnormalities. With the help of orthotics, specifically ankle-foot orthoses (AFOs), patients with CP can regulate their motions and reduce hypertonicity, or spasticity. According to an article published by the *Annals of Physical*

and Rehabilitation Medicine, ankle-foot orthoses (AFOs) are orthotic devices which aid in normalizing the walking patterns of children with CP (2017). The abnormal movements unique to cerebral palsy are mainly due to problematic positioning of joints, leading to a reflex which is pathologic and spastic. Some examples of pathological gait patterns seen in children with cerebral palsy include dynamic equinus and excessive ankle plantarflexion, which inevitably affect the proper functioning of the knee joint as well as overall gait patterns (Radtka et al, 1977). AFOs work to position the joints in a manner which reduces this pathologic reflex and stabilizes the gait patterns seen in these patients (Annals of Physical and Rehabilitation Medicine, 2017). For instance, the polypropylene AFO creates more stability and control around the ankle joint, specifically during the stance phase of the gait cycle. This AFO wraps around the calf, sole of the foot, tibia, and ankle. The support provided in multiple planes helps reduce the equinus and abnormal ankle plantarflexion seen in most CP patients. Several other AFOs with similar effects have been created over the years (Radtka et al, 1977). Another type of AFO is the dynamic ankle-foot orthosis (DAFO) which has a custom build based on the pathologies seen in each patient. It specifically targets the three arches of the foot (medial, lateral, and transverse) along with the region below the toes, near the metatarsal heads (Radtka et al, 1977). Modifications such as a plantarflexion stop and toe loop can be added to the DAFO in order to provide additional support to the subtalar joint and forefoot. A polypropylene stop specifically covers the forefoot, ankle, and posterior calf in order to reduce ankle plantarflexion. A toe loop covers the first digit, forefoot, and heel in order to reduce contact and keep the heel in place to reduce excessive plantarflexion and equinus of the ankle. Ankle-foot orthoses can vary slightly in their build and functions in order to better accommodate the patient's pathology (Radtka et al, 1977). Many other AFOs exist and range from dynamic (allows motion in several planes), solid (provides a lot of resistance to motion), posterior (reduces excessive inversion), and tuning (adjusted as needed) AFOs. Several studies have proven that the different mechanics and structures of AFOs can benefit cerebral palsy patients by improving joint range of motion, muscle timing, and function during the gait cycle, and even by aligning the abnormal anterior pelvic tilt which may be seen.

The effects of AFOs on managing symptoms experienced by cerebral palsy patients

The main motor symptom experienced by cerebral palsy patients is spasticity and a lack of gait regulation. CP is due to brain injuries which occur before the cerebrum, the main regulator of movements, has completed development. This leads to limitations in movements and incoordination. The ankle is greatly affected by this disability, which is why walking becomes more challenging for CP patients (Conner et al., 2022). Ankle-foot orthoses reduce the severity of these motor effects by normalizing gait and aiding in gross motor function and maintenance of balance through the control of the ankle joint range of motion. Lintanf's study states there is strong clinical evidence that AFOs do improve gait speed, gross motor function, balance, and stride length in children with cerebral palsy (2018). In Lintanf's systematic review and meta-analysis, a total of fifty-six studies regarding children with varying types of cerebral palsy were assessed. The authors quantified the effects of AFOs on several gait parameters including cadence (walking speed), velocity, stride length (the distance between two successive motions), energy expenditure, and overall speed. They found an increase in

stride length and overall gait speed. There was a decrease in cadence and no change in the patients' balance. (Lintanf et al., 2018). In another study conducted by Kerkum et al., the effects of ankle-foot orthoses in children with cerebral palsy were observed. Many children with CP experience a tremendous amount of knee flexion during the stance phase of the gait cycle, this is when one foot touches the ground and the other starts lifting off. Excessive knee flexion causes rigidity, impaired movement, and reduced efficiency of normal gait properties (Kerkum et al., 2015). The study involved fifteen children with spastic cerebral palsy who experience excessive knee flexion. The patients were given a special type of AFO called a ventral shell spring hinged AFO (vAFO). The mechanical structure of this AFO allows for enhanced push-off power, reduced knee flexion angle and internal knee flexor moment during stance (Kerkum et al., 2015). The adjustable hinge was capable of being a spring or rigid. Rigid hinged vAFOs had a similar intended effect on knee flexion as the springed hinged vAFOs. However, their effect on ankle range of motion was minimal (Kerkum et al., 2015). Researchers conducted a 3D gait analysis and a six-minute walk test on patients, and compared them to the baseline findings, which was when the participants were only wearing shoes. Kerkum et al. concluded that all ventral AFOs reduced the net energy expenditure and maximized gait efficiency. There were no notable differences found between the effects of springed or rigid AFOs. The positive impact of vAFOs on the patients were mainly the result of improved knee kinematics, not push-off power (Kerkum et al., 2015).

Ankle-foot orthoses can be used for intervention as well as post-operatively in patients with cerebral palsy. In a prospective cohort study conducted by Skaaret et al., the effects of AFOs on children with bilateral spastic cerebral palsy one year post-operatively were quantified. The reason many physicians include AFOs in the treatment modality of patients with CP after surgery is because they can help reduce the recurrence of the abnormalities noted before surgery (Skaaret et al., 2018). In this study, thirty-four children with cerebral palsy had a 3D gait analysis conducted before their lower limb surgery and one year after the surgery and using the AFO. A gait profile score was curated based on changes seen in step velocity, step length, and stance ankle dorsiflexion. Gait profile scores increased, and step length and velocity were improved as well. There was decreased stance ankle dorsiflexion while using an AFO versus while barefoot (Skaaret et al., 2018).

Types of AFOs	Effects on Cerebral Palsy Patient
Ankle-foot orthosis footwear combination (AFO-FC) Tuning (Eddison et al., 2019)	Improvement in the hip, and pelvic kinematics, knee extension in the stance phase, and knee flexion during the swing phase;

Hinged ankle-foot orthosis without a contoured footplate (Lindskov et al., 2019)	Higher activity in medial gastrocnemius during the late stance phase with the unmodified ankle-foot orthosis. Reduction in the activity in tibialis anterior for a shorter proportion of the swing phase at 8% compared to the ankle-foot orthosis with a contoured footplate at 21%.
Hinged AFO (Aboutorabi et al., 2017.) (Lintanf et al., 2018.)	Improvement in stride length, walking speed, single limb support, and gait symmetry.
Floor reaction orthosis (FRO) (Aboutorabi et al., 2017.)	Provide the integrity of the ankle plantarflexion– knee extension.
Customized external strap orthosis (Chang et al., 2015)	Improvement in gait abilities, gait speed (an increase of 1.67 m/min), cadence (an increase of 2.48 steps/min), and stride length (an increase of 0.02 m).
Posterior AFOs (Lintanf et al., 2018.)	Increase in ankle dorsiflexion at initial contact and during the swing phase.
Dynamic AFOs (Lintanf et al., 2018.)	Large effect on ankle kinematics at initial contact and stride length.
Solid AFOs (Lintanf et al., 2018.)	Large negative effect on propulsion.
Rigid ventral shell spring-hinged (vAFOs) (Kerkum et al., 2015)	Reduction in the knee flexion angle and internal knee flexor moment during stance. Improvement in gait efficiency compared to barefooted.

Spring-like vAFOs (Kerkum et al., 2015)	Reduced the knee flexion angle and internal knee flexor moment during stance. Favorable effects on ankle range of motion and power generation. Improvement in gait efficiency compared to barefooted.
Ground reaction ankle-foot orthosis (GRAFOs) (Skaaret et al. 2019)	Decrease in minimum knee flexion.

Table 1: The effects of different AFOs on cerebral palsy patients

CONCLUSION

Based on these studies, the use of ankle-foot orthoses in children with cerebral palsy is beneficial in the regulation of their gait and gross motor skills, as well as postoperatively. Previous studies have not reached a consensus about which AFO is best for CP patients. Additionally, gait abnormalities in patients were generalized into one large category, so the findings about the effects of AFOs on gait are not specific to certain abnormalities. Future studies which quantify the effects of AFOs may be beneficial in determining the absolute effects of orthoses in the symptom management of CP patients.

One[1] limitation of this systematic review is that since each paper uses different types of orthoses and measurements for assessing the gait of children with cerebral palsy, it is rather difficult to conclude which type of orthosis shows the best result in these patients. However, it should be noted that the type of orthoses used should be tailored to each patient's need in carrying out a more effective gait. Another limitation is the lack of statistical/explanatory analysis. Since most articles evaluated in this systematic review have different baselines when comparing the types of orthoses, it would be more reasonable in future studies to have similar measurements to conduct a meta-analysis.

Since cerebral palsy is a disease that still has no cure to it and AFOs alone, although beneficial to the patients, may not be sufficient treatment for this disease, more research on treatments needs to be done in order to help patients with cerebral palsy to maximize their quality of life.

REFERENCES

1. Albanese A, Bhatia K, Bressman SB, Delong MR, Fahn S, Fung VS, Hallett M, Jankovic J, Jinnah HA, Klein C, Lang AE, Mink JW, Teller JK. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013 Jun 15;28(7):863-73. doi: 10.1002/mds.25475. Epub 2013 May 6. PMID: 23649720; PMCID: PMC3729880.
2. Aboutorabi, Atefeh, Mokhtar Arazpour, Monireh Ahmadi Bani, Hassan Saeedi, and John S. Head. "Efficacy of Ankle Foot Orthoses Types on Walking in Children with Cerebral Palsy: A Systematic Review." *Annals of Physical and Rehabilitation Medicine* 60, no. 6 (2017): 393–402. https://doi.org/10.1016/j.rehab.2017.05.004.
3. Booth ATC, Buizer AI, Meyns P, Oude Lansink ILB, Steenbrink F, van der Krogt MM. The efficacy of functional gait training in children and young adults with cerebral palsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2018 Sep;60(9):866-883. doi: 10.1111/dmcn.13708. Epub 2018 Mar 7. PMID: 29512110.
4. Chang, Wen-Dien, Nai-Jen Chang, Hung-Yu Lin, and Ping-Tung Lai. "Changes of Plantar Pressure and Gait Parameters in Children with Mild Cerebral Palsy Who Used a Customized External Strap Orthosis: A Crossover Study." *BioMed Research International* 2015 (2015): 1–8. https://doi.org/10.1155/2015/813942.
5. Davids, Jon R. MD; Rowan, Ferris MS, PT; Davis, Roy B. PhD, PE. Indications for Orthoses to Improve Gait in Children With Cerebral Palsy. Journal of the American Academy of Orthopaedic Surgeons 15(3):p 178-188, March 2007.
6. Dobler, F. , Cip, J. , Lengnick, H. & Alexander, N. (9900). Effects of ankle-foot orthoses on different gait patterns in children with spastic cerebral palsy: A statistical parametric mapping study. *Prosthetics and Orthotics International, Publish Ahead of Print*, doi: 10.1097/PXR.0000000000000216.
7. Eddison, N., A. Healy, R. Needham, and N. Chockalingam. "The Effect of Tuning Ankle FootOrthoses-Footwear Combinations on Gait Kinematics of Children with Cerebral Palsy: A Case Series." *The Foot* 43 (2020): 101660. https://doi.org/10.1016/j.foot.2019.101660.
8. Graham, H. Kerr, Peter Rosenbaum, Nigel Paneth, Bernard Dan, Jean-Pierre Lin, Diane L. Damiano, Jules G. Becher, et al. "Cerebral Palsy." *Nature Reviews Disease Primers* 2, no. 1 (2016). https://doi.org/10.1038/nrdp.2015.8.
9. Kerkum, Yvette L., Annemieke I. Buizer, Josien C. van den Noort, Jules G. Becher, Jaap Harlaar, and Merel-Anne Brehm. "The Effects of Varying Ankle Foot Orthosis Stiffness on Gait in Children with Spastic Cerebral Palsy Who Walk with Excessive Knee Flexion." *PLOS ONE* 10, no. 11 (2015). https://doi.org/10.1371/journal.pone.0142878.
10. Kim HS, Hwang JH, Jeong ST, Lee YT, Lee PK, Suh YL, Shim JS. Effect of muscle activity and botulinum toxin dilution volume on

muscle paralysis. Dev Med Child Neurol. 2003 Mar;45(3):200-6. doi: 10.1017/s0012162203000380. PMID: 12613778.

11. Lindskov, Lærke, Ann-Britt Huse, Marie Johansson, and Ståle Nygård. "Muscle Activity in Children with Spastic Unilateral Cerebral Palsy When Walking with Ankle-Foot Orthoses: An Explorative Study." *Gait & Posture* 80 (2020): 31–36. https://doi.org/10.1016/j.gaitpost.2020.05.011.
12. Lintanf, Mael, Jean-Sébastien Bourseul, Laetitia Houx, Mathieu Lempereur, Sylvain Brochard, and Christelle Pons. "Effect of Ankle-Foot Orthoses on Gait, Balance and Gross Motor Function in Children with Cerebral Palsy: A Systematic Review and Meta-Analysis." *Clinical Rehabilitation* 32, no. 9 (2018): 1175–88. https://doi.org/10.1177/0269215518771824.
13. Palisano RJ, Rosenbaum P, Bartlett D, Livingston MH. Content validity of the expanded and revised Gross Motor Function Classification System. Dev Med Child Neurol. 2008 Oct;50(10):744-50. doi: 10.1111/j.1469-8749.2008.03089.x. PMID: 18834387.
14. Radtka, Sandra, et al, A Comparison of Gait With Solid, Dynamic, and No Ankle-Foot Orthoses in Children With Spastic Cerebral Palsy, *Physical Therapy*, Volume 77, Issue 4, 1 April 1997, Pages 395–409, https://doi.org/10.1093/ptj/77.4.395
15. Rosenbaum P, Paneth N, Leviton A, Goldstein M, Bax M, Damiano D, Dan B, Jacobsson B. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl. 2007 Feb;109:8-14. Erratum in: Dev Med Child Neurol. 2007 Jun;49(6):480. PMID: 17370477.
16. Skaaret, Ingrid, Harald Steen, Terje Terjesen, and Inger Holm. "Impact of Ankle-Foot Orthoses on Gait 1 Year after Lower Limb Surgery in Children with Bilateral Cerebral Palsy." *Prosthetics & Orthotics International* 43, no. 1 (2019): 12–20. https://doi.org/10.1177/0309364618791615.
17. Wright E, DiBello SA. Principles of Ankle-Foot Orthosis Prescription in Ambulatory Bilateral Cerebral Palsy. Phys Med Rehabil Clin N Am. 2020 Feb;31(1):69-89. doi: 10.1016/j.pmr.2019.09.007. PMID: 31760995.
18. Yang, Jojo, Wutshoff, Courtny J. "Cerebral Palsy in Children."American Academy of Pediatrics Healthy Children / Cerebral Palsy. (11/18/2022). https://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Cerebral-Palsy.aspx

Lower Extremity Amputation risk associated with using Sodium Glucose Cotransporter 2 (SGLT2) Inhibitors: A Literature Review

Kunali Patel, BS and Jacqueline Harris, BA

ABSTRACT

Introduction
Sodium-glucose cotransporter 2 (SGLT2) inhibitors are therapeutic agents used to treat high-risk type II diabetes mellitus (T2DM), heart failure and chronic kidney disease (CKD). Various adverse effects associated with SGLT2 inhibitor use have been reported, including diabetic ketoacidosis (DKA), urinary tract infection (UTI), mycotic genital infections (MGI), hypotension/volume depletion, hypoglycemia, fractures, and amputations. The aim of this study is to review the risk of lower extremity amputation associated with SGLT2 inhibitors in high-risk T2DM individuals.

Study Design: Qualitative Systematic Review of Literature

Methods
A literature search was performed on the PubMed database using "Amputation Risk" [MESH] AND "Using SGLT2 Inhibitor" [MESH]. The inclusion criteria applied to the articles were studies involving clinical trials, articles available in English, and those published between 2017/06 [PDAT]: 2022/05 [PDAT]. Articles were excluded if they did not investigate the risk of amputation or were a secondary analysis of the same original study. Applying the inclusion and exclusion criteria left 6 articles to be reviewed for this paper.

Results
The articles were all clinical trials investigating SGLT2 inhibitor safety and efficacy and the extent of adverse effects experienced with long-term use.

Discussions and Conclusions
Majority of the trials reported improved clinical outcomes in diabetic patients with the use of SGLT2 inhibitors, such as a lower risk of a cardiovascular event, but the Canagliflozin Cardiovascular Assessment Study (CANVAS) was the only study to demonstrate a higher incidence of amputations and fractures. Overall, the studies demonstrated that given the rate of amputation risk, the cardiovascular benefits linked to SGLT2 inhibitor use outweighed the multiple risks it poses.

Keywords: Amputation Risk, Sodium Glucose Cotransporter 2 Inhibitor
Level of Evidence: 4

INTRODUCTION

Diabetes Mellitus affects around 24 million people, with 90% of this population having type II diabetes. Type II diabetes is linked to a sedentary lifestyle and involves a genetic component. Some of the consequences of diabetes include end-stage renal failure, blindness, and lower extremity amputations. While behavioral modifications such as weight loss and change in diet are the first-line treatment for disease regulation, medications like metformin, the first-line drug, and sodium-glucose cotransporter 2 (SGLT2) inhibitors are often essential to improve clinical outcomes.[1]

SGLT2 inhibitors include dapagliflozin, empagliflozin, and canagliflozin, which are therapeutic agents indicated in patients with type II diabetes, heart failure, and chronic kidney disease (CKD).[2] The agents aforementioned facilitate natriuresis and glycosuria by reversibly inhibiting SGLT2 receptors in the proximal tubule of the kidney, thereby decreasing glucose reabsorption.[1,3] Through this mechanism, SGLT2 inhibitors promote weight loss and glycemic control, lower blood pressure, and decrease cardiovascular mortality risk in CVD patients.[1,4]

While SGLT2 inhibitors are considered relatively safe, the adverse effects include diabetic ketoacidosis (DKA), urinary tract infection (UTI), mycotic genital infections (MGI), hypotension/volume depletion, hypoglycemia, fractures, and amputations.[2] Since diabetic patients are already at high risk for lower limb amputations, one of the most pressing concerns for SGLT2 inhibitor use is its link to an increased amputation rate, as was noted in the Canagliflozin Cardiovascular Assessment Study (CANVAS).[1,3,5,6] This finding led to the FDA issuing a boxed warning for the use of canagliflozin in patients at high risk for amputation, such as patients with a history of prior amputation or diabetic ulcers.[1]

Multiple studies were conducted after CANVAS to determine whether the benefits of SGLT2 inhibitors outweighed the risks for high-risk diabetic patients.[2] These subsequent studies include the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) program, as well as the Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI 58), and Dapagliflozin Effect on Blood Glucose Level and Renal Safety in Patients With Type 2 Diabetes (DERIVE); however, all these studies conducted after CANVAS did not demonstrate a link between amputation rate and SGLT2 inhibitors.[1,4,5]

Researcher studies proposed various reasons to explain why the subsequent studies did not support the CANVAS finding or the connection between SGLT2 inhibitors and lower extremity amputations.[5,6] These explanations include that the amputation link in CANVAS could have been due to chance or that the data for the study was influenced by excluding high-risk subjects for undisclosed safety reasons.[5,6] This literature review aims to investigate whether SGLT2 inhibitor use should be guided by the CANVAS study or the findings of the subsequent studies in the high-risk diabetic patient population.

METHODS

A literature search was performed on the PubMed database using (Amputation risk) AND (using SGLT2 inhibitor) which resulted in one hundred and thirty-six articles. The inclusion criteria for the articles were studies involving clinical trials, articles

available in English, and those published between 2017/06 [PDAT]: 2022/05 [PDAT]. Articles were excluded if they did not investigate amputation risk, or were a secondary analysis of the same original study. After applying inclusions and exclusion criteria, six articles were left to be reviewed in this paper as seen in Figure 1.

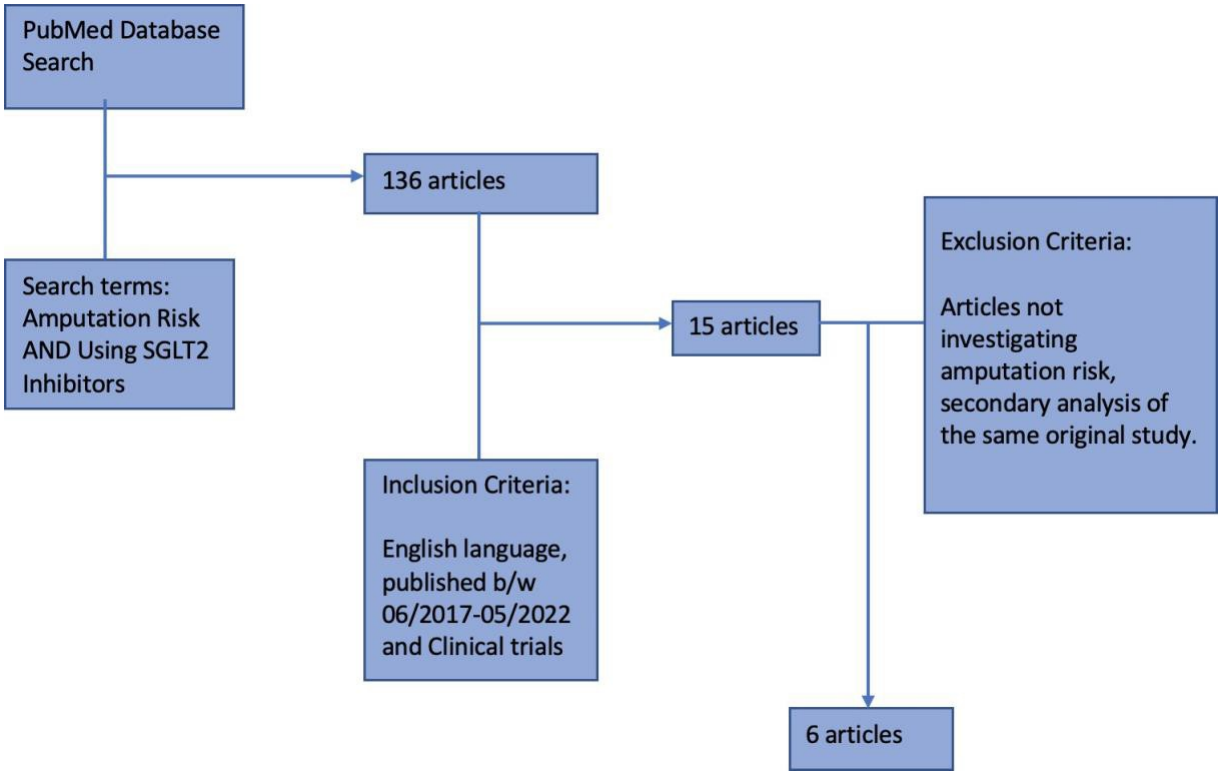


Figure 1 : PubMed Article Search and Exclusion Criteria

RESULTS

Doggrell et al analyzed the outcomes of the CANVAS study which showed a significant reduction in cardiovascular events in the patient group taking canagliflozin with a p value of 0.02. However, the study also found that patients who were not on any diuretic did not show reduction in cardiovascular event even when taking canagliflozin. Neuen et al. showed that within 13 weeks, more participants taking the placebo experienced a fall in eGFR (Glomerular filtration rate) when compared to those taking canagliflozin, and from week 13 onwards until the end of follow-up. Participants in the placebo group experienced a higher loss of kidney function in the placebo group ($p<0.001$).[3]

Arnott et al. found that patients from both CANVAS and CREDENCE program had to undergo amputations equally in the placebo (12.3%) and canagliflozin (11.2%) group. It was also noted that patients with previous amputations were at a higher risk of amputation through out the program.

Chiang et al. found that a one year amputation event rate for SGLT2 inhibitor (0.9%) treatment was similar to the placebo group (0.9%).

Article Title and Author	**Study Design**	**Study Demographics**
Cardiovascular outcomes with canagliflozin – is it on the CANVAS? (2017) Doggrell et al.	Randomized placebo-controlled	The CANVAS program was conducted in 30 countries with 10,142 subjects. Subjects were given a placebo or 100 or 300 mg doses. Data shows that there was a higher risk of amputation involving the toes, feet, or legs with canagliflozin use. Due to these results, the FDA issued a *Boxed Warning* which states that canagliflozin with or without metformin should not be given to subjects at high risk for amputations. High amputation-risk patients included those with a history of amputations, neuropathy, diabetic foot ulcers, and/or peripheral vascular disease.[1]

Outcome trial data on sodium-glucose cotransporter-2 inhibitors: Putting benefits and risks in perspective (2022) Chiang et al.	Seminal randomized placebo-controlled	Ten major randomized placebo-controlled outcome trials of SGLT2 inhibitors were included to simplify the risk-benefit decision for SGLT2 inhibitor treatment by comparing the number needed to treat and number needed to harm for efficacy and safety outcomes in the three broad patient subgroups of high-risk T2DM, HFrEF, and CKD.[2]
Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: Data from the CANVAS Program (2019) Neuen et al.	Double-blind randomized placebo-controlled	Two multicenter, double-blind placebo- controlled randomized trials from the CANVAS program were designed to assess the cardiovascular safety and efficacy of the SGLT2 inhibitor, canagliflozin along with effects on renal and safety outcomes in subjects with T2DM at high cardiovascular risk. The trials were conducted in 667 centers across 30 countries until early 2014. Primary outcomes with canagliflozin use were cardiovascular death, fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, and fatal heart failure.
Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE Study (2018) Fioretto et al	Double-blind, parallel-group, placebo-controlled, phase 3 study	A 24-week study that included 321 randomized patients of both sexes with uncontrolled T2D for more than a year and a BMI between 18-45 kg/m2 at visit 1. Around half of the subjects were randomized to 10 mg dapagliflozin and the other half designated to the placebo group. Exclusion criteria included uncontrolled hypertension, vascular diseases within 3 months before the study, or specific renal diseases.[4]

The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial (2020) Arnott et al.	Randomized placebo-controlled clinical trial	Analysis involved data from CANVAS, CANVAS-R, and the CREDENCE trials. Subjects in CANVAS were randomized to take canagliflozin 300 mg or 100 mg or placebo, and CANVAS-R were randomized to receive first 100 mg and then 300 mg of canagliflozin or placebo. CREDENCE was a placebo-controlled trial with canagliflozin that spanned 34 countries and included 4,401 participants with DM2, chronic kidney disease, albuminuria, and nephropathy. CREDENCE included men and women 30 years or older with prior history of symptomatic atherosclerotic cardiovascular disease with amputation or 50 years or older with two or more cardiovascular disease risk factors. [5]
Dapagliflozin and Cardiac, Kidney, and Limb Outcomes in Patients With and Without Peripheral Artery Disease in DECLARE-TIMI 58 (2020) Bonaca et al.	Randomized placebo-controlled clinical trial	DECLARE-TIMI included three subject groups which either did not have PAD or fit the PAD criteria. The PAD Criteria included subjects who had an ankle-brachial index < 0.90 in the 12 months before enrollment or a history of myocardial infarction or stroke. One group included subjects aged 40 or above with atherosclerotic disease. The other groups included men (≥ 55 years) or women (≥ 60 years) with multiple atherosclerotic vascular diseases, an hba1c between 6.5%-12%, and a creatinine clearance of a minimum of 60 ml per minute.[6]

DISCUSSION

Type 2 diabetic patients are prone to neuropathy which is correlated with an increased risk of trauma leading to infection.[6] Data from DECLARE-TIMI showed that the subjects who received dapagliflozin did not have an increased risk for adverse events such as limb ischemia, amputations, and foot infections compared to those who received placebo.[6] Furthermore, evidence showed that the main cause of amputation was an infection.[6] Since

In the DERIVE study, researchers found that the short-term effects of dapagliflozin included a decrease in eGFR and blood urea nitrogen levels, especially in stage 3 CKD.[4] However, in patients without a history of kidney disease, there was a return to normal eGFR rates seen at follow-up week 24 with the use of dapagliflozin.[4] The CANVAS study, however, excluded patients with CKD which likely resulted in similar kidney injury rates observed in both canagliflozin and placebo groups.[1] Therefore, the DERIVE study expanded on the potential adverse events of SGLT-2 inhibitors, which were not previously elucidated from the data collected in CANVAS.

Throughout the treatment period and the beginning of the follow-up in CANVAS, there was a decrease in HbA1c, which showed the benefit of SGLT-2 inhibitor use.[1] However, after the study, the data shows that there was a 9.3% reduction in the use of anti-hyperglycemic agents in the group that was taking canagliflozin. The aforementioned finding may help explain why there was an increased risk of poor cardiovascular, renal, and amputation risks in the canagliflozin group.

Extrapolating data from multiple studies, Chiang et al. showed that participants on CANVAS, CREDENCE, and DECLARE-TIMI included subjects with uncontrolled type 2 diabetes, the correlation between SGLT-2 inhibitors and the increased risk lower limb amputation seen in CANVAS may have been due to the number of subjects who are more likely to have complications due to neuropathy.[5] Subjects who, for example, did not have equal access to healthcare could have been at higher risk for complications pertaining to uncontrolled diabetes.

SGLT2 inhibitors demonstrated a reduction in hospitalizations for heart failure, cardiovascular deaths, and renal deterioration. High-risk T2DM group participants showed similar benefits and a reduced incidence of diabetic ketoacidosis, UTIs and fractures.[2]

In cases where filtered albumin increases, it has been proposed that this may lead to direct damage to the glomerulus and tubule.[3] Canagliflozin slowed the loss of kidney function in participants with normal to moderately increased albuminuria, while significant benefits were noted in participants with severely increased albuminuria. The acute decrease in eGFR with canagliflozin, followed by long-term preservation of kidney function, indicated decompression of the glomerulus and correction of glomerular hyperfiltration.[3]

CONCLUSION

Majority of the trials reported improved clinical outcomes in diabetic patients, such as lower risk of a cardiovascular event, but the Canagliflozin Cardiovascular Assessment Study (CANVAS) was the only study to demonstrate higher incidence of amputations and fractures. The claim of a class effect should have only been limited to these comorbidities. Furthermore, during the

study canagliflozin was found to increase amputation risks in patients not taking diuretics. A clarification was required on whether canagliflozin increased the risk of nonfatal stroke or not.[1]

Higher resting heart rate and lower heart rate variability are both risk factors for end stage renal disease and CKD related hospitalizations. There were notable reductions seen in systolic blood pressure with the use of dapagliflozin which were not accompanied by changes in heart rate. Furthermore, reductions in body weight were also reported regardless of baseline renal functions.

Even with a growing body of evidence demonstrating significant non-endocrine benefits of SGLT2 inhibitors in multiple patient populations, there is a prescribing reticence due to the broad potential adverse effect profile and risk-benefit concerns. According to the study data, the benefits of using SGLT2 inhibitors far outweigh the risks it poses. Patient education and clinical acumen can be helpful in maintaining a lower limb ischemia and amputation-risk profile while prescribing SGLT2 inhibitors.[2]

Uncontrolled type II diabetes is a risk factor for amputations; therefore, patients included in the CANVAS, CREDENCE, and DECLARE-TIMI were already at high risk of lower limb amputation despite SGLT2 inhibitor use. While the findings in the CANVAS study showed an increase in amputations with canagliflozin use, the following cohort studies did not show a difference in the risk of an SGLT2 inhibitor, like canagliflozin, and a non-SGLT2 inhibitor anti-hyperglycemic agents with risk of lower limb amputation.[1] Furthermore, the studies represented a statistical analysis but did not inform statistical significance.

AUTHORS' CONTRIBUTION

Both authors equally contributed to his literature review. Both authors agreed upon and approved the final submission.

Statement of Competing Interests

The authors declare that they do not have any competing interests associated with this manuscript.

REFERENCES

1. Doggrell SA. Cardiovascular outcomes with canagliflozin - is it on the CANVAS? *Expert opinion on pharmacotherapy*. 2018;19(2):163-166. https://www.tandfonline.com/doi/abs/10.1080/14656566.2017.1418855. doi: 10.1080/14656566.2017.1418855.

2. Chiang B, Chew DP, De Pasquale CG. Outcome trial data on sodium glucose cotransporter-2 inhibitors: Putting clinical benefits and risks in perspective. *International journal of cardiology*. 2022;349:96-98. https://dx.doi.org/10.1016/j.ijcard.2021.12.015. doi: 10.1016/j.ijcard.2021.12.015.

3. Neuen BL, Ohkuma T, Neal B, et al. Effect of canagliflozin on renal and cardiovascular outcomes across different levels of albuminuria: Data from the CANVAS program. *Journal of the American Society of Nephrology*. 2019;30(11):2229-2242. https://www.narcis.nl/publication/RecordID/oai:pure.rug.nl:publications%2F2b12cec7-da1b-43da-b827-281574d64da7. doi: 10.1681/ASN.2019010064.

4. Fioretto P, Del Prato S, Buse JB, et al. Efficacy and safety of dapagliflozin in patients with type 2 diabetes and moderate renal impairment (chronic kidney disease stage 3A): The DERIVE study. *Diabetes*

Obes Metab. 2018;20(11):2532. doi: 10.1111/dom.13413.

5. Arnott C, Huang Y, Neuen BL, et al. The effect of canagliflozin on amputation risk in the CANVAS program and the CREDENCE trial. *Diabetes Obes Metab*. 2020;22(10):1753. doi: 10.1111/dom.14091.

6. Bonaca M, Wiviott S, Zelniker T, et al. Dapagliflozin and cardiac, kidney, and limb outcomes in patients with and without peripheral artery disease in DECLARE-TIMI 58. *Circulation (New York, N.Y.)*. 2020;142(8):734-747. https://www.ncbi.nlm.nih.gov/pubmed/32795086. doi: 10.1161/CIRCULATIONAHA.119.044775.

Fish Skin Graft Versus Dermal Matrix Allograft in the Treatment of Lower Extremity Diabetic Wounds: A Systematic Review

Lauren Wasserman, BS; Amanda Varveris, BS; Edgar Lu, BS; Jennifer Bloom, MA

ABSTRACT

Introduction

Diabetic foot ulcer (DFU) is a major complication for diabetic patients and is heavily associated with morbidity and mortality. Traditionally, a variety of different treatments exist that healthcare providers utilize to aid in the healing of these ulcers. The aim of this review is to assess the efficacy and accuracy of Fish skin grafts in comparison to Tissue Matrix Allografts in the treatment of diabetic foot ulcers. Successful treatment findings have the potential to implement significant changes in diabetic foot ulcers routine care.

Methods

The PubMed database was searched using the queries '(fish skin grafts) AND (diabetic foot ulcers)' and '(foot ulcer, diabetic [MeSH Terms]) AND acellular dermal matrix).' The results were then filtered for articles written in English and available with full text. Twelve articles were included for review after meeting requirements for inclusion.

Results

Of the 12 articles included in this review, six focused on the use of fish skin grafts as a treatment for diabetic wounds and six focused on the use of acellular dermal matrix. Clinical outcomes were reported as healing time and wound size.

Discussion and Conclusion

Studies on acellular dermal matrices (ADM) showed better healing times and wound closure compared to the standard of care. However, results were mixed when comparing dermal matrix allografts to fish skin grafts. ADM appears to be more cost effective and suitable for use in larger and more complex lower extremity diabetic wounds. More research is required, however, to determine if fish skin grafts can be a viable alternative to existing ADMs in terms of wound area reduction and closure rates.

INTRODUCTION

Diabetes mellitus is an ever-growing concern in modern medicine. More than 22 million Americans and more than 400 million people worldwide are diabetic.[1,2] It is estimated that 18% of the US population will be diagnosed with diabetes by the year 2060.[3] Diabetes is a multi-system disease with many serious consequences. Two thirds of people with diabetes, for example, will develop diabetic peripheral neuropathy and one fourth of those will develop a diabetic foot ulcer (DFU).[4] More than one half of DFUs become infected and one fifth of these infected DFUs lead to an amputation.[1] Lower extremity amputations can cause increased mortality rates – minor and major amputations are associated with a 45% and 65% 4-year mortality rate, respectively.[5] DFUs also place a massive burden on our current healthcare system, with increased costs in excess of $10,000 per patient compared to diabetics without DFUs.[6] Since DFUs can have such fatal sequelae, it is extremely important to heal DFUs as quickly and efficiently as possible.

Many treatments have been used for DFUs. The standard of care for DFUs includes offloading, dressing, debridement, vascular assessment, and glycemic and infection control.[5] More advanced treatments include both cellular and acellular grafts. Cellular grafts are those that contain skin cells, such as fibroblasts and keratinocytes, which are used as a source for growth factors and cytokines, crucial elements for tissue regeneration. Acellular grafts, in contrast, are cellular grafts that undergo decellularization which leaves behind an intact extracellular matrix. Two examples of acellular grafts are dermal matrix allografts and fish skin grafts. Dermal matrix allografts (ADM) such as DermACELL and Alloderm are derived from human tissue that have had their epidermal layer removed. The resulting graft mimics a normal tissue environment and serves as a scaffold for host cells to migrate into, followed by supporting structures like vasculature and lymphatics.[7] This process eventually leads to the incorporation of the graft that contributes to greater and faster rates of complete wound healing.[8]

Fish skin grafts such as Kerecis's Omega 3 Wound are xenografts taken from fish, such as Atlantic Cod, and have an advantage over mammalian grafts in that they are rich in omega-3 fatty acids.[4] The detergent agents used in mammalian grafts to prevent disease transmission are not used with fish skin grafts, allowing them to retain omega-3 fatty acids, which are important for reducing inflammatory processes.[4] This is because, unlike with mammalian grafts, there is no risk of disease transfer when using fish skin grafts.[9] Moreover, fish skin grafts promise to offer lower costs in comparison with the current standard of care.[10]

This systematic review seeks to evaluate fish skin grafts and dermal matrix allografts to ascertain which type of ADM is more effective in terms of patient care. This will be determined using wound size, percent area reduction of wound size, and percentage of complete wound healing.

METHODS

Eligibility Criteria & Search Strategy

The inclusion criteria for this systematic review consisted of articles published after 2010 with sample sizes of five or more adult patients that had lower extremity diabetic foot ulcers. Studies with sample sizes of five or more patients were included to minimize selection and reporting bias. Exclusion criteria consisted of

non-English articles, literature review articles, and studies that pooled treatment data of different types of wounds or treatment types together. PubMed was used to search for studies that matched these criteria. Two separate searches of the database were made: '(fish skin grafts) AND (diabetic foot ulcers)' and '(foot ulcer, diabetic[MeSH Terms]) AND (acellular dermal matrix).' Both searches were filtered for English language articles and articles with full text access.

Selection Process

The first search regarding fish skin grafts yielded a total of nine results (Figure 1). Two articles were exlcuded based on the title and abstract and the remaining seven were assessed for eligibility. Of these remaining seven articles, one was excluded for combining results of diabetic foot ulcers with venous ulcers and the other was a literature review. The references of the latter article yielded an additional article that, along with the 5 remaining articles from the database search, was included in the systematic review.

The second search regarding acellular dermal matrix grafts yielded 23 results. All 23 results were assessed for eligibility. Of these results, 10 were excluded for combining results of different treatment modalities together; two were literature reviews and excluded; one was on treatment of non-diabetic foot ulcers; four were using xenografts. The remaining six results were included in the systematic review.

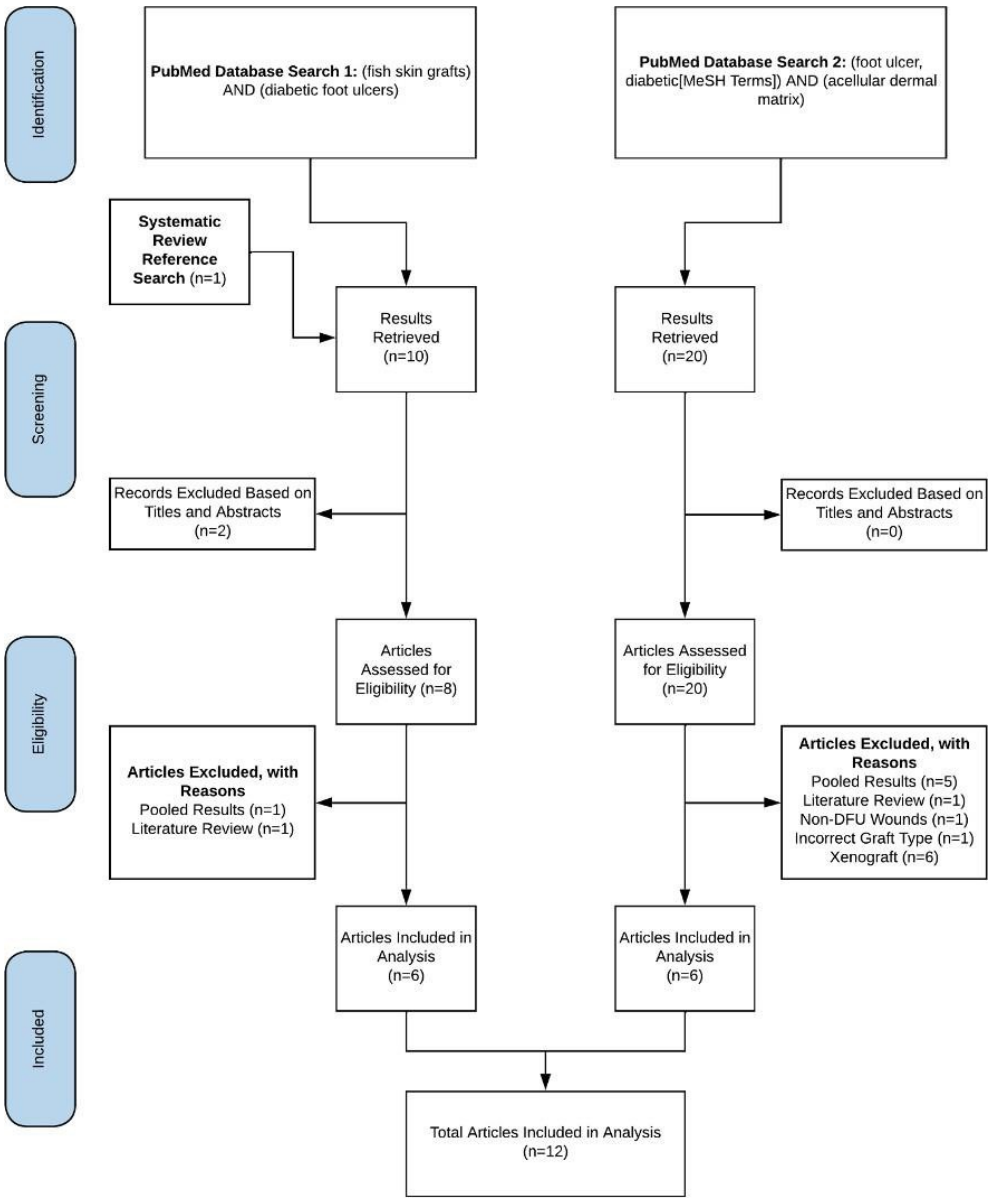


Figure 1 – Study Selection Process

Table 1- Studies

Article Title and Authors	Study Design	Participants	Study Aim	Study Results
Acellular Fish Skin Graft Use for Diabetic Lower Extremity Wound Healing: A Retrospective Study of 58 Ulcerations and a Literature Review Michael et al.[11]	Retrospective	51 participants 13 Women 38 Men Mean age 66 years old with a total of 58 diabetic foot ulcers	Evaluate the efficacy of acellular fish skin grafts for the treatment of full-thickness diabetic foot ulcers and calculate the total wound surface area (cm2) healed over a 16-week period, from initial wound surface area at first application of graft to final wound surface area	Mean wound size = 3.02cm2 Mean ulcer duration time = 18 weeks Mean reduction of wound surface area by 87.57% and 35 of 58 wounds fully healed at 16 weeks. >90% reduction in surface area was achieved in 43 DFUs and > 75% reduction was seen in 49 at 16 weeks. Mean time to achieve full healing in 35 wounds = 10 weeks Mean number of fish skin grafts applied per person = 4.9. Mean number of grafts applied to fully healed patients = 4.5 Only 2 wounds with no reduction in surface area at 16 weeks; 1 healed at 24 weeks with two

				additional grafts applied, 1 healed at 36 weeks with 3 additional debridement and no additional grafts
Evaluating the Effect of Omega-3–rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers: Penultimate Analysis of a Multicenter, Prospective, Randomized Controlled Trial Lullove et al.[9]	Prospective multicenter randomized controlled trial	94 participants 46 participants in study arm 1 received fish skin graft and standard of care collagen alginate dressing 48 participants in study arm 2 received standard of care collagen alginate dressing	Assess the efficacy of fish skin grafts in the management of diabetic foot ulcers compared to the standard of care collagen alginate dressing treatment	Acellular fish skin graft and control groups had mean healing time of 7 weeks Mean number of fish skin graft applications to achieve healing was 6 At 12 weeks, 63% of ulcers in fish skin graft group were healed (29 out of 46) and 31.3% of ulcers in the control group were healed (15 out of 48). P-value = .0036 Non-healing wounds in fish skin graft group at 12 weeks had wound area reduction of 87.1%. Control had 54%. P-value = .0039

A Multicenter, Blinded, Randomized Controlled Clinical Trial Evaluating the Effect of Omega-3–Rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers Lullove et al.[12]	Prospective multicenter parallel-group randomized controlled trial	58 Participants screened, 9 exhibited >20% healing during the screening period and were removed. 49 participants total were split into two groups, group 1 received fish skin graft and standard of care collagen alginate dressing. Group 2 received only the standard of care collagen alginate dressing.	This study compared the use of acellular fish skin grafts and standard of care (SOC) collagen alginate dressing in the management of treatment-resistant diabetic foot ulcers (DFUs).	At 6 weeks the wound area reduction for group 1 was 72.8% and 41.2% in group 2. P-value =.044 At the end of 12 weeks 67% of ulcers in group 1 had fully closed, while only 32% had closed in group 2. P-value = .0152 In both groups it took approximately 6 weeks for the wounds to heal and close Median number of fish skin graft + SOC applications in order to achieve complete wound closure was 5 in group 1

The marine Omega3 wound matrix for treatment of complicated wounds A multicenter experience report Dorweiler et al.[13]	Prospective multicenter randomized controlled trial	7 Patients at Mainz hospital center with diabetic foot wounds 3 Patients at Hamburg hospital center with diabetic foot wounds 1 Patient at Karlsruhe hospital center with diabetic foot wound	The aim of this study was to evaluate the use of Kerecis Omega3 in the healing of complicated and diabetic wounds from the cumulative findings of three vascular surgery centers that used this matrix.	7 Patients at Mainz mean treatment duration was 26.3 weeks, mean wound size was 27.6cm2, mean residual wound size was 0, the mean number of kerecis patches used was 15.3 3 Patients at Hamburg mean treatment duration was 14 weeks, mean wound size was 10.3cm2, mean residual wound size was 3.7cm2, mean number of kerecis patches used was 3 1 Patient at Karlsruhe mean treatment duration was 3 weeks, only partial healing achieved, mean number of kerecis patches used was 2

Cost Effectiveness of Fish Skin Grafts Versus Standard of Care on Wound Healing of Chronic Diabetic Foot Ulcers: A Retrospective Comparative Cohort Study Winters et al.[10]	Retrospective comparative cohort	55 Diabetic Patients who had fish skin grafts applied to their full-thickness foot ulcerations (n=59 ulcerations)	The aim of this retrospective comparative cohort study was to evaluate the cost effectiveness of fish skin therapy compared with standard of care (SOC) on chronic diabetic foot ulcers (DFUs)	Lower costs for fish skin graft patients per wound at $11,210 vs patients with only SOC at $15,075 83.2% fish skin graft wounds healed vs 63.4% SOC patient wounds Fish skin graft patient group amputations were less than SOC group at 4.6% and 6.9% respectively Fish skin graft group had a higher score on the quality-adjusted life year than SOC at .676 vs .605

Treatment of diabetic foot wounds with acellular fish skin graft rich in omega-3: a prospective evaluation Woodrow et al.[4]	Prospective observational	9 patients, 5 male, 4 female, 1 patient required lower limb amputation due to ischemia unrelated to treatment and was removed from study	The aim of this study was to evaluate whether acellular fish skin grafts rich in omega-3 were beneficial in the treatment and management of postoperative diabetic foot wounds	6 acute wounds < 3months duration and 2 chronic wounds > 3months duration Wound size ranged .94cm2 to 29.55cm2 3 patients achieved full healing in 6 weeks Overall median wound healing was 84.9%. Healing for the 6 acute patients was 93.3%. Healing for the 2 chronic patients was 41.1% and 41.2% at 6 weeks. No reports of skin irritation, increased pain or odor at time of treatment. No deterioration in wound bed quality and no significant new infections were found. In acute group at one year follow up two patients had died with intact wounds and four remain healed. In chronic group, one wound healed and the other progressed to

				major limb amputation.
Clinical Efficacy of Acellular Dermal Matrix Paste in Treating Diabetic Foot Ulcers Lee et al.[14]	Retrospective	49 participants All with Wagner grade 2 or 3 DFUs	Evaluate the efficacy of applying a paste formulation of acellular dermal matrix (ADM) to DFUs	At the 60-day primary outcome mark, 56.52% (13/23) of the DFUs in the treatment group were healed, compared with 23.08% (6/26) of DFUs in the control group. Mean rates of wound area resolution in the treatment and control groups were 74.17% ± 30.84% and 51.87% ± 32.81%, with mean times to heal (within 60 days) of 13.54 ± 9.18 days and 21.5 ± 11.98 The ADM paste effectively enhanced tissue regeneration, shortening ulcer duration and preventing associated complications, while eliminating the need for supplemental ulcer management procedures. The paste formulation of ADM provides

				a matrix for tissue ingrowth, promoting the healing of DFUs.
A Prospective, Multicenter, Single-Arm Clinical Trial for Treatment of Complex Diabetic Foot Ulcers with Deep Exposure Using Acellular Dermal Matrix Cazzell et al.[15]	prospective, multicenter study	61 patients with Wagner grade 3 or 4 DFUs	Evaluate the efficacy and safety of an acellular dermal matrix allograft, DermACELL in the treatment of large, complex diabetic foot ulcers (DFUs) that probed to tendon or bone	The mean time to 100% granulation was 4.0 weeks with an average of 1.2 applications of D-ADM. Mean percent wound area reduction was 80.3% at 16 weeks Those DFUs 15 cm2 or smaller were substantially more likely to close than DFUs larger than 29 cm2 over a 16-week duration The D-ADM demonstrated the ability to rapidly reduce the size of large, complex DFUs with exposed bone

Human Reticular Acellular Dermal Matrix in the Healing of Chronic Diabetic Foot Ulcerations that Failed Standard Conservative Treatment: A Retrospective Crossover Study Zelen et al.[16]	Retrospective	12 patients with DFUs that failed the standard of care(SOC) treatment from a previous prospective randomized, controlled trial (RCT). That trial compared the efficacy of human reticular acellular dermal matrices (HR-ADMs) with the SOC	Evaluate the efficacy of human reticular acellular dermal matrices (HR-ADMs) with the SOC in comparison to SOC alone.	Of the 12 patients who were eligible for the HR-ADM, 10 (83%) achieved complete wound healing, with a mean healing time of 21 days to closure. The corresponding wound area reduction was from 1.7 cm to 0.6 cm.
Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience Martin et al.[17]	Prospective control	17 patients with DFUs 76.5% males, mean age 61.5 presenting for care at a large, multidisciplinary wound care center	Evaluate outcomes of persons with UT grade 2A neuropathic diabetic foot wounds treated with an acellular matrix	82.4% of wounds measuring a mean 4.6 cm2 healed in the 20-week evaluation period. For those that healed in this period, healing took place in a mean 8.9 weeks
Clinical effectiveness of an acellular dermal regenerative Tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective,	Prospective control	Eighty-six patients were randomized into study (47 patients) and control (39 patients) group	Compared the proportion of healed diabetic foot ulcers and mean healing time between patients receiving acellular matrix (AM) (study	Complete healing and mean healing time were 69.6% in 5-7 weeks, for the study group and 46.2% and 6-8 weeks, for the control group. The odds of healing in

randomized, multicentre study Reyzelman et al.[18]			group) and standard of care (control group) therapies.	the study group was 2.7 times higher than in the control group
A prospective, randomized, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers Zelen et al.[19]	Prospective control	40 patients with a diabetic foot ulcer of at least 4 weeks in duration	Compare clinical outcomes of a novel, open-structure human reticular acellular dermis matrix (HR-ADM) to facilitate wound closure in non-healing diabetic foot ulcers (DFUs) versus DFUs treated with standard of care (SOC)	At 6 weeks, 65% of the HR-ADM-treated DFUs healed (13/20) compared with 5% (1/20) of DFUs that received SOC alone. At 12 weeks, the proportions of DFUs healed were 80% and 20%. Mean time to heal within 12 weeks was 40 days for the HR-ADM group compared with 77 days for the SOC group. Proportion of completely healed wounds at 12 weeks was also significantly higher for the HR-ADM plus SOC group compare to the SOC group (80% versus 20%); time to heal within 6 and 12 weeks was also significantly faster for the HR-ADM plus SOC group compare to the SOC

				group

DISCUSSION

Efficacy

Existing mammalian acellular dermal allografts and fish skin grafts both produced better results than traditional standard of care (SOC) for lower extremity diabetic ulcers. Randomized controlled trials of ADMs by Reyzelman et al. reported complete healing, for example, in 69.6% of ulcers at 12 weeks compared to 46.2% receiving only the SOC ($p = 0.0289$).[18] The fish skin trial by Lullove et al. reported similar rates at 67% at 12 weeks compared to 32% in their SOC arm ($p = 0.0152$).[12] Overall reduction in ulcer area and time to healing produced similarly statistically significant gaps between arms.[12,18]

Efficacy results between the two grafts appear to be mixed. Fish skin graft studies such as Michael et al. and Lullove et al. reported greater percent area reduction (PAR) in the size of their ulcers but lower proportions of complete wound healing in comparison to studies using traditional ADM products like Lee et al. and Zelen et al. which had similar study end points and mean ulcer areas.[11,12,14,19] Traditional ADM grafts appeared to be particularly effective for more complex ulcers. The participants in the fish skin graft studies largely had ulcers that were less complicated to heal as evidenced by exclusion criteria for participants in Lullove et al. were ulcers greater than 25cm^2; participants in Michael et al. had ulcers that were mostly classified as Wagner grade 1 or 2.[11,12] In contrast, the mean ulcer area in Cazzell et al. was 29 cm^2 and Wagner grade 3 and 4. Despite the complexity of those ulcers, Cazzell et al. saw a percent area reduction of 80.3% to an average ulcer area of 5.7cm^2 at 16 weeks.[15]

Cost Effectiveness

Accounting for the ballooning costs of diabetic foot ulcers, cost effectiveness of these products is also an important factor to consider, especially in the complex ulcers that ADMs and fish skin grafts are indicated for. Fish skin grafts, according to Winters et al., yielded significant cost savings over SOC. Models made for that study estimated a cost of $11,210 USD per wound using fish skin compared to $15,075 with the current SOC. These savings largely came from fasting ulcer healing rates which translated to lower rates of amputation.[10] When compared to ADMs, however, fish skin grafts appear to be more expensive in terms of cost per graft and total cost. Winters et al. reported in their study averages of 11.3 weeks for ulcers to heal using 5.5 fish skin grafts and a weekly cost of $252.40 for their application, totaling $2852.12 on average.[10] In contrast, Zelen et al. reported a mean $1475 at 12 weeks for their weekly use of ADM.[16]

Limitations of this Review

One of the most significant limitations of this review is the lack of studies comparing dermal matrix allografts and fish skin grafts. Of the 11 articles included in this review, three studied the efficacy of human acellular allografts, two compared the efficacy of human acellular allografts and SOC treatment, four studied the efficacy of fish skin grafts, and three compared the efficacy of fish skin grafts with SOC treatment. Furthermore, only two of these were randomized controlled trials, while five were prospective studies, and four were

retrospective studies. Future randomized control studies comparing the efficacy of these two skin grafts would be beneficial to understand a true comparison of their effectiveness.

In addition, much of the data collected to determine efficacy of the treatments was not comparative. Some studies collected data on the mean time to achieve wound healing, while others looked at healing at different time spans (6 weeks versus 12 weeks). Meanwhile, other studies looked at mean time to granulation and quality of life associated with treatments. Some studies also treated wounds that were more complex than in other studies, making healing times non-comparable. This lack of comparative data made it impossible to draw statistical analysis of the treatments.

CONCLUSION

Both dermal matrix allografts and fish skin grafts are effective methods of healing diabetic foot ulcers. These treatments both showed increased healing time in comparison with standard of care treatment. While dermal matrix allografts are more cost effective, conclusions about the efficacy of each graft when comparing them cannot necessarily be made due to variable types of data collection and differing wound severity. Further studies comparing the two grafts are needed to conclude if one graft is more effective than the other.

REFERENCES

1. Luthringer M, Mukherjee T, Arguello-Angarita M, Granick MS, Alvarez OM. Human-derived Acellular Dermal Matrix Grafts for Treatment of Diabetic Foot Ulcers: A Systematic Review and Meta-analysis. *Wounds Compend Clin Res Pract*. 2020;32(2):57-65.
2. Fridman R, Rafat P, Van Gils CC, Horn D, Vayser D, Lambert JC. Treatment of Hard-to-heal Diabetic Foot Ulcers With a Hepatic-derived Wound Matrix. *Wounds Compend Clin Res Pract*. 2020;32(9):244-252.
3. Lin J, Thompson TJ, Cheng YJ, et al. Projection of the future diabetes burden in the United States through 2060. *Popul Health Metr*. 2018;16(1):9. doi:10.1186/s12963-018-0166-4
4. Woodrow T, Chant T, Chant H. Treatment of diabetic foot wounds with acellular fish skin graft rich in omega-3: a prospective evaluation. *J Wound Care*. 2019;28(2):76-80. doi:10.12968/jowc.2019.28.2.76
5. Huang W, Chen Y, Wang N, Yin G, Wei C, Xu W. The Efficacy and Safety of Acellular Matrix Therapy for Diabetic Foot Ulcers: A Meta-Analysis of Randomized Clinical Trials. *J Diabetes Res*. 2020;2020:6245758. doi:10.1155/2020/6245758
6. Rice JB, Desai U, Cummings AKG, Birnbaum HG, Skornicki M, Parsons NB. Burden of diabetic foot ulcers for medicare and private insurers. *Diabetes Care*. 2014;37(3):651-658. doi:10.2337/dc13-2176
7. Boháč M, Danišovič Ľ, Koller J, Dragúňová J, Varga I. What happens to an acellular dermal matrix after implantation in the human body? A histological and electron microscopic study. *Eur J Histochem EJH*. 2018;62(1):2873. doi:10.4081/ejh.2018.2873
8. Guo X, Mu D, Gao F. Efficacy and safety of acellular dermal matrix in diabetic foot ulcer treatment: A systematic review and meta-analysis. *Int J Surg Lond Engl*. 2017;40:1-7. doi:10.1016/j.ijsu.2017.02.008
9. Lullove EJ, Liden B, McEneaney P, et al. Evaluating the effect of omega-3-rich fish skin in the treatment of chronic, nonresponsive diabetic foot ulcers: penultimate analysis of a multicenter, prospective, randomized controlled trial. *Wounds Compend Clin Res Pract*.

2022;34(4):E34-E36. doi:10.25270/wnds/2022.e34e36
10. Winters C, Kirsner RS, Margolis DJ, Lantis JC. Cost Effectiveness of Fish Skin Grafts Versus Standard of Care on Wound Healing of Chronic Diabetic Foot Ulcers: A Retrospective Comparative Cohort Study. *Wounds Compend Clin Res Pract*. 2020;32(10):283-290.
11. Michael S, Winters C, Khan M. Acellular Fish Skin Graft Use for Diabetic Lower Extremity Wound Healing: A Retrospective Study of 58 Ulcerations and a Literature Review. *Wounds Compend Clin Res Pract*. 2019;31(10):262-268.
12. Lullove EJ, Liden B, Winters C, McEneaney P, Raphael A, Lantis Ii JC. A Multicenter, Blinded, Randomized Controlled Clinical Trial Evaluating the Effect of Omega-3-Rich Fish Skin in the Treatment of Chronic, Nonresponsive Diabetic Foot Ulcers. *Wounds Compend Clin Res Pract*. 2021;33(7):169-177. doi:10.25270/wnds/2021.169177
13. Dorweiler B, Trinh TT, Dünschede F, et al. The marine Omega3 wound matrix for treatment of complicated wounds: A multicenter experience report. *Gefasschirurgie Z Vaskulare Endovaskulare Chir Organ Dtsch Osterreichischen Ges Gefasschirurgie Unter Mitarbeit Schweiz Ges Gefasschirurgie*. 2018;23(Suppl 2):46-55. doi:10.1007/s00772-018-0428-2
14. Lee M, Jun D, Choi H, Kim J, Shin D. Clinical Efficacy of Acellular Dermal Matrix Paste in Treating Diabetic Foot Ulcers. *Wounds Compend Clin Res Pract*. 2020;32(1):50-56.
15. Cazzell S, Moyer PM, Samsell B, Dorsch K, McLean J, Moore MA. A Prospective, Multicenter, Single-Arm Clinical Trial for Treatment of Complex Diabetic Foot Ulcers with Deep Exposure Using Acellular Dermal Matrix. *Adv Skin Wound Care*. 2019;32(9):409-415. doi:10.1097/01.ASW.0000569132.38449.c0
16. Zelen CM, Orgill DP, Serena TE, et al. Human Reticular Acellular Dermal Matrix in the Healing of Chronic Diabetic Foot Ulcerations that Failed Standard Conservative Treatment: A Retrospective Crossover Study. *Wounds Compend Clin Res Pract*. 2017;29(2):39-45.
17. Martin BR, Sangalang M, Wu S, Armstrong DG. Outcomes of allogenic acellular matrix therapy in treatment of diabetic foot wounds: an initial experience. *Int Wound J*. 2005;2(2):161-165. doi:10.1111/j.1742-4801.2005.00099.x
18. Reyzelman A, Crews RT, Moore JC, et al. Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. *Int Wound J*. 2009;6(3):196-208. doi:10.1111/j.1742-481X.2009.00585.x
19. Zelen CM, Orgill DP, Serena T, et al. A prospective, randomised, controlled, multicentre clinical trial examining healing rates, safety and cost to closure of an acellular reticular allogenic human dermis versus standard of care in the treatment of chronic diabetic foot ulcers. *Int Wound J*. 2017;14(2):307-315. doi:10.1111/iwj.12600

Literature Review of Pediatric Obesity in Relation to Gait Morphology

Anna Nicole Dartley BA; Annmarie Abodeely BS; Troy Gubler MS; Janice Therese Bautista DPM, MPH

ABSTRACT

Introduction

Pediatric obesity is a global health challenge that adversely impacts the lower extremity. Excess body weight can lead to various comorbidities and effects related to gait biomechanics of the lower limb and feet. Simple tasks such as walking plays a role in gait pressure, loading characteristics and gait modifications. There is research on gait studies in pediatric obese populations, however, there is limited literature that reviews foot and ankle changes during gait. This literature review examines the influence of obesity on the walking gait cycle with a focus on the foot and ankle in the pediatric population. We hypothesize that pediatric obesity significantly influences gait morphology of the lower extremity.

Study Design: Systematic Review of Literature

Methods

A literature search was done using the PubMed database for terms concerning pediatric obesity, physical activity, gait, and footloading from 2000 to October 14, 2022. With inclusion and exclusion criteria applied, 13 unique articles are included in this study.

Results

The thirteen studies analyzed the relationship between childhood obesity and various aspects of the lower extremity related to foot shape, pressure and loading, gait, and motion, mean walking velocity and slope incline, muscle alignment and development, and neuromuscular changes and development. In nearly all areas, childhood obesity affected these categories with the exception being in walking gait of the cross-sectional study by Montes-Alguacil *et al.*[9] showing no significant correlation.

Conclusion

In conclusion, childhood obesity plays an integrative role in gait. The increased body adipose contributes to adaptive weight, pressure and load related to the lower extremity. Future studies should focus on ways to decrease such load and pressure during gait and physical activity.

Keywords: Pediatric, Obesity, Walking, Gait

Level of Evidence: 4

INTRODUCTION

Pediatric obesity is now one of the most critical public health problems of the 21st century, and its prevalence has increased remarkably worldwide over the past 3 decades.[1,2] Overweight and obesity are both defined as "abnormal or excessive fat accumulations that present a risk to health" and is so significant because children who are obese tend to stay obese into adulthood.[2] Obesity can lead to development of noncommunicable diseases such as cardiovascular disease, diabetes, musculoskeletal disorders and cancers at a younger age.[2] Obesity has detrimental contributions to not only diabetes, but also poor development of the skeletal-articular system has resulted in recent studies providing evidence of negative effects in basic and necessary aspects of life such as walking.[3]

Research regarding pediatric obesity's effect on gait and biomechanics has shown unfavorable anatomical changes, joint stress, foot-loading, spatial temporal, foot arch, and deformity, amongst others.[1,3-10] Regarding the gait cycle, pathologies in one joint may lead to transfer of increased pressure onto an adjacent joint. Feka *et al.* reported that adolescent obese girls place more weight in their rearfoot compared to boys.[11] Another study reported that overweight or obese pediatrics may influence the development of future musculoskeletal disorder.[12] Spech *et al.* proposed that during high impact activities, adolescents were subjected to increased load forces, which may be a risk factor for development of early degenerative joint destruction.[13]

The importance of continuing pediatric obesity research can help us better understand and treat the impairments that our juvenile population is encountering. By reducing this multifactorial chronic disease, obesity, we can have a healthier society and decrease the burden that the medical community will face in the future. There is limited, comprehensive research on the current findings of the pediatric obese population. This literature review will examine the current findings on alterations in foot loading, gait, foot, and ankle motion in pediatric populations during low energy activities like walking.

Aim: This paper seeks to explore major themes in how obesity affects plantar pressure during the gait cycle with focus on the foot and ankle in the pediatric population and how pediatric obesity influences gait morphology of the lower extremity.

METHODS

A literature search was employed utilizing the PubMed database. Keywords in this search included: pediatric obesity, physical activity, and gait. The key phrases in search included: pediatric obesity physical activity gait, pediatric obesity gait pressure, and pediatric obesity footloading which yielded 56 articles from 2000 to October 14, 2022. One search terms set was followed: ("pediatric obesity"[MeSH Terms] OR ("pediatric"[All Fields] AND "obesity"[All Fields]) OR "pediatric obesity"[All Fields]) AND ("gait"[MeSH Terms] OR "gait"[All Fields]) AND ("pressure"[MeSH Terms] OR "pressure"[All Fields] OR "pressures"[All Fields] OR "pressures"[All Fields] OR "pressurisation"[All Fields] OR "pressurised"[All Fields] OR "pressuriser"[All Fields] OR "pressurization"[All Fields] OR "pressurizations"[All Fields] OR "pressurize"[All Fields] OR "pressurized"[All Fields] OR "pressurizer"[All Fields] OR "pressurizes"[All Fields] OR

"pressurizing"[All Fields]). The second search set was, ("gait"[MeSH Terms] OR "gait"[All Fields]) AND ("foot"[MeSH Terms] OR "foot"[All Fields]) AND ("loaded"[All Fields] OR "loading"[All Fields] OR "loadings"[All Fields] OR "loads"[All Fields]) AND ("pediatric obesity"[MeSH Terms] OR ("pediatric"[All Fields] AND "obesity"[All Fields]) OR "pediatric obesity"[All Fields]). The third search was, ("pediatric obesity"[MeSH Terms] OR ("pediatric"[All Fields] AND "obesity"[All Fields]) OR "pediatric obesity"[All Fields]) AND ("exercise"[MeSH Terms] OR "exercise"[All Fields] OR ("physical"[All Fields] AND "activity"[All Fields]) OR "physical activity"[All Fields]) AND ("gait"[MeSH Terms] OR "gait"[All Fields]).

The inclusion factors were: articles related to pediatrics, obesity, physical activity, articles written in English, gait pressure, and walking, which limited the results to 37 articles. The exclusion factors were: articles not written in English, those outside the pediatric age range, or those not involving gait pressure, walking, and gait physical activity, which resulted in 16 articles. Redundant articles were removed, which left 13 unique articles for evaluation.

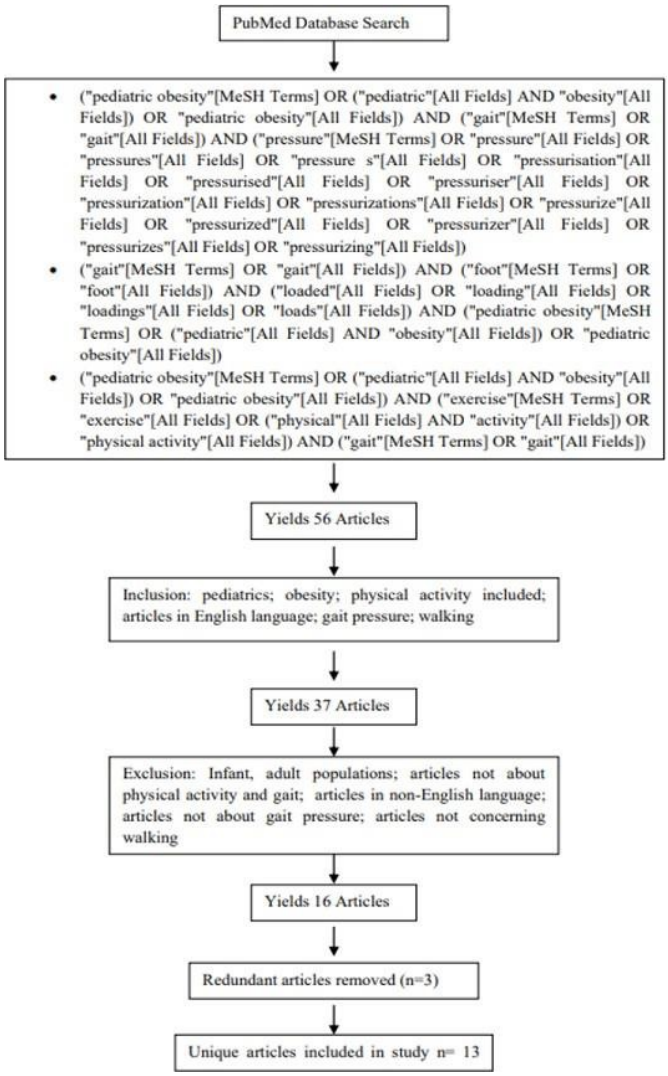


Figure 1. PubMed article search with inclusion and exclusion criteria for articles from 2000 to October 14, 2022. Three database searches were implemented, yielding 13 unique articles.

RESULTS

Author	Study design	Number of participants	Study Aim	Study Results
Mahaffey *et al.*[8]	Cross sectional	55	Evaluated impact of body fat during ambulation	Relationship between higher body fat and greater calcaneus plantarflexion

Shultz *et al*. (2009)[1]	Cross sectional	20	Evaluated joint kinematics and kinetics during walking cadences	Overweight children had greater absolute peak joint moments of the hip, knee, and ankle
Yan *et al*.[10]	Cross sectional	776	Investigated relationship between obesity, plantar pressures, and center of pressure	Obese children are likely to develop flatfoot without the accompanying structural changes
Shultz *et al*. (2014)[6]	Cross sectional	40	Investigated kinematic joint malalignment during gait	Obese children had increased genu valgum, peak displacement for hip adduction, foot abduction and hip internal rotation
Song-Hua *et al*.[7]	Cross sectional	40	Evaluated plantar pressure during walking, jogging, and running	Plantar pressure, peak pressure and arch index was greatest during jogging compared to the other movements
Montes-Alguaci l *et al*.[9]	Cross sectional	238	Investigated spatiotemporal gait parameters using Optogait system	Optogait system provided spatiotemporal parameters during gait, there was no spatial variable significance
Horset *et al*.[5]	RCT*	48	Neuromuscular strengthening exercise program decreases joint loading during walking	Results have yet to be reported
Mueller *et al*.[14]	RCT*	10382	Examined effect of different body mass on plantar pressure distribution characteristics during gait	Obese children had larger values for foot contact area, arch index, and overall foot loading

Schultz, *et al*. (2012)[4]	Cross sectional	20	Compared structural and functional characteristics of foot and ankle complex	Obese children had significantly greater arch drop and lower arch rigidity index ratios, and significantly less active ankle dorsiflexion at 90 degrees of knee flexion
Szczepanowska, *et al*.[3]	Cross sectional	194	Investigated association of BMI, adipose tissue content in body composition, and the actual distribution of foot loads	Assessment of BMI and foot load dependence showed obese tend to put more load on metatarsal. Adipose tissue content with body weight against food weight found overweight individuals put more load on the metatarsal (C zone)
Lerner and Browning[15]	Cross sectional	20	Relationship between body mass and compressive and shear joint contact forces at the hip joint during walking	Body mass predicted hip joint contact forces, which increased in obesity. Hip flexor moments were smaller in obese children
Oliveira *et al*.[16]	Cross sectional	24	Examined mechanical work and energy expenditure at different walking speeds	Obese children had increased internal mechanical work when walking at 4 km/h and 5 km/h. The average speed was 0.4 km/h slower in obese vs. non-obese
Strutzenberger *et al*.[17]	Cross sectional	22	Studied angles of joints, joint moment and joint power while walking at an incline	Obese children had increased hip joint, joint loading, hip flexion and adduction during inclined path

*RCT= Randomized Clinical Trial

Table 1. Summary of Articles Reviewed.

Mahaffey *et al.* (2016) evaluated the impact of body fat on the pediatric foot during ambulation.[8] This study used 55 local schoolboys aged 7-11 (BMI: 12.34-29.62, mean of 18.41±4.00). They captured 3D foot motion using an 8-camera Vicon Nexus motion capture system with skin mounted reflective markers at 200Hz. This system was employed during "self-selected" walking speeds. After statistical analysis of the results the study found a relationship between higher body fat and increased calcaneus plantarflexion. Overweight children were more externally rotated than normal weight children. Overweight children also exhibited greater midfoot dorsiflexion, or a pronated foot.

Shultz *et al.* (2009) evaluated the joint kinematics and kinetics of 20 volunteers between 8 and 12 years of age, 10 overweight (BMI: 30.47±5.54) and 10 of normal weight (BMI: 16.85±1.31), at two different walking cadences.[1] Measuring ground reaction forces using two force plates and analyzing motion with a 5-camera Vicon 460 system kinematic and kinetic data was collected simultaneously. After running the data through an independent t-test, ANOVA, ANCOVA, and Bonferroni correction the researchers found that overweight children had greater absolute peak joint moments of the hip, knee, and ankle when compared to normal-weight children. The results were conclusive regardless of different walking cadences and are concerning for increased lower extremity joint stress. These results point to higher risk of and prevalence of injury.

Yan *et al.* (2020) evaluated 436 girls and 340 boys before selecting a group of 21 obese children with flatfoot (BMI: 25.58±3.50), 21 obese children without flatfoot (BMI: 26.22±2.83), and 21 normal-weighted children (BMI: 17.35±2.50) to see how obesity and flatfoot affected plantar pressures and center of pressure.[10] Using a footscan plate system at 250Hz, data was collected as the participants walked "naturally" across with two complete steps being evaluated. Feet were split into forefoot, midfoot, and rearfoot sections for evaluation. After statistical analysis was performed using the Kolmogorov-Smirnov test and an independent t-test, the results showed that PF (peak force), PP (peak pressure), and PTI (pressure-time integral) all had an upward trend with excessive body mass. Obese children with flatfoot had lower PP and PTI compared to obese children with normal feet. This is suggestive of flatfoot and obesity having opposite effects. However, the data implies that obese children are likely to develop into flatfoot without the structural changes that accompany it. The researchers recommend excluding flatfoot as a screening criterion for future participants in foot biomechanical studies that investigate plantar pressures and foot function to avoid confounders. They also note obese children with or without flatfoot require modified footwear and orthotics to improve foot pathology.

Shultz *et al.* (2014) did a study which included 40 children (half were obese and half were nonobese) between the ages of 8-12 years old.[6] Frontal, sagittal, and transverse planes were taken during hip, knee, and ankle kinematic analysis. Walking speed was significantly larger for nonobese children. For the sagittal plane, not much difference was found for maximal angular displacement. Obese children had decreased maximal hip and knee flexion compared to nonobese children. For the frontal plane, the nonobese group had greater maximal hip and knee abduction (P=0.06), while the

obese group had greater maximal hip and knee adduction. This study found various distinctions for the transverse plane between obese and nonobese. For frontal and transverse planes, obese children tend to utilize the genu valgum position, knees closer together and feet far apart.

Song-hua *et al.* studied the biomechanical effects of plantar pressure distribution during walking, jogging, and running with children who attended Primary School in Beijing, China.[7] Parameters studied were support subphase (heel, strike, midstance and propulsion), peak pressure, arch index (AI), and angle of foot axis using a 2m foot scan plantar pressure plate (RS International). Forty children: twenty obese between 8.51 to 12.8 years old with a BMI between 24.73 to 31.53 kg/m^2 and twenty nonobese children between the ages of 10.01 to 12.03 years old with a BMI between 15.87 to 19.01 kg/m^2.
To compare statistical comparisons (significant if $p < 0.05$) a paired t-test and independent sample t-test was used, and an ANOVA compared gait parameters during the 3 different movement modes. For obese children during jogging, propulsion was the longest (p=0.02) and AI was the largest of the left foot (p=0.04). During jogging, peak pressures were largest under metatarsal head IV (p=0.005), metatarsal head V (p=0.003), midfoot (p=0.004), medial heel (p=0.03) and lateral heel (p=0.01). Due to excess fat weight, the results show a greater overload and an increase in foot pain. Song-hua et al concluded that obese children are likely to redistribute plantar pressure surfaces, increase angle foot axis, have out-toe feet, and more injuries related to foot especially during jogging.

Montes-Alguacil *et al.* conducted a study aimed to determine the influence of childhood obesity using OptoGait, a transportable photocell program.[9] This program measured anthropometric data and spatiotemporal gait parameters. BMI was assessed using the Orbegozo system, which was broken down into underweight ($P < 3$), normal weight (P 3-90), overweight (P 91-97) and obesity ($P > 97$). Participants included 238 healthy children (114 girls and 124 boys) in primary school between the ages of 7-11 years old in Spain. The average age was 9.25 years, with average BMI 20.41 kg/m2 but did not report for obese and non-obese participants. Montes-Alguacil *et al.* reported a significant gait difference during stance phase of 58% in normal weight, with a difference of -4.4% for obese population (p=0.0001), swing phase 38% but not significantly different, and load response 10% and in obese a difference of 3.2% (p=0.016), and pre-swing phase of 10% and in obese a difference of -2.5% (p=0.0001) between obese and nonobese children, with an average walking speed of 1.24 m/s. No significant differences for spatial variables were reported. Obese and overweight children spent a longer time in the stance, load response and pre-swing phases, but they spent a shorter time during the heel contact phase compared to normal weight children.

Horsak *et al.* conducted a single assessor blinded, pre and post randomized control trial with a control and an intervention group in Vienna, Austria.[5] A total of 48 boys and girls between the ages of 10-18 years old with a BMI greater than 97% participated in baseline measurements and a 12 week follow up after intervention. The intervention focused strengthening exercises related to quadriceps, hip and neuromuscular. The goal of these strengthening exercises was to improve positioning of knees during hip and ankle movements. Primary outcome measures included 3D gait analysis during walking for

external frontal knee motion, while secondary outcome parameters focused on sub knee injury, Osteoarthritis Outcome Score (KOOS), lower extremity kinetics and kinematics during natural walking, and the training program. The focus was to examine if a neuromuscular strengthening exercise program decreases joint loading during walking. Results have yet to be reported.

The study by Mueller *et al.* aimed to examine the effect of different body mass in normal-weight, overweight, and obese children aged 1-12 years on plantar pressure distribution characteristics during gait.[14] The study was conducted in 61 cities across Germany and involved 10,382 children enrolled on a volunteer basis. It was found that obesity does influence values such as mean walking velocity, arch index, peak pressure, and overall foot loading. In determining mean walking velocities, this study found normal weighted children presented smaller contact areas than overweight children, with the highest values of foot contact areas in obese children. In examining arch index, the smallest was seen in normal weighted children, followed by overweight, followed by obese. There was a consistent increase of overall foot loading, with the obese children recording the highest and the normal weighted children recording the lowest. For peak pressure, there was an overall increase from youngest to oldest and differences in body mass were smaller than for FTI with highest for obese children.

Schultz *et al.* (2012) conducted a cross-sectional study among 20 healthy children (10 obese average BMI 30.47 +/- 5.4 and 10 normal weight with average BMI 16.85 +/- 1.31) to compare the structural and functional characteristics of the foot and ankle complex in obese and non-obese children.[4] This study found that obese participants had significantly greater arch drop and a trend toward lower arch rigidity index ratios, in addition to significantly less active ankle dorsiflexion at 90 degrees of knee flexion vs non obese. Therefore, structural and functional differences do exist in the characteristics of the foot and ankle between obese and non-obese children. Obese participants had less active ankle dorsiflexion with the knee at 90 degrees of flexion. Obese participants had 19.5 +/- 5.17 degrees, while non-obese had 29.07 +/- 3.06 degrees of dorsiflexion, which was statistically significant at $P < .001$. They also examined arch height while sitting and standing, and forefoot to rearfoot alignment while loaded and unloaded, and RCSP and malleolar valgus index, all of which had no significant differences.

Szczepanowska *et al.* conducted a study with 194 children (101 girls and 93 boys) aged 12-14 who were randomly selected from primary schools representing both urban and rural environments.[3] The average age was 12.84 years, with average BMI for girls 19.7 +/-3.2 (range 12.9-28.8) and for boys 20.2 +/- 4.2 (range 13.8-36.5). The study aimed to gain an insight into how BMI, adipose tissue content in body composition, and distribution of foot loads was associated in school aged children. This group used Stabilometric platform scan and mapped the foot into 6 divided zones (zones A-F). Zone A is the lateral forefoot, Zone B is the medial forefoot, Zone C is the lateral midfoot, Zone D is medial midfoot, Zone E is the lateral hindfoot, and Zone F is the medial hindfoot. No correlation between foot load and gender was found; however, assessment of foot load and BMI showed that obese individuals tend to place far more load on the metatarsals than on the zone B medial forefoot. A juxtaposition of adipose tissue content with body weight against foot weight proved another significant correlation which found overweight

individuals put far more load on the metatarsal especially in the C zone.

Lerner and Browning examined the relationship between body mass and compressive and shear joint contact forces at the hip joint during walking.[15] The study group included 10 obese and 10 healthy-weight children and observed their walk at 1 m/s (3.6 km/h). They calculated that peak compressive shear was 1.77 times greater in obese compared to normal-weight participants and that vertical shear forces were 1.81 times greater in obese compared to normal-weight participants. There was strong positive correlation with compressive shear and vertical shear forces and total body mass. For every kilogram of body mass, there was an increase in compressive shear by 41N and in vertical shear there was an increase by 48N. First peak forces were similar, and second peak forces were smaller in obese children compared to normal weight-children. Bodyweight-normalized data on hip flexor moments were smaller in obese children compared to normal-weight children.

Oliveira *et al.* (2015) examined mechanical efficiency at different walking speeds in the pediatric population.[16] Internal work was increased when walking speed increased for both groups, and there was a marked increase in the obese population compared to the control group. The difference of work demand was statistically significant when walking at 4 km/h and 5 km/h speeds ($P < 0.001$ for both). When comparing total mechanical work, there were no significant differences when comparing groups. However, there were significant differences between the groups when comparing different walking speeds. Walking at 5 km/h required statistically significantly more total energy than when walking at 1, 2, and 3 km/h speeds for the obese group ($P = 0.002$, 0.025, 0.001 respectively). Walking at 4 km/h was statistically significantly different when compared with 2 km/h in the obese group. With regards to the control population, total energy when walking at 1 km/h compared to 3 km/h. They also examined efficiency, which was affected by speed and not by group type. The efficiency was greatest for both groups when walking at 3 km/h speed. They looked at oxygen consumption, which was affected by speed with $P < 0.001$ which increased as speed increased from 1 to 5 km/h.

Strutzenberger *et al.* (2017) examined characteristics of step, sagittal and frontal joint angles, and joint moments and joint power different inclinations in adolescents who are obese and normal-weight adolescents.[17] They studied 11 obese (14.5 ± 1.41 years, BMI: 31.1 ± 3.5 kg/m ^{2}) and 11 normal-weight adolescents (14.3 ± 1.86 years, BMI: 19.0 ± 1.7 kg/m^2). They walked on a ramp with two force plates embedded at three inclinations (level, 6°, 12°) at a speed of 1.11 m/s. They looked at kinematic data, examining the hip, knee, and ankle joint during gait. They found that there were significant differences between the groups during stance and swing phase duration during level walking and 6 degrees uphill walking (p-value not reported). Regarding the sagittal plane, they did not find statistically significant data, however they found that obese adolescents flexed their hips and knees more than normal group during initial contact. Regarding frontal plane joint, they found increased knee valgus angle during initial contact at 0° and 6° inclination (p-value not reported).

DISCUSSION:

Foot shape plays a large role in the efficiency of ambulation, pain, and injuries. Unfortunately, studies have shown that obesity increases the likelihood of pain and

injuries by changing the shape of the foot and that the obese child's foot exhibits similarities to the pes planus foot. Shultz *et al.* confirms this by demonstrating that the medial longitudinal arch is flatter due to increased pressure from excess mass and the decrease in total area of center of pressure excursion[4]. Chronic weight bearing injuries of the lower extremity, such as medial tibial stress syndrome and plantar fasciitis, have been associated with the pes planus foot type[18]. Yan *et al*. also evaluated foot structure but did so by various measurements including peak force (PF), plantar pressure (PP), pressure-time integral (PTI), contact area (CA), center of pressure (COP), and the ten anatomical regions of the foot (T1, T2-T5, metatarsals, midfoot, etc.). Their study found that flatfoot has the opposite effects on pressure when comparing the results to obesity but that obese children have a higher chance of developing flatfoot than normal weight children[10]. As such, flatfoot should not be a screening criterion for future studies, but rather foot loading patterns should be examined.

Excess body weight contributes to abnormal motor development, agility, and overall coordination of movements, and adversely affects the development of skeletal-articular system, leading to postural defects[3]. Obesity directly affects the way foot biomechanics are developed, especially foot loading, which is subject to several adverse modifications due to associations with BMI and more specifically adipose tissue content in the body. With the study by Szczepanowska, *et al.*, the distribution of foot loads using scans divided into six zones, [A: lateral forefoot; B: medium forefoot; C: lateral midfoot; D: medium midfoot; E: lateral hindfoot; F: medium hindfoot] showed a significant correlation between BMI and foot load dependence in overweight and obese individuals, as compared to the ones characterized by normal weight, which clearly showed that obese individuals tend to put far more load on metatarsals. In addition, juxtaposition of adipose tissue content with body weight against food weight proved another significant correlation as overweight individuals were found to put far more load on the metatarsal especially in C zone[3]. In addition to foot loading, heel strike, plantar pressure, plantar peak pressure, and arch index, when compared between obese and non-obese children showed no significant difference other than in arch index; however, obese children still showed elevated plantar and peak plantar pressures. Song-Hua *et al*. found that obese children are more likely to redistribute plantar pressure surfaces, have increased angle foot axis, and are more prone to foot related injuries[7]. Thus, not only is plantar pressure affected, but also joint pressures of the hip during walking are more strongly correlated with an increase in body mass. Obese individuals had a significantly greater peak compressive shear contact force than nonobese as indicated by Lerner and Browning[15]. The placement of the load on the foot may be correlated with the compressive shear at the hip joints, which could be further studied for causation.

Kinematic references the mechanics of motion without the forces which cause said motion. As such, kinematics is important when investigating gait, especially how gait can be affected in an obese population. Shultz *et al.* had various studies evaluating joint kinematics during movement.[6] When looking at the sagittal, frontal, and transverse planes of the hip, knee, and ankle during walking it was seen that there were both similarities and differences between the overweight/obese groups and normal weight groups. Significantly greater hip flexor, extensor, abductor, knee flexor, ankle plantar

flexor, external and internal rotator moments were seen in the overweight group. In another Shultz et al. study obese pediatric participants were found to have decreased maximal hip extension, knee extension, and significantly greater maximal hip adduction when compared to the nonobese participants. These studies showed lower extremity joint dysfunction and malalignment, leading obese adolescents to move with their knees closer together and feet farther apart, a genu valgum position. When body weight was controlled for as a covariate, the significant differences in peak joint moments were eliminated[1]. This research continued to highlight that overweight children experience increased forces, which increased the risk of stress fractures and foot and ankle pain. Strutzenberger *et al.* examined joint angles and moments at various inclinations, to examine the extent of change, identifying that there is increased involvement and demand in proximal joints.[17] Although there was one study concerning ambulation at an incline, this study also found an increase in tendency of genu valgum position of the knee while at 6° inclination. Future studies could seek to quantify to estimate the relationship of weight and biomechanical changes.

Comparing the structural and functional characteristics of the foot and ankle complex in obese and nonobese children showed significantly decreased active ankle dorsiflexion at 90 degrees of knee flexion in obese individuals, which may correlate to the increase the foot contact for a longer period of the stance of phase of gait[4]. Obese individuals also showed a more flexible foot when bearing weight[4]. Horsak *et al.* published a study protocol which sought to analyze neuromuscular strengthening exercises to improve the positioning of knees in obese individuals during hip and ankle movements. The goal would be to determine if this type of training program could decrease joint loading during walking; however, results on this have yet to be reported[5]. It would be interesting for further studies to examine the improvement of ankle and knee position and motion with intervention by strengthening exercises.

Although Horask *et al.* have not published study results, there were similarities to Shultz *et al.* related to muscular aspects of the lower extremities of obese children. Horask *et al.* results from the neuromuscular strengthening program study may decrease the amount of joint loading during motion and therefore minimize joint diseases [5]. Shultz *et al.* (2012) noted previous studies concluded that intense physical activity may influence musculoskeletal pain from knee and foot in obese children. Shultz *et al.* suggested proper footwear to support the pes plantar foot [4]. Both studies also mentioned that obese children compensate for gait due to increased body mass.

With regards to walking gait cycle, stance was increased in the studies by Montes-Alguacil and Strutzenberger.[9,17] It is known that the gait cycle is 60% stance phase, 40% swing phase. Strutzenberger reported 61.2% for normal and 63.4% for obese patients. Montes-Alguacil reported stance phase of 58% in normal weight, with a difference of -4.4% for obese population ($p=0.0001$), swing phase 38% but not significantly different, and load response 10% and in obese a difference of 3.2% ($p=0.016$), and pre-swing phase of 10% and in obese a difference of -2.5% ($p=0.0001$). This communal finding of increased time in the stance phase may be explained by the need to balance the body with an increased mass and increased ground reactive force in each step. The increase in time for the stance phase may assist with balance as the body

moves against gravity to advance the non-weight bearing leg.[9] Further studies may illuminate a more accurate numeric change of the phases.

With regards to walking velocity, Oliviera *et al.* attempted to quantify the amount of internal work expended at different speeds.[16] They determined that energy used was significantly different and energy was increased between obese and non-obese participants for a set speed of 5 km/h (1.38 m/s). This is justified as there is increased body mass to translate the body across a surface over a certain speed, which is higher than the reported speeds among other studies. Not many of the other studies reported average velocity. Mueller et al. examined plantar pressure at the average walking velocity of 0.95 m/s.[14] Lerner and Browning investigated compressive and shear joint contact forces while walking at 1 m/s (3.6 km/h).[15] Additional studies or combination of approaches may provide more detail on each of the gait cycle phases, or more studies on a consistent velocity.

This literature review had some limitations. The major limitation being sample size of some of the studies, with increases in reliability for studies that have a larger sample population. Although obese children adapt their gait during various physical exercises there is no standard protocol for obese children to minimize potential pain or exacerbation of lower foot and ankle pain. Prospective studies should be conducted to understand alternative ways (i.e. swimming, cycling, elliptical, yoga, stairmaster, etc.) to help obese children build strength in the lower extremities and improve foot and ankle mobility.

CONCLUSION

This paper explored major themes of how obesity affects plantar pressure, arch changes, joint pressure, and malalignments during the gait cycle in the pediatric population. These included increased dorsiflexion and flexibility of foot when bearing weight, increased walking gait cycle stance, and decreased walking velocity. A correlation between kinematics and gait compensation, abnormal motor development, overall coordination, and how foot shape plays a role in ambulation, pain and injuries was found with increased body mass. Childhood obesity is a critical health concern of the 21st century. Therefore, understanding the impact pediatric obesity has on gait morphology and its comorbidities, especially if carried into adulthood, will help us to treat and reduce the impending burden on the global health care system. However, with only a handful of research, we recommend more should be completed regarding pediatric obesity's effect on gait morphology. Future studies should focus on establishing guidelines for those at risk of injury and exercise programs that minimize foot load in obese children to increase stability and decrease foot disorders.

AUTHOR'S CONTRIBUTION

All authors contributed equally to this literature review. All authors drafted and reviewed the final manuscript.

STATEMENT OF COMPETING INTEREST

Authors declare no competing interests related to completing this manuscript.

REFERENCES

1. Shultz SP, Sitler MR, Tierney RT, Hillstrom HJ, Song J. Effects of

pediatric obesity on joint kinematics and kinetics during 2 walking cadences. Archives of Physical Medicine and Rehabilitation. 2009;90(12):2146-2154.

2. Güngör NK. Overweight and obesity in children and adolescents. *J Clin Res Pediatr Endocrinol*. 2014;6(3):129-143. doi:10.4274/Jcrpe.1471

3. Szczepanowska-Wolowiec B, Sztandera P, Kotela I, Zak M. Body weight-dependent foot loads, assessed in terms of BMI and adiposity, in school-aged children: a cross sectional study. Sci Rep. 2020;10(1):12360. Published 2020 Jul 23.

4. Shultz SP, Sitler MR, Tierney RT, Hillstrom HJ, Song J. Consequences of pediatric obesity on the foot and ankle complex. J Am Podiatr Med Assoc. 2012;102(1):5-12.

5. Horsak B, Artner D, Baca A, et al. The effects of a strength and neuromuscular exercise programme for the lower extremity on knee load, pain and function in obese children and adolescents: study protocol for a randomised controlled trial. Trials. 2015;16:586.

6. Shultz SP, D'Hondt E, Fink PW, Lenoir M, Hills AP. The effects of pediatric obesity on dynamic joint malalignment during gait. Clin Biomech (Bristol, Avon). 2014;29(7):835-838.

7. Song-Hua Y, Lu W, Kuan Z. Effects of different movement modes on plantar pressure distribution patterns in obese and non-obese Chinese children. Gait Posture. 2017;57:28-34.

8. Mahaffey R, Morrison SC, Bassett P, Drechsler WI, Cramp MC. The impact of body fat on three dimensional motion of the paediatric foot during walking. Gait Posture. 2016;44:155-160. doi:10.1016/j.gaitpost.2015.12.009Mahaffey R, Morrison SC, Bassett P, Drechsler WI, Cramp MC. The impact of body fat on three dimensional motion of the paediatric foot during walking. Gait Posture. 2016;44:155-160.

9. Montes-Alguacil J, Páez-Moguer J, Jiménez Cebrián AM, Muñoz BÁ, Gijón-Noguerón G, Morales-Asencio JM. The influence of childhood obesity on spatio-temporal gait parameters. Gait Posture. 2019;71:69-73.

10. Yan S, Li R, Shi B, Wang R, Yang L. Mixed factors affecting plantar pressures and center of pressure in obese children: Obesity and flatfoot. Gait Posture. 2020;80:7-13.

11. Feka K, Brusa J, Cannata R, et al. Is bodyweight affecting plantar pressure distribution in children?: An observational study. Medicine (Baltimore). 2020;99(36):e21968.

12. Molina-Garcia P, Migueles JH, Cadenas-Sanchez C, et al. A systematic review on biomechanical characteristics of walking in children and adolescents with overweight/obesity: Possible implications for the development of

musculoskeletal disorders. Obes Rev. 2019;20(7):1033-1044.

13. Spech C, Paponetti M, Mansfield C, Schmitt L, Briggs M. Biomechanical variations in children who are overweight and obese during high-impact activities: A systematic review and meta-analysis. Obesity Reviews. 2022;23(6):e13431.

14. Mueller S, Carlsohn A, Mueller J, Baur H, Mayer F. Influence of Obesity on Foot Loading Characteristics in Gait for Children Aged 1 to 12 Years. PLoS One. 2016;11(2):e0149924. Published 2016 Feb 25. doi:10.1371/journal.pone.0149924

15. Lerner ZF, Browning RC. Compressive and shear hip joint contact forces are affected by pediatric obesity during walking. Journal of Biomechics. 2016;49(9):1547-1553.

16. Oliveira HB, da Rosa RG, Gomeñuka NA, Carvalho AR, Costa RFD, Peyré-Tartaruga LA. When mechanical work meets energetics: Obese versus non-obese children walking. Exp Physiol. 2020;105(7):1124-1131.

17. Strutzenberger G, Alexander N, Bamboschek D, Claas E, Langhof H, Schwameder H. Uphill walking: Biomechanical demand on the lower extremities of obese adolescents. Gait Posture. 2017;54:20-26.

18. Wong L, Hunt A, Burns J, Crosbie J. Effect of foot morphology on center-of-pressure excursion during Barefoot Walking. Journal of the American Podiatric Medical Association. 2008;98(2):112-117.

Posterior Tibial Tendon Transfers in Treating Foot Drop Patients: A Systematic Review.

Christina Yerdon, BS; Chiara Mercado, BS; Milana Mayzlish, BS; Demiana Ishak, MS; Andrew Bastauross, BS; Sally Nagib, MD

Abstract

Foot drop is a disorder characterized by the partial or total loss of dorsiflexion and eversion at the level of the talo-crural joint. Some common etiologies of drop foot are injury or trauma to the common peroneal nerve, sciatic nerve injuries, leprosy, Charcot-Marie-Tooth Disease, and Cerebral Palsy; of these the most common etiology is injury to Common Peroneal Nerve (CPN). This condition can be debilitating as it disrupts patients ability to perform daily activities. The gait cycle in patients with foot drop is characterized by the inability to lift the forefoot upon the initiation of the gait cycle, causing the forefoot to strike the ground prior to the heel. This type of gait is otherwise known as steppage gait. Conservative treatment, such as the use of ankle foot orthoses (AFOs), are typically the first line of management in foot drop patients. However, if conservative treatment methods are unsuccessful, the next appropriate treatment option is surgical intervention, including tendon transfers to correct the drop foot deformity. Of these tendon transfer operative procedures, the posterior tibial tendon transfer is the most frequently used to treat drop foot deformity. This article aims to analyze the effectiveness of posterior tibial tendon transfers in patients with foot drop secondary to peroneal nerve trauma or injury.

INTRODUCTION

The peroneal nerve is the most frequently affected peripheral nerve of the lower extremity leading to foot drop.[9] Injury to the nerve is varied in etiology and may include trauma, infection, congenital, or iatrogenic. Injury to the nerve results in loss of dorsiflexion, ankle eversion, and toe extension. [1] Injury is also characterized by an equinovarus deformity of the ankle and hindfoot. [10]

During a normal gait cycle, when the heel strikes the ground, the ankle remains in either a slight extension or a neutral position. During the swing phase, an active extension of the toes and ankle is required to clear the ground. [1] However, with foot drop, the patient slaps the foot on the ground and drags it along the ground during the swing phase of gait. The patient has to flex the hip more than normal to lift the entire foot off the ground, which is known as high steppage gait. [1]

Conservative treatment for drop foot includes the use of Ankle Foot Orthosis (AFO). The use of AFOs helps maintain the foot in a plantigrade position during the loading response phase of gait and prevents foot dropping during the swing phase. [10] However, this treatment is not well tolerated, especially in the active young adult population. [9] The AFO can be uncomfortable and not visually appealing in shoes because of its bulkiness. The increase in material between the foot and the ground causes challenges with balance.[13] The brace may also lead to ulcerations with footwear due to the decrease in air circulation around the foot and ankle.

Various surgical techniques have been described in literature to address a drop foot, but the gold standard is considered to be dynamic tendon transposition of the tibialis posterior tendon.[9] Codivilla in 1899 and Putti in 1914 are credited for first describing the transfer of the posterior tibial tendon to the dorsum of the foot to restore appropriate dorsiflexion in the foot. [9] This transfer allows for almost normal functional gait and prevents the possible equinovarus deformity caused by the tibialis posterior tendon.[1] Possible arising questions such as the best route of transfer, the type of insertion, the place of insertion, the best candidate for transfer, and the tension of the transferred tendon are essential and still being researched.[6]

Many techniques have been discussed and implemented for tibialis posterior tendon transfer. Putti, in 1914, transferred the tendon anteriorly through the interosseous membrane to the dorsum of the foot. In 1954, Watkins et al. reported ‘good’ or ‘excellent’ results in 24 out of 25 patients using this technique. [9] Many modifications have been discussed since then in literature, including the Bridle procedure, which was first described by Daniel Riordan in 1973.[10] This procedure was designed to address under or over-correction of coronal plane position where the attachment of the tibialis posterior tendon was either placed too far lateral or medial.[9] The Ober procedure was described in 1933, whereby the muscle belly lies in contact with the tibia.[3] Other modifications include different attachment sites of the tendon in the foot. One attachment may be tendon-to-bone fixation, in which the tibialis posterior tendon is looping around the second metatarsal (modified Ober procedure), and another is tendon-to-tendon fixation, where the attachment site is the tibialis anterior tendon.[1]

The focus of this systematic review is to utilize the reported outcomes of each chosen retrospective or case studies to evaluate the effectiveness of posterior tibial tendon

transfer in patients with drop foot secondary to peroneal nerve trauma or injury.

METHODS

10 articles were identified and analyzed after meeting the inclusion and exclusion criteria. Data from 157 patients and 161 feet were used to assess the effectiveness and patient satisfaction after undergoing posterior tibial tendon transfers as a treatment for foot drop secondary to common peroneal nerve injury. Post-operative Stanmore, AOFAS, or patient satisfaction grading assessments were then completed. Of the patients assessed using the Stanmore grading system, 92 patients recorded good or excellent results, 22 patients recorded moderate results, and 9 patients recorded poor results.

Conclusion

Posterior tibial tendon transfer procedures provide a benefit that outweighs that of conservative treatment for patients experiencing long term foot drop secondary to peroneal nerve trauma or injury and should be considered as a treatment option for these patients.

Search Strategy and Criteria

This comprehensive systematic literature study was conducted according to PRISMA guidelines. The search term "Tibialis Posterior Tendon Transfer for Foot Drop" was used to seek out relevant articles. The electronic databases used to find relevant articles to the aforementioned search term were PubMed and Google Scholar. All studies published up until September 2022, at which point this study was conducted, were evaluated and screened for inclusion. In addition, all references cited in identified reviews were manually searched for potentially relevant information on the topic of this article.

Inclusion and Exclusion Criteria

The literature was screened for subjects that underwent some form of Tibialis Posterior tendon transfer for the treatment of foot drop; with or without additional procedures and disregarding age, sex, ethnicity, etc. All studies were included, disregarding year of publication as well.

Identified studies were included if they met all of the following inclusion criteria: (1) articles written in English or translated to English; (2) articles with full-access to readers via electronic databases PubMed and Google Scholar; (3) acquired etiology of CPN injury leading to foot drop; (4) retrospective case studies, case studies, and prospective interactive case series'; (5) follow-up time of at least 6 months; (6) clinical scores taken using approved clinical methods.

Case reports, cadaver studies, publications including subjects with congenital or infectious disease etiology of CPN injury leading to foot drop, or publications failing to mention etiology of CPN injury leading to foot drop were excluded from this systematic review. Studies without a full-text article available on either PubMed or Google Scholar were also excluded.

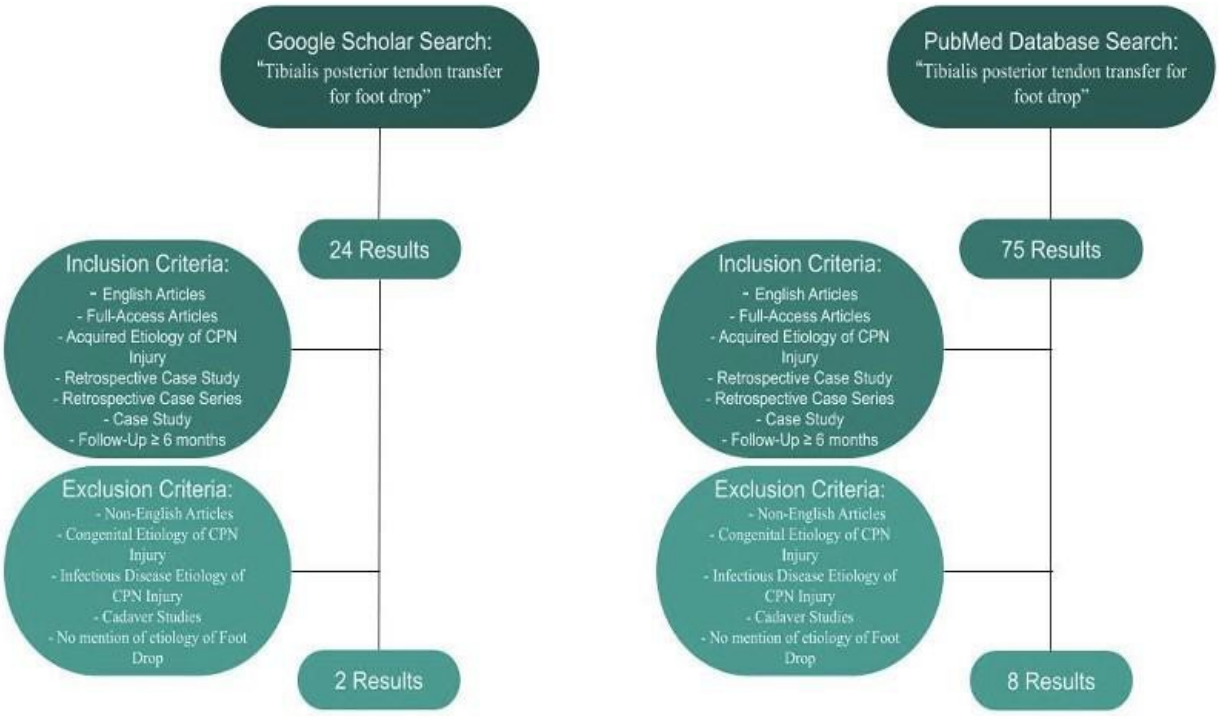
Assessment of Study Quality

The assessment of the quality of included studies was done by all authors of the study and then later screened for a second time by two authors— sophomore and junior podiatric medical students using the same consensus rule. The purpose of the second screening was to ensure that all articles definitively met the inclusion and exclusion criteria outlined above.

Data Collection and Abstraction

All abstracts identified from PubMed and Google Scholar literature search were manually screened against the outlined inclusion and exclusion criteria. During the second screening process, for each publication, two authors— sophomore and junior podiatric medical students— assessed the included literature based on the following criteria: study design, follow-up, and population. Any disagreements on the inclusion of publication were discussed between all authors of literature to come to a consensus. After the abstracts were reviewed and screened for inclusion, the authors assessed the remaining included publications' full-text articles.

For all remaining eligible studies, the following characteristics were extracted: author(s), publication year, study type, time to follow-up assessment, number of subjects, number of feet, number of male subjects, number of female subjects, and age range of subjects in each publication. Said data was extracted from article texts and any tables or figures reported in article texts.



RESULTS

A total of 99 potential articles were collected from online databases. After the addition of inclusion and exclusion criteria, 10 articles were found to be relevant for the purpose of this review. Of those articles, one article was a case study, and the remaining nine articles were retrospective studies. The publication dates of the articles ranged from 2001-2021. It should be noted that each patient included in this review experienced trauma or injury to the peroneal nerve or fibular portion of the sciatic nerve. Central neurological causes of foot drop were not considered.

Study Number	Authors	Publication Year	Study Type	Time of Follow-up Assessment
1	Muhammad Imran Khan et al.	2021	Retrospective Study	6 months (mean 34.3 months)
2	Adolfo Vigasio et al.	2008	Retrospective Study	24 months (mean 65 months)
3	Yeap et al.	2001	Retrospective Study	6 months (mean 64.6 months)
4	Yeap and Birch et al.	2001	Retrospective Study	24 months (mean 90.4 months)
5	Cho et al.	2017	Retrospective Study	12 months (mean 65.6 months)
6	Kilic et. al	2008	Retrospective Study	Not specified (mean 25.3 months)
7	Niranj	2020	Case Study	6 months
8	Yeganeh et al.	2013	Retrospective Study	6 months
9	Johnson et al.	2015	Retrospective Study	12 months (mean 22.8 months)
10	Flynn et al.	2014	Retrospective Case Series	44.4 months (mean 61 months)

Table 1: Studies included in this Review

Patient Characteristics

There were a total of 157 patients and 161 feet that met the criteria for this review. Of those, 104 patients were men, and 53 patients were women. The total age range of patients was 10-73 years old, with the specific age ranges per article broken down in Table 2. From the included cohorts, there were a total of 157 patients, and 161 posterior tibial tendon transfers were performed as several patients had operations bilaterally.

Study Number	Number of Patients	Number of Feet	Male	Female	Age Range
1	32	32	28	4	28-34 yr
2	16	16	10	6	11-44 yr

3	18	18	9	9	12-73 yr
4	12	12	7	5	12-56 yr
5	17	17	10	7	18-59 yr
6	13	15	7	6	10-46 yr
7	1	1	1	0	24 yr
8	14	15	9	6	10-55 yr
9	19	19	14	4	23-57 yr
10	15	16	9	6	17-72 yr

Table 2: Cohort Characteristics

Scoring Criteria

Five of the studies utilized the Stanmore assessment questionnaire. The Stanmore questionnaire assesses pain, need for orthoses, ability to wear normal shoes, ability to complete daily function, degree of active dorsiflexion (measuring both muscle strength and degrees), and foot posture. Each of these criteria is graded with a total possible score of 100. Excellent or Very Good scores achieve 100-85 points, Good scores achieve 84-70 points, Fair or Moderate scores achieve 69-55 points, and Poor scores achieve <55 points. Study one utilized their own scoring criteria where they measured the success of the posterior tibial tendon transfer procedure on the patient's ability to actively dorsiflex at the ankle. Excellent scores achieved >15 degrees active dorsiflexion, Good scores achieved 5-15 degrees active dorsiflexion, Moderate scores achieved no active dorsiflexion and no foot drop, and Poor scores presented with plantarflexion. Study 4 measured their outcomes based on patient satisfaction. Study seven measured their success based on active dorsiflexion and physician satisfaction. Studies five and ten measured their success using an array of different criteria such as the American Orthopaedic Foot & Ankle Society (AOFAS) ankle-hindfoot scores, Foot and Ankle Outcome Score (FAOS), Foot and Ankle Ability Measure (FAAM) scores, Hindfoot Scale and Short Form (SF)-36 forms and objective clinical and radiographic measurements.

Study Number	Scoring Criteria	Patient Scoring Results	Postoperative AFO Usage
1	Excellent, Good, Moderate, Poor Active Dorsiflexion Assessment	7, 14, 9, 2	2

2	Stanmore Grading System	8, 5, 2, 1	2
3	Stanmore Grading System	4, 7, 2, 5	13 once weekly, 1 twice weekly, 0 constantly
4	Patient Satisfaction: Excellent, Good, Moderate, Poor	6, 4, 2, 0	1 constantly, 1 intermittently
5	AOFAS, FAOS, FAAM	N/A	1 (occupationally)
6	Stanmore Grading System	7, 3, 3, 2	1
7	Physician Assessed	N/A	0
8	Stanmore Grading System	10, 4, 0, 0*	0
9	Stanmore, Statistical Analysis	12, 7, 9, 0	2 (for athletic purposes)
10	AOFAS	N/A	0

Table 3: Procedure Scoring Criteria *In Study 8, one patient did not complete the follow up questionnaire.

Of the 123 patients whose follow up progress was graded using the Stanmore criteria or a similar satisfaction criteria, 92 (74.8%) patients recorded excellent or good results. 22, (17.8%) of patients recorded moderate results, and 9 (7.4%) of patients achieved poor results. The patients in study 5 were scored according to the AOFAS, FAOS, and FAAM; the results, discussed below, favored posterior tibial tendon transfer as a viable method to restore function in foot drop patients. According to the cohort in study 10, all patients verbally communicated they were satisfied with the procedure and would undergo a posterior tibial tendon transfer again. Postoperatively, 15 patients required the use of an AFO intermittently during the course of a week, 1 patient required the use of an AFO occupationally, 2 patients required the use of an AFO for athletic purposes, and 6 patients required the use of an AFO consistently to perform daily functions.

DISCUSSION

This systematic review analyzed various articles that focused on the transfer of the Posterior Tibial Tendon in patients diagnosed with drop foot secondary to Peroneal Nerve injury or trauma. This review was conducted to analyze the efficaciousness of the aforementioned tendon transfers utilizing the reported outcome measures of each article. Stevoska et al. has conducted a similar review and analysis on the topic, citing another article

by Wagenaar et al. that performed a similar discussion on the topic at hand. [11]

Alternative Procedure Effectivity Grading Criteria

Tibialis posterior tendon transfer is the gold standard in treating foot drop secondary to peroneal nerve injuries. Multiple attachment sites have been suggested based on the etiology and the desired correction.[1] The route through which the tendon is passed to the dorsum of the foot is also dependent on the etiology, skill of the surgeon, and the severity of the drop foot. Two commonly used attachment sites are to the 2nd metatarsal bone and to the tibialis anterior tendon.[1] Khan et al. initially looked at whether one of those attachment sites was superior to the other. At the 6th postoperative month, both groups had similar results, with 80% of the patients having good to excellent dorsiflexion. However, at the 34th postoperative month, significant differences were being observed between the groups, indicating that long term differences were likely to be observed when using these two specific attachment sites.[1] The group that had a tendon-to-tendon fixation showed deterioration of function;only a minority of patients had reported excellent results and 40% had moderate results. The authors addressed the shortcomings of the interosseous route by lengthening the tibialis posterior tendon before fixating it to the 2nd metatarsal. This allowed the tendon to have enough length to maintain its strength, restore adequate dorsiflexion and prevent an equinovarus deformity that could potentially result from an unopposed pull of a short tibialis posterior tendon.[1] This lengthening of the tibialis posterior tendon was hypothesized to lead to slippage or rupture due to the thinning of the tendon, but such complications were not observed in the study. Although tendon to bone fixation is surgically demanding in terms of dissection and insertion, this article highlighted that the interosseous route with a 2nd metatarsal insertion led to better outcomes when it came to restoring function and providing patients with normal gait without a need for ankle foot orthoses.[1] Limitations included a smaller sample size.

Yeap et al. used patient satisfaction,which correlated with the muscle power and degree of active dorsiflexion, to determine the success of their surgery. The authors found that the best results were achieved in the younger population, specifically in males under 30 years of age.[4] This demographic showed excellent results and were able to achieve active dorsiflexion beyond neutral.[4] Although the ankle range of motion upon dorsiflexion increased significantly postoperatively, the torque generated by the affected limb was only around 30% of the torque generated by the unaffected limb.[4] The authors could not comment on whether stretching the tendon or attaching the tendon distally to the cuneiform resulted in function deterioration, except that some patients reported weaker dorsiflexion following pregnancy and recent falls. The authors also did not comment on some patients having multiple procedures to reach adequate results. In this study, the interosseous route was preferred over the subcutaneous route even though it was more surgically challenging because it was more direct, produced less pronation, and achieved more dorsiflexion.[4] They admitted that, despite all procedures having undergone the interosseous route, patients had different tendon attachment sites depending on the case's severity. This made it difficult to interpret the results and compare the groups. This also meant that they could no longer isolate the success of the tendon transfer to the initial procedure. The authors overall recommended tibialis posterior tendon transfer as it potentially improved the function of 80% of patients, especially

males under 30.[4], but were not able to provide insight on whether a distal or a proximal tendon attachment would be beneficial for the patients.

Cho et al. found that the long-term function of patients following tibialis posterior tendon transfer was satisfactory. The most important factor to highlight was that daily activities, and gait functionality improved at the 3 year follow up and thereafter.[5] The authors were also able to restore considerable ankle range of motion, but the dorsiflexion strength was only about 33% of the unaffected limb, which was in line with what Yeap et al. found.[4,5] Although some patients were able to achieve a more significant power output, they were considered above average. The authors found no clinical or radiographic evidence of progression to flat feet in this retrospective study. The authors were not able to determine which tendon transfer method was the best for the patients, but they highlighted the fact that the most important prerequisite for post operative success was to be careful with patient selection,to be thorough in preoperative examination and to only offer surgical intervention to patients who would clinically benefit from the tendon transfer.[5] The article highlighted the importance of passing the tibialis posterior tendon under the extensor retinaculum if a subcutaneous route is chosen for the surgery. It also highlighted the importance of appropriate rehabilitation at six weeks postoperative to increase mobilization and range of motion.[5] The study mentioned that there was an iatrogenic collapse of the medial longitudinal arch that has been described as a potential adverse effect of the tendon transfer. This was limited to a few case reports of which, according to the authors, surgical intervention should have never been offered in the first place as these cases were unlikely to be successful long term.[5] The authors claimed that sacrificing the tibialis posterior tendon would not lead to any medial arch vulnerability and stated that an acquired flat foot deformity as a result of the tibialis posterior tendon transfer was debatable in the literature.[5] In this study, they did not find any long term arch issues. The authors recommended further long term studies to assess whether sacrificing the tibialis posterior tendon would directly lead to an acquired flat foot. The authors also highlighted the fact that although adequate peak torque and range of motion were to be restored towards dorsiflexion, active plantarflexion at push-off was significantly reduced as the Tibialis posterior tendon could no longer contribute to plantarflexion.[5] Limitations for this retrospective study included that the corresponding physicians did preoperative muscle strength and assessments and therefore the authors were not able to determine the accuracy of these measurements. This study also did not include any gait analysis and dynamic electromyography postoperatively or during the rehabilitation period. The authors did not comment on why they chose to pass the tendon from under the extensor retinaculum as it might lead to impingement. This may be because of cosmetic reasons or to avoid adhesions, however these are our speculations, as no comments were made in the discussion.

Abdelaziz et al. looked at common peroneal nerve injury patients who had not had any intervention for over a year. They were careful in their population selection to not include any patients with an equinus that needed a tendo-achilles lengthening. They also made sure that all the patients selected had supple ankle joints as to guarantee the best outcome and to isolate potential failures to be only due to failure of the tibialis posterior tendon transfer and not due to another etiologies at play. The researchers

highlighted the importance of stretching exercises for the achilles tendon for patients who could not dorsiflex their ankles past neutral. This was crucial because delaying the time of the tibialis posterior tendon transfer leads to shortening of the achilles tendon due to the unopposed pull and the weakness of the opposing anterior crurals; therefore, preoperative stretching of the achilles tendon was very important for the success of the tendon transfer.[12] The authors highlighted the importance of the degree of tension in the tibialis posterior tendon after it was tied down because the tibialis posterior has an excursion of only 2 cm when compared to opposing muscles like the tibialis anterior and extensor hallucis longus, which have excursions between 3-5 cm.[12] If the tibialis posterior was to be sutured to one of those tendons in a tendon to tendon fashion, the degree of tension needs to be adjusted accordingly as the passive arc of movement would always be less on the operated side than the unaffected side.[12] The authors preferred the interosseous route over the subcutaneous route mainly for cosmetic reasons and to avoid adhesions that were likely to result. They highlighted the fact that the interosseous route was more surgically challenging but provided better results, including less pronation and greater dorsiflexion. They chose to stay superficial to the extensor retinaculum to have a longer moment arm and avoid impingement. They also chose a tendon-to-tendon fixation as inserting the tendon to bone required a tendon graft which was not available to them. All the patients reported excellent results and were satisfied with the tendon transfer. The results were in line with the existing literature.[12,4,5]

The Bridle procedure combines a tri-tendinous anastomosis to restore active dorsiflexion of the ankle.[10] Flynn et al. highlighted one of the modifications to the original Bridle, which was to include a subtalar arthroeresis in their patients. This modification caused some mild pain at the sinus tarsi, but the patients were able to maintain a plantigrade position.[10] The idea behind the implant was to prevent a long-term acquired flat foot deformity from forming despite sacrificing the tibialis posterior tendon. This was done to guarantee no long term pronation issues. The authors highlighted that 3 of their patients complained of a lack of hallux extension, which was also mentioned in previous literature and is an important side effect of the bridle procedure.[10] The authors admitted that their patients had no midfoot motion during heel rise and did not develop a flat foot postoperatively. However, the authors did not show any radiographic or clinical evidence of an acquired flat foot in the patients who did not receive the subtalar implant. The study did show that the patients who received the implant did not go on to develop a flat foot. This raises the question as to whether the arthroeresis was a necessary modification or whether it was not needed. The authors highlighted the limitations as being the small number of patients, particularly with long term follow up. The authors admitted that only 3 patients continued to follow up long term, and those 3 patients did not receive the implant, so the authors were not able to determine the significance of the implant. The authors complained of loss to follow up, with only 8 patients in total returning out of 15. Nonetheless, the authors were pleased with the outcome of both groups and recommended the Bridle procedure with or without the arthroeresis for the treatment of foot drop.[10]

Stanmore Score Outcome Measures

The Stanmore assessment questionnaire, otherwise known as the Stanmore Score, is focused on the goals of the posterior tibial tendon transfer.[11] This assessment system

offers an objective evaluation of posterior tibial tendon transfer, it facilitates comparison of diverse modifications to operative technique.[3] It is commonly used to assess the functional outcome of patients undergoing tendon transfer following peroneal nerve injury and was used in 5 of the 10 articles (50%) included in this review.

A common theme in articles assessing posterior tibial tendon transfer is the difficulty in objectively comparing outcome measurements. Yeap et al. proposed a new system for assessment of posterior tibial tendon transfer for treatment of dropfoot resulting from nerve palsy. [3] In their article, Yeap et al. highlighted the deficit in previous evaluation methods to provide clear definitions of the methodology used to analyze posterior tibial tendon transfer outcomes.[3] The authors proposed a scoring system consists of seven sections: pain, orthosis necessity, ability to wear normal shoes, level of activity, ankle dorsiflexion muscle power, degrees of active dorsiflexion, and foot posture. [3] Yeap defined the maximum total score as 100, with different classifications assigned to ranges of scores.[3] Excellent results were defined as scores between 85 and 100, good results between 70 and 84, fair between 55 and 69, and poor as scores lesser than 55.[3]

The retrospective study initially included 25 patients, of which only 18 were considered in the final representation due to refusal of participation, death, and loss of follow up.[3] The age of the patients spanned from 12 to 25 years old, the gender of patients was not specified in the article.[3] The cohort characteristics exhibited limitations in the study population that could impact result interpretation. The cohort represented an incomplete population of patients who had underwent treatment, which could lead to a biased sample population due to lacking patient results. Yeap et al. disclosed that one patient who refused to participate potentially had a poor outcome, citing that the patient's mother was dissatisfied with the results.[3] This highlighted the potential bias that could occur due to the excluded patients from the original population. Additionally, the wide range in age between patients could affect ability to objectively compare components of the proposed scoring system such as level of activity and ankle dorsiflexion muscle power. Yeap et al. had accounted for the potential discrepancy in level of activity and assessed functional outcome by observing the ability of the patient to conduct activities of daily living as well as recreational activities.[3] The possibility of the older cohort population having other conditions that could impact activity levels was considered, and the author decided that only functional limitation secondary to foot drop was considered in this study.[3] However, the author did not disclose how functional limitation secondary to foot drop was determined and did not disclose potential health conditions, the addition of this information would offer a more transparent and accurate interpretation of results on behalf of the reader.

The Stanmore system showed 22% of cohort had excellent results, 38.8% had good results, 11.1% had fair results, and 27.7% had poor results.[3] An average score of 67.2% was calculated, correlating to overall fair results of the tendon transfer.[3] In contrast, patient ratings showed 38.8% excellent results, 27.7% good results, 16.6% fair results, and 16.6% had poor results.[3] The article discussed the American Orthopaedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale, aimed at assessing surgical outcomes for painful foot and ankle pathologies. In agreement with the author, this outcome measure does not adequately evaluate tendon transfer of the

tibialis posterior because the aim of posterior tibial tendon transfer is functional control of the deformity and not pain control.[3] This outcome measure is cited in other systematic reviews , even though it may not be the most appropriate measurement to assess effectivity of tendon transfer procedure. [11] Similarly, the author brings attention to the contrast in outcome scores when assessed via an objective scale like Stanmore versus a more subjective scale such as patient rating. Conflicting results of both outcome measurements, coupled with the inadequacy of the AOFAS Ankle-Hindfoot scale, agree with the author's rationale behind a new proposed scaling system.

Yeap et al. states that the suggested scaling system would offer a better objective evaluation that may be better tailored to assessing tibialis posterior tendon transfer outcomes.[3] The system can be assessed and recorded both preoperatively and postoperatively, providing a baseline reading to compare to the final patient outcomes. This could potentially increase accuracy in evaluating surgical outcomes. Yeap et al. states that although the patient is the final assessor in the outcome, the evaluation of procedure outcome based solely on patient assessment could pose inaccurate and unreliable results.[3] Patient satisfaction is easily biased as a result of different expectations, and varying degrees of pain unique to each individual. An objective form of analysis would be beneficial to accuracy and theoretically decrease subjective bias. The author specifies that this system would be specific for posterior tibial tendon transfer surgical results, facilitating accurate comparison of patient outcomes without the limitation of factoring in differing operative techniques.[3] To aid in the comparison of different surgical modifications to the procedure, an additional objective measurement such as the Stanmore scale, could be used.[3]

From the introduction of posterior tibial tendon transfer in 1933 by Ober, there have been several developments in surgical techniques, procedures, and fixation techniques.[8] Commonly, the tibialis posterior tendon is transferred to the dorsum of the foot, anchored to cuneiforms or metatarsals, to compensate for the forfeiture of the tibialis anterior muscle.[8] Yeganeh et al. conducted a case study to find an alternative fixation point on the dorsal surface of the foot to prevent adverse effects of skin problems and ulceration caused by protuberance along plantar anchorage site of tendon transfer.[8] The author recruited patients with post-traumatic common peroneal nerve palsy from 2009 until 2012, explaining the benefits of the original tendon transfer compared to the proposed benefits of transferring the tendon to the dorsal aspect of the foot.[8] The cohort included 9 men and 6 women, ranging in age from 20 to 55 years old.[8] The procedure with alternative dorsal anchorage site was conducted on 15 patients, dependent on patient preference and inclusion criteria of the study. The cohort presented with non-improving peroneal nerve palsy after 18 months despite nerve repair or releasing procedures, confirmed by electromyography and nerve conduction velocity tests.[8] The cohort had follow up evaluations at the 2 month, 3 month, and 6 month range.[8] One could argue that more than the maximum follow up time of 6 months is needed to adequately assess surgical results. A longer follow up period could add more insight into the long term effects of the procedure. Some limitations included a lack of control group, as well as a small case population, and retrospective nature of the study.[8] Another limitation was the failure of a patient to complete the therapy, reducing the already

small cohort population.[8] All of these limitations were determined using the Stanmore scoring system. Despite the limitations, the study yielded adequate results of the tendon transfer with Yeganeh's new proposed fixation method.

In Johnson et al's retrospective study, the aim was to analyze clinical outcomes and objective functional measurements in patients that underwent the Bridle procedure for dropfoot management secondary to traumatic peroneal nerve injury.[9] The study included 19 patients who had suffered traumatic peroneal nerve injury from 2005 to 2010, having underwent the Bridle tibialis posterior tendon modification procedure by one of two surgeons.[9] The author disclosed that some patients within the cohort had previously undergone other procedures, such as peroneal nerve neurolysis, nerve repair, or grafting.[9] This disclosure prevented assumption bias of the reader to erroneously think that the subjects had only underwent the Bridle operation. Additionally, the author stated the etiology of the peroneal nerve injury within the cohort, preventing the assumption that all etiology was the same within study population. The study also included an initial period of conservative nonoperative treatment, showing that these patients had no improvement prior to surgery and highlighting the effectiveness of the Bridle procedure on functional outcome. There was a descriptive analysis of the cohort based on chart review and history intake, providing a well-rounded foundation of each patient's condition and presentation. A control group was formed of 10 participants without foot and ankle injury; they were then matched to the study participants by age, weight, gender, and height [9]. The availability of a control group in this retrospective study added to the viability of result interpretation and functional outcome measurements. Matching the control group to the study population also provided a personalized comparison while minimizing variables that could potentially affect accurate evaluation between cohorts. Johnson et al. described the operative procedure in detail, allowing the reader to factor in all aspects of surgical technique and fixation methodology when evaluating the study results. Functional outcomes were assessed subjectively via a patient questionnaire, which included activity levels, VAS scale measurements, and AFO use.[9] It was also assessed objectively via AOFAS Hindfoot Ankle scale, Stanmore scale, ankle range of motion, Star excursion balance, radiographic alignment, and muscular strength of ankle dorsiflexors and plantar flexors.[9] The objective measurements were standardized, and a detailed statistical analysis was conducted, allowing for comparison of sex, race, and similarity of involved sides.[9] Due to assumptions needed for this statical analysis, the author evaluated multiple joints' range of motion as well as ankle dorsiflexor strength and transverse plane alignment to counteract the limitations set by this method of analysis.[9] The author also disclosed the exact statistical tests used to assess multiple outcome measurements, providing the reader with detailed methodology and emphasizing the accuracy of their results.

The author described the original Bridle procedure article written by McCall et al. in 1991 and compared their results to the results yielded in Johnson's retrospective study. Additionally, there was mention of the Modified Bridle procedure study done by Rodriguez et al. Both of the aforementioned studies rarely discussed the clinical outcome and objective measures and contained few details of operative technique.[9] In contrast, Johnson et al. discussed all of the previously mentioned factors and highlighted the

importance of including them in the study. This case controlled retrospective study yielded high satisfaction rates with good or excellent self reported outcomes, as well as having a 100% success in the cessation of AFO use for daily activities.[9] Johnson et al's outcomes are in agreeance with the notion that the Bridle procedure is an appropriate and effective treatment option in traumatic peroneal injury induced dropfoot. Although the Foot and Ankle Assessment Measurement (FAAM) scores were lower in the Bridle population versus the control group, there was still improvement seen in daily activity ability and sports activity.[9] This result was compared to a similar study conducted by Rodriguez et al. in which better results were noted concerning range of motion. Despite the better results, Johnson et al. states that Rodriguez et al's results were not measured using validated outcome measures, objective assessments, or a control group comparison.[9] Similarly, Johnson et al. provides a comparison to other studies assessing operative techniques of posterior tibial tendon transfer and provides evidence as to why the results may differ from those seen in his study.

The limitations of this study included its retrospective nature, a lack of preoperative data in some of the cohort population, and a decreased sample size from the original 30 patients due to inclusion criteria.[9] The study group also possessed heterogenous nature of injury, included various sites and mechanisms of injury and a wide age range.[9] However, the potential limitations of the study that could be counteracted by additional evaluations or alternative assessments were proactively addressed by Johnson et al. and seemingly reared no harmful effects to result interpretation or accuracy in functional outcome measurement. The remaining limitations, such as heterogenous nature of injury and those regarding cohort characteristics, are seemingly on par with other studies focused on posterior tibialis tendon transfer assessment. Despite all limitations, a well rounded evaluation of surgical outcome of the Bridle procedure was achieved, with standardized results and strongly backed by evidence obtained by objective measurements and statistical analysis.

CONCLUSION

The results of this analysis were conclusive with that of the studies used. Posterior tibial tendon transfer procedures provide a benefit that outweighs that of conservative treatment for patients experiencing long term foot drop secondary to peroneal nerve trauma or injury. Possible limitations to this study include failure of patients to follow-up, potential population bias, and different postoperative scoring criteria, and a small sample size. Should a similar analysis be conducted, it would be beneficial to have cases utilizing the same scoring criteria or review both retrospective and prospective studies to compare results.

REFERENCES

1. Khan, M. I., Ahmed, O., Yasmeen, S., Saadique, R., & Beg, M. (2021). Tibialis Posterior Transfer for Foot Drop: The Difference in Outcome for Two Different Attachment Sites. Cureus, 13(10), e18461.

2. Vigasio, A., Marcoccio, I., Patelli, A. et al. New Tendon Transfer for Correction of Drop-foot in Common Peroneal Nerve Palsy. Clin Orthop Relat Res 466, 1454–1466 (2008).

3. Yeap, J. MB, BCh, BAO*; Singh, D. MBBS**; Birch, R. MBBS**. A Method for Evaluating the Results of

Tendon Transfers for Foot Drop. Clinical Orthopaedics and Related Research: February 2001 - Volume 383 - Issue - p 208-213

4. Yeap, J., Birch, R. & Singh, D. Long-term results of tibialis posterior tendon transfer for drop-foot. International Orthopaedics (SICOT) 25, 114–118 (2001).

5. Cho B-K, Park K-J, Choi S-M, Im S-H, SooHoo NF. Functional Outcomes Following Anterior Transfer of the Tibialis Posterior Tendon for Foot Drop Secondary to Peroneal Nerve Palsy. Foot & Ankle International. 2017;38(6):627-633.

6. Aydin A, Topal M, Tuncer K, Canbek U, Yildiz V, Kose M. Extramembranous transfer of the tibialis posterior tendon for the treatment of drop foot deformity in children. Arch Iran Med. 2013; 16(11): 647 – 651.

7. Niranj, GR. (2020). OUTCOME OF TIBIALIS POSTERIOR TENDON TRANSFER FOR A CASE OF POST TRAUMATIC FOOT DROP. University Journal Of Surgery And Surgical Specialities, 6(4).

8. Yeganeh, A., Motaghi, A., Shahhoseini, G., & Farahini, H. (2013). New method for fixation point of tibialis posterior tendon transfer. Medical journal of the Islamic Republic of Iran, 27(4), 163–167.

9. Johnson, J. E., Paxton, E. S., Lippe, J., Bohnert, K. L., Sinacore, D. R., Hastings, M. K., McCormick, J. J., & Klein, S. E. (2015). Outcomes of the Bridle Procedure for the Treatment of Foot Drop. Foot & ankle international, 36(11), 1287–1296.

10. Flynn J, Wade A, Bustillo J, Juliano P. Bridle Procedure Combined With a Subtalar Implant: A Case Series and Review of the Literature. Foot & Ankle Specialist. 2015;8(1):29-35.

11. Stevoska, S., Pisecky, L., Stadler, C., Gahleitner, M., Klasan, A., & Klotz, M. C. (2021). Tendon transfer in foot drop: a systematic review. Archives of orthopaedic and trauma surgery, 10.1007/s00402-021-04162-x.

12. Abdelaziz, A., Wael Aldahshan, M. D., & Elsherief, F. A. H. (2018). Tibialis posterior tendon transfer for correction of drop-foot in common peroneal nerve palsy. *Age*, *24*, 9-45.

13. Denslow, Elizabeth. “A Therapist’s Guide to Finding the Perfect AFO Brace for Foot Drop.” *Flint Rehab*, 31 Aug. 2022,

Podiatric Manifestations of Illicit Drug Use: A Literature Review

Harneet Jaswal, BS

ABSTRACT

Introduction

Many complications arise with illicit drug use that cause detrimental effects on the physical health of the body. As an estimate, almost 16 million people worldwide aged 15 to 64 inject illicit drugs regularly (Canales et al., 2015). Aside from death, major complications consist of Chronic Venous Disease (CVD), venous breakdown, infections, and damage to the musculature and nerve fibers amongst other things (Pieper et al., 2007). Although most users typically start by injecting drugs in their torsos and upper extremities, they may choose to move further down to the lower extremities, as available injection sites disappear due to vein deterioration (Canales et al., 2015). This tissue damage not only leads to scars, but can also cause cellulitis, abscesses, and infection. More specifically, infection from illicit drug use commonly occurs due to impurities in the drug itself or because of a lack of sterile practices. This generates contamination in the preparation phase or contamination attributable to practices like sharing needles (Canales et al., 2015). The aim of this paper is to present an analysis and review of multiple case studies that demonstrate the relationship between dermatological and podiatric conditions and illicit drug use.

Study Design: Systematic Review of Literature

Methods

A literature search was completed using three separate inquiries on the PubMed Database. The key phrases used were "injected illicit drug use", "skin popping legs", and "injection lower extremity leg". The inclusion criteria for all articles consisted of being written within the last 23 years and incorporating human subjects. The exclusion criteria included scoping reviews, questionnaires, difficult to access articles, articles not relevant to the study, or articles that had already been accounted for in a previously conducted search. In the end, 13 articles fit the applied criteria and were selected for further analysis.

Results

There are many issues with illicit drug use that affect the whole body. One big issue is Chronic Venous Disease (CVD) or rather Chronic Venous Insufficiency (CVI). This condition arises due to injection of drugs affecting the veins and gets worse due to lack of movement in the calf (Pieper et al., 2007). Other issues brought about by illicit drug use include osteomyelitis and amyloidosis. Both conditions were once rare with drug use but have recently become more commonplace.

Conclusion

The focus of this paper is to highlight the relationship between illicit drug use and the podiatric dermatological manifestations it presents in the skin of patients' lower extremities. One recurring problem seen is the dermatological display of round papules, plaques, or wounds on the legs caused by a method known as skin-popping. This method enables drug users to get their fix in an

easier manner rather than inserting drugs into their veins and dealing with the complication of thrombosis (Canales et al., 2015). It is difficult to completely understand how patients use illicit drugs, as many obfuscate this information. As a result, it is very important that physicians take the time to thoroughly investigate the entire body to find evidence of any obscure infirmities. This will allow the patient and physician to build a better relationship and enable the physician to keep the patient as healthy as possible.

Keywords: drug-use, skin-popping, heroin, lower extremity

Levels of Evidence: 4

INTRODUCTION

Among the various definitions for illicit drugs, the baseline description depicts them as addictive substances not used for medical reasons (Teoh et al., 2019). The substance being used is not legally allowed for human consumption or it may be legally allowed but the drug usage is improper. Illicit drug use affects many people around the world and is recognized as a global health crisis. The United States, in particular, is facing many problems associated with drug usage due to opioids (Vearrier, 2019). The most common route of administration is through injection, with the two biggest problems being overdose or contraction of HIV through the apparatus. This process of injecting the drugs is what most commonly causes podiatric dermatological complications.

One of the most substantial complications of injecting illicit drugs in the lower extremities is due to the method known as skin-popping, where the drug is inserted under the dermal layer of the skin (Canales et al., 2015). The lower extremities are commonly chosen injection sites due to a multitude of factors: they allow for untroubled entry, they are easy to hide, and often are the last remaining areas of uninjured skin the addict has. This forces the abuser to use that region to receive their fix (Canales et al., 2015).
Although it may be difficult, the best method of treatment is abstinence of injection (Teoh et al., 2019). Drugs such as methadone can be used to help an addict lessen their cravings. However, if the person decides to keep using, other entry techniques may be used to allow the skin injuries to heal (Canales et al., 2015).

METHODS

Three separate inquiries were used on the PubMed database using the key phrases "injected illicit drug use", "skin popping legs", and "injection lower extremity leg". The search for "injected illicit drug use" resulted in 2,444 articles. Six were included after applying both the inclusion and exclusion criteria. The phrase "skin popping legs" resulted in 6 articles. Three were included and three were excluded. The keyword "injection lower extremity" resulted in 7,322 articles, with three of them being included after the criteria was applied. The inclusion criteria included articles written in the last 23 years and those incorporating human subjects. The exclusion criteria included scoping reviews, questionnaires, difficult to access articles, articles not relevant to the study, or articles that had already been accounted for in the previously conducted search. In total, 12 articles were used to review.

RESULTS

Although limited information exists, one way to understand more thoroughly how illicit drug use affects the lower extremities is through evaluation of case reports. One surprising issue seen in multiple patient cases was osteomyelitis in people that used the skin-popping method of drug injection. Osteomyelitis, a bone infection, can spread directly through blood or through the movement of bacteria itself (Canales et al., 2015). People afflicted with osteomyelitis may also have uncovered ulcers and granulation tissue over the area of infected bone. In one case, a patient's skin-popping wound became erythematous. She initially had no bone involvement when labs were first done, although bacteria strains of *Staphylococcus aureus* and *Streptococcus viridians* were found in the area. However, when the patient returned after two years of continuous drug usage, both the tibia and

fibula had undergone modification. Along with a few more strains of bacteria found in her leg ulcer, bone destruction and even bone regrowth were found in the tibia (Canales et al., 2015). In this case, osteomyelitis was verified by the histological confirmation of osteoblast lacunae lacking a nucleus, along with an increased occupancy of leukocytes.

In another patient, strains of *Pseudomonas aeruginosa*, methicillin resistant *Staphylococcus aureus, Enterococcus avium,* and *Klebsiella pneumoniae* were found in wounds of both legs. Radiographs showed the patient had bone involvement in the distal part of their fibula (Canales et al., 2015). Another occurrence discussed a patient who presented with a two year long chronic ulcer of the leg. No medical care was sought for the ulcer because the patient used the site for continuous drug injection. During examination, bone changes were evident, and the patient's main ulcerated wound had extended deep enough to detrimentally affect the fibula. This patient was compliant with all treatments (debriding and antibiotics) and eventually was given a skin graft to cover the damaged area after all traces of osteomyelitis were cleared (Iyer et al., 2011). Although problems like osteomyelitis were uncommon and not previously noted in users, the affliction has increased as more research has continued to be conducted.

In addition to osteomyelitis, people using the skin-popping method can also have secondary amyloidosis (Cooper et al., 2013). This is when fragments of serum amyloid A protein (SAA) aggregate into extracellular tissues as beta-pleated sheets once they reach a certain size. Cooper et al. demonstrate a case of this. One patient, a 37-year-old woman, came in with a complaint of pain in her right armpit, along with several skin abscesses. She relayed that her many abscesses were due to skin-popping. Both of her legs were also edematous up to the knee and she complained they had been swollen for two weeks. Upon completion of her blood test, she displayed elevated levels of SAA protein (more than 300 mg/dL). For treatment, the patient was given methadone in addition to anti-microbial therapy. She was also advised to stop illicit drug use, as it was negatively affecting her kidney function; however, she did not return for a follow up visit. In another instance, a former drug user came to the clinic for treatment of a leg wound that had manifested five years prior. Although his wound was originally used as a site for skin-popping, he'd been compliant with medical care and was eventually allowed to leave treatment after receiving a skin graft four years earlier. During his revisit, the patient was hospitalized for optimal healing but soon developed kidney failure due to his secondary amyloidosis (Bhat et al., 2018).

For patients with amyloidosis, deposition of amyloid protein is typically first seen in the kidneys. Once it builds up, it can travel and deposit in other organ systems. Essentially, amyloid proteins are made in the liver and transported in the blood through lipoproteins. When inflammation is present, it's a sign of increased amyloid protein aggregation, which leads to chronic inflammation and the eventual occurrence of amyloidosis (Bhat et al., 2018). To limit further problems from kidney damage, inflammation must be controlled. This is important when discussing podiatric manifestations due to the correlation between nephrotic disorders and leg edema. To work appropriately, kidneys require an environment where all aspects of the body are in homeostasis so that any peripheral edema in the body can be compensated for (Cooper et al., 2013).

Another complication of skin-popping is wound botulism, a possibly fatal disease caused by Clostridium Botulinum bacteria recently on the rise due to an increased association with injection of street drugs. These bacteria affect the presynaptic membrane, leading to neuromuscular issues (Qureshi et al., 2017). The most common drug association is black tar heroin (BTH). In the case series retrospectively reported by Qureshi et al., the patients commonly reported weakness of the lower extremity muscles as one of their major symptoms. Proximal muscle weakness of the upper and lower extremities was the most common feature noted by physicians in their physical examinations as well. These skin-popping injections had a mortality rate of 15% (Qureshi et al., 2017).

Another illicit drug with increased usage worldwide is cocaine (Camilleri et al., 2020). Studies have shown an increased association between cardiovascular issues and patients hospitalized for cocaine overdose. However, there is limited knowledge regarding cocaine's effects on the lower extremities aside from an unexplored association with vascular disease. In an article by Camilleri et al., researchers tried to understand how cocaine usage affected the lower limbs. What they found was an association with cocaine and decreased arterial perfusion of the lower extremities. Patients acquired more peripheral arterial disease and foot ulcerations that led to expanded amputation rates (Camilleri et al., 2020).

DISCUSSION AND CONCLUSION

The use of illicit substances, particularly the increased use of injectable drugs, is considered a pandemic by many health professionals. In western countries such as the United States, rates of other methods of drug use have decreased, while rates of injection have risen (Vearrier, 2019). Canada, another western country, has also seen a peak in rates of illicit drug injection that began after the year 2000 (Fischer et al., 2016). Even countries like Afghanistan, that have historically used drugs through inhalation, are moving towards illicit drug injection as their main method of use. This recent adoption is likely the country following the lead of their neighboring countries of Iran and Pakistan (Nafeh et al., 2022).

There are many issues with illicit drug use that affect the whole body. One big issue is CVD (or CVI), accelerated by injection drugs on the veins and worsened by lack of movement in the calf (Pieper et al., 2007). Injection of drugs increases pain in the leg, leading to a lack of ambulation. It also decreases movement of the talocrural joint, which can also lead to decreased ambulation (Pieper et al., 2007). Additionally, after injecting drugs, people usually remain in a daze or stupor. This stupor can lead to a lack of leg movement, causing blood to pool and the individual to experience pain and other complications. CVI occurs when the veins in the lower extremities are used as injection sites repeatedly (Pieper and Templin, 2003). Muscles and nerves in this area can be damaged in addition to veins. CVI was shown to be involved with approximately 87% of former drug users that were in treatment for methadone (Pieper and Templin, 2003).

One of the biggest issues seen in these case reports was the unwillingness of drug abusers to obtain treatment for the "shooter's patch". This area, usually seen on extremities, begins as an ulcer but after becoming the main injection site, can grow larger with increased exposure of

granulation tissue. This allows for an easier method of drug injection. This usage of skin-popping can yield more infections when compared to drug users that rely on intravenous methods, however patients are typically non-compliant to heal the abscess with antibiotics or skin grafts (Canales et al., 2015). Even though the best course of treatment is to give the patient antibiotics intravenously, it is not recommended for these patients due to their drug usage history. This results in patients not receiving the most effective course of treatment, which coupled with their usual lack of adherence to treatment can be disadvantageous (Iyer et al., 2011).

It is hard to completely understand how many patients use illicit drugs as they may not be forthcoming with this information. As a result, it is very important that physicians take the time to thoroughly investigate. This will allow the patient and physician to have a better relationship, as well as allow the provider to keep their patient as healthy as possible. Although the common response to drug use has been to suppress people from using, that method does not stop overdose related deaths, and instead causes social issues, such as imprisonment (Vearrier, 2019). As an effect of the continuation of overdoses, some are questioning whether the laws should move away from drug-opposition and move towards health-focused policies. This would allow people that use illicit substances to do so safely (Fischer et al., 2016).

LIMITATIONS

Although rates of drug injection have increased, manifestations in the lower extremities are not a big area of focus, which is why source material and the amount of research is limited. The population of illicit drug users with podiatric manifestations is small and isolated. Furthermore, it is difficult to recognize people that use, which makes it harder to find sources to study. This small population size can skew information, so an issue like osteomyelitis due to skin-popping, can seem like a rare manifestation rather than a more commonly known effect. Another limitation is patient compliance. As seen in these case studies, one of the biggest hindrances in caring for patients is a failure to return for treatment, which causes further complications that could have been mitigated early on.

STATEMENTS OF COMPETING INTERESTS

The author does not have any competing interests.

REFERENCES

1. Bhat, D., Asif, M., Cooney, C. M., Schwartz, D., Milner, S. M., & Caffrey, J. A. (2018). Amyloidosis associated with skin popping: a case report and review of literature. *International journal of dermatology*, *57*(12), 1504–1508. https://doi.org/10.1111/ijd.14009

2. Camilleri, N., Mizzi, A., Gatt, A., Papanas, N., & Formosa, C. (2020). Peripheral vascular changes in the lower limbs following cocaine abuse. Journal of Addictive Diseases, 38(3), 326–333. https://doi.org/10.1080/10550887.2020.1764160

3. Canales, M., Gerhard, J., & Younce, E. (2015). Lower extremity manifestations of “skin- popping” an illicit drug use technique: A report of two cases. The Foot, 25(2), 114–119. https://doi.org/10.1016/j.foot.2015.03.003

4. Cooper, C., Bilbao, J. E., Said, S., Alkhateeb, H., Bizet, J., Elfar, A., Davalos, O., Meza, A. T., & Hernandez, G. T. (2013). Serum amyloid A renal amyloidosis in a

chronic subcutaneous ("skin popping") heroin user. Journal of nephropathology, 2(3), 196–200. https://doi.org/10.12860/JNP.2013.31
5. Fischer, B., Murphy, Y., Rudzinski, K., & MacPherson, D. (2016). Illicit drug use and harms, and related interventions and policy in Canada: A narrative review of select key indicators and developments since 2000. The International journal on drug policy, 27, 23–35. https://doi.org/10.1016/j.drugpo.2015.08.007
6. Iyer, S., Subramanian, P., & Pabari, A. (2011). A devastating complication of 'skin popping'. The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland, 9(5), 295–297. https://doi.org/10.1016/j.surge.2010.08.010
8. Nafeh, F., Fusigboye, S., & Sornpaisarn, B. (2022). Understanding injecting drug use in Afghanistan: A scoping review. Substance abuse treatment, prevention, and policy, 17(1), 65. https://doi.org/10.1186/s13011-022-00491-1
9. Pieper B, Kirsner RS, Templin TN, Birk TJ. Injection Drug Use: An Understudied Cause of Venous Disease. Arch Dermatol. 2007;143(10):1305–1309. doi:10.1001/archderm.143.10.1305
10. Pieper, B., & Templin, T. (2003). Lower extremity changes, pain, and function in injection drug users. Journal of Substance Abuse Treatment, 25(2), 91–97. https://doi.org/10.1016/s0740-5472(03)00113-2
11. Qureshi, I. A., Qureshi, M. A., Rauf Afzal, M., Maud, A., Rodriguez, G. J., Cruz-Flores, S., & Kassar, D. (2017). Black tar heroin skin popping as a cause of wound botulism. Neurocritical Care, 27(3), 415–419. https://doi.org/10.1007/s12028-017-0415-6
12. Teoh, L., Moses, G., & McCullough, M. J. (2019). Oral manifestations of illicit drug use. *Australian dental journal*, *64*(3), 213–222. https://doi.org/10.1111/adj.12709
13. Vearrier L. (2019). The value of harm reduction for injection drug use: A clinical and public health ethics analysis. *Disease-a-month : DM*, *65*(5), 119–141. https://doi.org/10.1016/j.disamonth.2018.12.002

Rapid Detection of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Methicillin Sensitive *Staphylococcus Aureus* (MSSA) among Patients with Foot Infection.

Opemipo Akin-Adejimi, BS

ABSTRACT

Introduction

Methicillin-Resistant *Staphylococcus Aureus* (MRSA) is a bacterium that has become increasingly concerning due to its resistance to a wide range of antibiotics. In contrast, Methicillin-Sensitive *Staphylococcus Aureus* (MSSA) is a regular *staphylococcus aureus* that has yet to evolve and exhibit the virulence factors that lead to antibiotic resistance. The emergence of MRSA has created a need for more efficient diagnostic tools to minimize the negative impact of prolonged MRSA and MSSA foot infections on low and high-risk patients.
Various diagnostic techniques have been developed to detect MRSA and MSSA, including Nasal swabs, Real-time PCR, and novel molecular tests such as Gene Xpert® MRSA/SA SSTI, CRISPR-Cas12a, BBL CHROMagar MRSA, and Phage-mediated molecular detection. These techniques have shown promising results in providing accurate and rapid detection of MRSA and MSSA, thereby enabling early intervention and treatment.

Study Design: Systematic Review of Literature

Methods

PubMed Database search was conducted using search ("Methicillin-Resistant Staphylococcus Aureus" [All Fields]) OR ("MSSA" [All Fields]) AND ("Rapid Test" [All Fields]), yielding 62 results. The inclusion criteria included articles written in English, research conducted on humans and publication date within 10 years. The exclusion criteria for this review include articles that are not relevant to the topic or do not contain the keywords used in the search query.

Results

After a thorough assessment of the abstract of the articles, 13 were relevant to the topic of this review and were included. Gene Xpert® MRSA/SA SSTI, BBL CHROMagar MRSA, *CRISPR-Cas12a,* and Phage-mediated molecular detection were able to rapidly identify MRSA or MSSA faster than conventional Susceptibility Testing.

Discussion and Conclusion

While conventional plate-based culture testing methods are available for the detection of Methicillin-Resistant *Staphylococcus Aureus* (MRSA) and Methicillin-Sensitive *Staphylococcus Aureus* (MSSA), faster testing procedures are advantageous in implementing effective preventative or precautionary infection control measures. Rapid diagnostics can help in the application of appropriate and specific therapy, thereby avoiding unnecessary use of antibiotics

in cases where MRSA or MSSA is present in foot infections. This article presents a systematic review of rapid molecular diagnostic methods for the detection of MRSA and MSSA, with a focus on their value to antimicrobial stewardship and in making informed infection control decisions.

Keywords: MRSA, MSSA, Infection, Nasal carriage, PCR

Level of Evidence: 4

INTRODUCTION

Staphylococcus aureus is a part of the harmless skin's floral microbiome; however, it could cause devastating infections and sepsis when introduced into the bloodstream. *Staphylococcus aureus* is classified into Methicillin-Resistant Staphylococcus aureus (MRSA) and Methicillin-Sensitive *Staphylococcus Aureus* (MSSA) based on sensitivity to antibiotics drug. Today, it is very likely that a *staphylococcus aureus* infection is Methicillin-Resistant *Staphylococcus Aureus* (MRSA). Strains like MRSA have developed increasing resistance against antibiotics. The elevated use of antibiotics in the Hospital to kill off microorganisms causes a spontaneous mutation in the genetic makeup of these microorganisms in the long run. People at risk for MRSA and MSSA foot infections by MRSA ad MSSA are diabetic patients, amputees, trauma patients, and many more. A study in the United Kingdom found that one year after diabetes diagnosis, 55% of diabetic patients had diabetic foot ulcerations that were infected (Diabetic Foot Infection), and about 15% had undergone amputation.[1] Likewise, the leading cause of lower extremity amputations in the United States is Diabetic Foot Infections. Diabetic Foot Ulcers have a higher chance of MRSA infection or colonization than non-diabetic foot ulcerations.[2,3]

Traditional culture-based method, which includes growth-based bacteria viability assays, culture, serology, and broth microdilution testing, is time-consuming, and to say the least, laborious. Identification of a causal microorganism by staphylococcal culture and antibiotic resistance testing takes 48-72 hours. Negative culture results can have significant clinical implications, potentially depriving patients of optimal treatment options for their infections.[4]

Knowing the nasal carriage status of a patient serves as targeted antibiotic therapy for patients. Testing for nasal carriage is said to be the usual way for *S. aureus* strain carriage screening.[5] A patient that develops *S. aureus* bacteremia is said to have nasal colonization of the infecting *S. aureus* strain.[6] Therefore, a patient that develops an infection shortly after colonization by a strain of *S. aureus* is likely infected by the colonizing strain. Consequently, patients colonized with MSSA have a lesser likelihood to get MRSA infections.[7] Shrestha et. al in a study emphasized that nasal colonization by *S. aureus* has a great association with *S. aureus* Diabetic Foot Infection.[7] BBL CHROMagar MRSA (C-MRSA) medium is a selective and differential medium that uses MRSA isolates from the anterior nares using swabs and identifies it within 24 hours.

CRISPR-Cas12a, an emerging nucleic acid detection technology in combination with the RAA method, is said to have a high sensitivity detection of MRSA with results consistent with the traditional AST and PCR laboratory diagnostic tool.[9] PCR amplification showed that the *mecA* gene in MRSA could not be observed at the dilution concentration of 105 copies/µl but was detected at the dilution concentration of 10 copies/µl at 60 min of reaction when the RAA-Cas12a system was used.[9] Hence, the novel RAA-Cas12a system helps in pathogen detection, identification of drug-resistance genes, and rapid diagnosis of MRSA infection.[9] CRISPR-Cas12a has a high specificity and sensitivity.

In a study using the fast-track program, Gene Xpert® MRSA/SA SSTI was used to

evaluate the impact of skin and soft tissue infection and the rapid diagnosis of the causal microbe.[11] The molecular test assessed the presence or absence of *staphylococcus aureus* in the skin and soft-tissue infection with results that yielded an accuracy of 97.4% for MSSA and 99.4% for MRSA.[11] The time taken to produce a test result was 4 hours compared to 99 hours of the conventional culture. The results of the study allowed for targeted antimicrobial stewardship for the patient.[11]

Matrix-assisted laser desorption/ionization-time-of-flight mass spectrometry (MALDI–TOF MS), combined with the Machine-learning (ML) model, was built using 20,000 clinical MSSA and MRSA isolates as markers for rapid diagnosis.[12] The purpose of this invention was to allow appropriate antimicrobial treatment and infection-control intervention across Hospitals.

A molecular detection method for *staphylococcus aureus*, Phage-mediated molecular detection (PMMD), incorporates a short incubation of the culture from a body tissue with a *staphylococcus aureus*-specific phage.[13] The process is then followed by RNA extraction of the bacteria and RT-PCR. This method has high sensitivity and specificity. This method was not only able to identify MRSA but was able to differentiate MRSA from MSSA.[13]

METHODS

This study was conducted using a systematic review of literature from three PubMed searches. The first search used the terms ("Methicillin-Resistant *Staphylococcus Aureus*" [All Fields]) OR ("MSSA" [All Fields]) AND ("Rapid Test" [All Fields]), yielding 62 results. The inclusion criteria included articles written in English, research conducted on humans and publication date within 10 years. The exclusion criteria consist of articles that are not free full text on PubMed. 13 articles were used in this study.

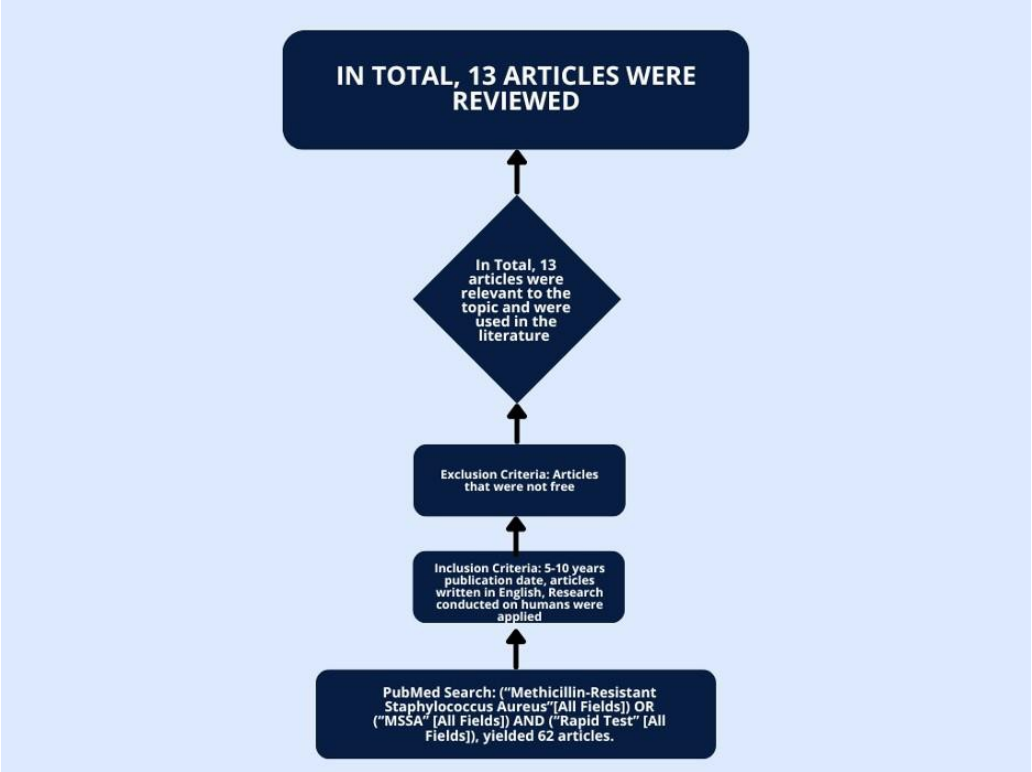


Figure 1. PubMed Article Search with Inclusion and Exclusion Criteria

RESULTS

BBL CHROMagar MRSA Medium

Using the C-MRSA, mauve-colored colonies at 16 to 48 h were reported as MRSA isolates while MSSA isolates grew poorly on the medium.[8] The criteria used during the study to confirm the presence of MRSA were colony morphology, Gram stain morphology, and coagulase testing, ruling out any bacteria that did not fall into these categories.[8] The General specificity of C-MRSA was 99.7%, with an MRSA isolates recovery rate of 95.2%.[8] About 86% of MRSA isolates were recovered at 24 hours and the remaining at 48 hours.[8] Methicillin-resistant coagulase-negative staphylococci were visualized as white or light blue colonies.[8]

CRISPR-Cas12a

The gold standard for MRSA isolate detection is the antimicrobial susceptibility test (AST).[9]

The significance of the RAA-Cas12a detection system was assessed using 83 clinical samples of Staphylococcus aureus strain using AST, Polymerase Chain Reaction (PCR), and RAA-Cas12a detection system. After careful evaluation, 41 MRSA isolates and 42 MSSA isolates were reported for the three diagnostic tools.[9] AST, PCR, and RAA-Cas12a detection systems had the same Negative predictive value, positive predictive value, sensitivity, and specificity indicating that the RAA-Cas12a detection system is consistent with AST and PCR.[9] RAA-Cas12a did not only detect the mecA gene present in MRSA but showed resistant strains of E. coli, S. epidermidis, H. pylori, S. sonnei, K. pneumoniae, and S. typhimurium.[9] The distinguishing factor was that bacteria containing mecA had an amplification curve while the others did

not.[9] PCR amplification showed that the mecA gene in MRSA could not be observed at the dilution concentration of 10^5 copies/µl but was detected at the dilution concentration of 10 copies/µl at 60 min of reaction when the RAA-Cas12a system was used.[9] Recent research on the rapid detection of Norovirus proved that RT-RAA-Cas12a-mediated fluorescent and LFS assay has a 95.7% and 94.3% positive predictive value and 100% negative predictive value.[10]

Gene Xpert® MRSA/SA SSTI

GeneXpert® MSSA/MRSA SSTI management program is a rapid molecular test for skin and soft tissue infection (SSTI).[11] In the Bouza et al. study clinical specimens from patients with SSTI were run through the GeneXpert® MSSA/MRSA SSTI test. Results were effectively communicated to respective and assigned physicians.[11]

The GeneXpert® MRSA/SA SSTI assay was 96.8% accurate; 95% CI 93.7-99.9 in the identification of both MSSA and MRSA.[11] The intervention cohort (GeneXpert®) results with antimicrobial stewardship advice were 4 hours while the comparison cohort (conventional culture) was 99 hours.[11] According to statistical analysis, days of therapy (DOT) for the intervention cohort was 22.0 as compared to 24.3 days for the comparison cohort. Treatment duration per SSTI episode (14.1 intervention vs. 15.0 conventional), Length of Stay (18.6 days for intervention vs 20.7 days for conventional), and related mortality (1 vs. 4 patients).[11]

MALDI–TOF MS

MALDI-TOF is a rapid method for identifying bacterial strains that can provide results within 25 minutes.[12] In contrast to conventional AST methods, which require up to 48 hours for MRSA and MSSA identification, MALDI-TOF in combination with machine learning can provide results within 10 seconds.[12] There is a specific mass-to-charge ratio (m/z) range between 6,590 to 6,599 that can be used to distinguish between Methicillin-resistant Staphylococcus aureus (MRSA) and Methicillin-sensitive Staphylococcus aureus (MSSA) using a digital biomarker.[12]
The use of SHAP and Pseudogel visualization methods can identify molecular features that are important in outcome prediction.[12] Specifically, the UPF0337 protein SACOL1680 (m/z 6,590 to 6,599) of MRSA has been identified as a mutated form of MSSA's UPF0337 protein SA1452 (m/z 6,550 to 6,559), which alters the methicillin binding ligand of MRSA.[12] This drug resistance mechanism is due to methicillin's inability to bind to the UPF0337 protein SACOL1680 (36VI37, m/z 6,593) of MRSA. MALDI-TOF MS has been used to detect the presence of the UPF0337 protein in MRSA isolates at a peak of m/z 6,593.2, while the UPF0337 protein has been identified in MSSA isolates at a peak of m/z 6,550.0.[12] Overall, MALDI-TOF in conjunction with machine learning and protein identification techniques has the potential to rapidly and accurately differentiate between MRSA and MSSA.[12]

Phage-mediated molecular detection (PMMD)

The PMMD uses the approach of incorporating bacteriophages (phage K) into staphylococcus aureus. Phage K, in the lysogenic phase, fuses with the staphylococci aureus genome.[13] RNA from the prophage is then extracted and reverse transcribed by reverse transcriptase.[13]

Finally, PCR amplification is carried out on the gp125 gene of the reverse transcribed RNA. The gp125 gene is specifically selected because it is an intron-containing gene; contains a DNA polymerase enzyme and two group-1 introns.[13] Agarose gel electrophoresis is carried out on the PCR of Phage K infected staphylococci aureus genomic DNA and compared to the reverse-transcribed PCR (RT-PCR) of phage K lysates and staphylococcus aureus cells (SA).[13]
A 2.6kb band served as a diagnostic band corresponding to the spliced RNA (mRNA) while a regular PCR of genomic phage K DNA should produce a single band of 4.6 kb.[13]

DISCUSSION

BBL CHROMagar MRSA medium directly detects MRSA isolates from anterior nares surveillance swabs.[8] The C-MRSA medium had a higher recovery rate than the traditional susceptibility testing such as broth microdilution, oxacillin screen agar, PBP2′ latex agglutination, cefoxitin disk diffusion, and mecA PCR.[8]
Due to the specificity of the C-MRSA medium, a mauve colony that resembles staphylococcus can be reported as MRSA at 24 hours.[8] The specificity can be increased to as high as 100% if an optional coagulase test was included. The use of an additional coagulase test becomes necessary if the mauve colony is yet to be visualized in 48 hours. According to the study, C-MRSA could detect dual infection by MSSA and MRSA.[8] C- MRSA had an overall specificity of 99.7%, comparable to the 5 conventional susceptibility testing identified in the study.[8] The research yielded a 95% isolate rate of MRSA while the traditional medium was 86%.[8]

The RAA-Cas12a method is a less laborious process, requiring a water bath or a small incubator. In addition, the process can function at 37^{o}C does not require complex thermal cycling.[9] Nowadays, the reverse transcription-polymerase chain reaction (RT-PCR) is one of the most used methods for the detection of bacteria, however, this method requires the use of technical laboratory types of equipment and specialized professionals.[10] The innovation of ingraining the RAA-Cas12a method in lateral slip is an efficient nucleic acid-based diagnostic tool. The lateral slip uses visual highlighting nucleic acid to detect specific resistant genes or gene mutations.[9]

Over 20,000 clinical MSSA and MRSA isolates were used to build a Machine Language (ML) model to recognize and differentiate MSSA from MRSA and discovered reliable markers with possible drug-resistant properties.[12] The machine learning technique is excellent at mapping molecular feature peaks and identifying relationships in large data sets of MALDI-TOF spectra.[12] MALDI-TOF combined with the ML model rapidly identified MRSA or MSSA in about 10 seconds as compared to about 18 h to 48 h spent by conventional AST methods.[12]

The GeneXpert® MRSA/SA SSTI assay is FDA approved for the diagnosis of SSTI directly on clinical specimens.[11] The accuracy of this molecular test was 97.4% for MSSA and 99.4% for MRSA.[11]

Phage-mediated molecular detection (PMMD) is a novel molecular technique that detects and assesses bacterial resistance to antibiotics. PMMD can distinguish MRSA from MSSA.[13] The method is fast; with an estimated implementation time of ~3 hours or ~5 hours.[13] The time variation is dependent on whether only a detection

process is carried out or detection and an antibiotic sensitivity test are conducted.[13] Finally, the simplicity of PMMD results in less genetic engineering of the phage; implying that this technique can be efficiently extended to other bacterial species.[13]

CONCLUSION

As established in the Flayhert study, C-MRSA can satisfy the need for a rapid diagnostics tool in the community and healthcare facilities.[8] The RAA-Cas12a method can be used easily in primary healthcare facilities and requires less laborious equipment.[9] The lateral flow strip technology is rapid and portable easy gene identification with the naked eye.[9] Nevertheless, these rapid screening tools cannot substitute more sensitive and specific methods of MRSA detection.[12] More research is being done as additional development such as a Phage cocktail that can cover most bacterial strains of a given species.[13]

MRSA foot infections can be more difficult to treat than other types of bacterial infections (MSSA) because MRSA is resistant to some commonly used antibiotics. As a result, it is critical for healthcare providers to detect MRSA in patients with foot infections as soon as possible to select the most appropriate treatment. The key to successful rapid diagnostic testing is creating a link between the clinical microbiologists and the antimicrobial stewardship team or responsible physicians.[11] Results are communicated to guide the decision on suitable antimicrobial therapy.[11] It is therefore recommended that additional research be conducted to establish the efficacy of enhancing communication between clinical microbiologists, antimicrobial stewardship teams, and podiatrists in guiding the selection of appropriate antimicrobial therapy. Such efforts are expected to contribute to a reduction in mortality rates.

Podiatry plays a critical role in the prevention and management of lower limb infections, including those caused by MRSA and MSSA. The implementation of diagnostic techniques such as Nasal swabs, Real-time PCR, and novel molecular tests such as Gene Xpert® MRSA/SA SSTI, CRISPR-Cas12a, BBL CHROMagar MRSA, and Phage-mediated molecular detection can significantly improve diagnostic accuracy and guide appropriate treatment decisions. Future studies focusing on the use of these diagnostic techniques in podiatry should aim to investigate their efficacy in identifying MRSA and MSSA infections in a timely and cost-effective manner.

For example, studies have shown that the use of Nasal swabs can improve the detection of MRSA colonization and reduce the spread of the pathogen in Hospital and community settings. Real-time PCR has also been demonstrated to provide rapid and accurate identification of MRSA and MSSA infections, enabling prompt initiation of targeted antimicrobial therapy. Additionally, Gene Xpert® MRSA/SA SSTI is a promising technique that can identify MRSA and MSSA infections in wound samples, while CRISPR-Cas12a can rapidly differentiate between MRSA and MSSA strains. BBL CHROMagar MRSA is a selective chromogenic agar medium that can detect MRSA with high specificity and sensitivity, while Phage-mediated molecular detection can detect MRSA and MSSA infections using bacteriophages that target specific bacterial strains. Studies evaluating the use of these techniques in podiatry can

provide valuable insights into their practicality and usefulness in the clinical setting.

Overall, the use of rapid and accurate diagnostic techniques for the detection of MRSA and MSSA in podiatry can enhance infection control and antimicrobial stewardship practices. Further studies are needed to validate these techniques in the podiatric setting and identify opportunities for their incorporation into routine clinical practice.

REFERENCES

1. Ndosi M, Wright-Hughes A, Brown S, Backhouse M, Lipsky BA, Bhogal M, et al. Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study. Diabet Med. 2018;35(1):78–88.

2. Cadena J, Thinwa J, Walter EA, Frei CR. Risk factors for the development of active methicillin-resistant Staphylococcus aureus (MRSA) infection in patients colonized with MRSA at hospital admission. Am J Infect Control. 2016;44(12):1617–21.

3. Lin J, Xu P, Peng Y, Lin D, Ou Q, Zhang T, et al. Prevalence and characteristics of Staphylococcus aureus and methicillin-resistant Staphylococcus aureus nasal colonization among a community-based diabetes population in Foshan, China. J Diab Investig. 2017;8(3):383–91.

4. Chen K, Wang Y, Yuan Y, Qin W, Sheng Y-J, Ahmed S, Sun C, Deng C-L and Ojha SC. Molecular Tools for Guiding Therapy in Patients With Staphylococcal Bone and Joint Infections: A Diagnostic Test Accuracy Meta-analysis. Front. Endocrinol. 2022;13:792679. doi: 10.3389/fendo.2022.792679.

5. Wertheim HF, Melles DC, Vos MC, et al. The role of nasal carriage in Staphylococcus aureus infections. The Lancet Infectious Diseases. 2005;5(12):751-762. doi:10.1016/s1473-3099(05)70295-4 .

6. von Eiff C, Becker K, Machka K, Stammer H, Peters G. Nasal Carriage as a Source of Staphylococcus aureus Bacteremia. New England Journal of Medicine. 2001;344(1):11-16. doi:10.1056/nejm200101043440102.

7. Shrestha NK, Fraser TG, Gordon SM. Methicillin resistance in Staphylococcus aureus infections among patients colonized with methicillin-susceptible Staphylococcus aureus. Clinical Microbiology and Infection. 2019;25(1):71-75. doi:10.1016/j.cmi.2018.03.045.

8. Flayhart D, Hindler JF, Bruckner DA, et al. Multicenter Evaluation of BBL CHROMagar MRSA Medium for Direct Detection of Methicillin-Resistant Staphylococcus aureus from Surveillance Cultures of the Anterior Nares. Journal of Clinical Microbiology. 2005;43(11):5536-5540. doi:10.1128/jcm.43.11.5536-5540.2005.

9. Wang Y, Liang X, Xu J, Nan L, Liu F, Duan G and Yang H. Rapid and Ultrasensitive Detection of Methicillin-Resistant Staphylococcus aureus Based on CRISPR-Cas12a Combined with Recombinase-Aided Amplification. Front. Microbiol. 2022;13:903298. doi: 10.3389/fmicb.2022.903298.

10. Qian W, Huang J, Wang T, Fan C, Kang J, Zhang Q, Li Y, Chen S. Ultrasensitive and visual detection of human norovirus genotype GII.4 or GII.17 using CRISPR-Cas12a assay. Virol J. 2022 Sep 17;19(1):150. doi: 10.1186/s12985-022-01878-z. PMID: 36115975; PMCID: PMC9482751.

11. Bouza E, Onori R, Semiglia-Chong MA, Álvarez-Uría A, Alcalá L, Burillo A. Fast track SSTI management program based on a rapid molecular test (GeneXpert® MRSA/SA SSTI) and antimicrobial stewardship. J Microbiol Immunol Infect. 2020 Apr;53(2):328-335. doi: 10.1016/j.jmii.2018.07.008. Epub 2018 Aug 31. PMID: 30224283.

12. Yu J, Tien N, Liu YC, Cho DY, Chen JW, Tsai YT, Huang YC, Chao HJ, Chen CJ. Rapid Identification of Methicillin-Resistant Staphylococcus aureus Using MALDI-TOF MS and Machine Learning from over 20,000 Clinical Isolates. Microbiol Spectr. 2022 Apr 27;10(2): e0048322. DOI: 10.1128/spectrum.00483-22. Epub 2022 Mar 16. PMID: 35293803; PMCID: PMC9045122.

13. Malagon F, Estrella LA, Stockelman MG, Hamilton T, Teneza-Mora N, Biswas B. Phage-Mediated Molecular Detection (PMMD): A Novel Rapid Method for Phage-Specific Bacterial Detection. Viruses. 2020; 12(4):435. https://doi.org/10.3390/v12040435.

SECOND RAY PATHOLOGY FOLLOWING 1ST RAY PROCEDURES AS RELATED TO METATARSAL PROTRUSION DISTANCE. DO PREOPERATIVE LENGTHS MATTER?

Dolly Basaldua, DPM; Emanoil Shafik, DPM; Andrew Bastauross DPM; Anthony Ghali, BS

ABSTRACT

Introduction

Postoperative metatarsalgia is a painful condition characterized by tenderness and inflammation at the plantar aspect of the metatarsal heads following surgical shortening of the 1st ray with an osteotomy. The lesser digits refer to digits 2 through 5 which receive the transferred load from the ground reaction force when weight bearing. Shortening of the first ray is a common outcome during osteotomy and arthrodesis procedures that address common foot pathologies including hallux valgus, hallux limitus and/or hallux rigidus deformities. Excessive shortening of the first ray can potentially impact the biomechanics and weight distribution in the foot. Altering the normal length relationship between the first and lesser rays may result in abnormal loading patterns and increased stress on the remaining metatarsals, particularly the second metatarsal. This change in the foot's mechanics can lead to metatarsalgia of the lesser rays, where the second to fifth metatarsals bear excessive weight and pressure during gait. The abnormal redistribution of forces causes increased pressure and strain on the lesser rays, leading to pain, inflammation, and other associated symptoms. the altered biomechanics resulting from the first ray shortening can affect the stability of the foot. The arch structure may be compromised, leading to excessive flattening of the foot and a loss of shock absorption capacity. As a result, the metatarsals experience greater impact and repetitive stress during activities, contributing to the development of metatarsalgia.

The aim of this study was to determine the incidence of development of postoperative metatarsalgia of the lesser rays after shortening of the first ray for correction of hallux valgus, hallux varus, hallux limitus, and/or hallux rigidus deformity.

Study Design

This is a retrospective observational study that is examining data from operative outcomes from the New York College of Podiatric Medicine: Foot Clinic of New York following Institutional Review Board approval.

Methods

Ninety-nine procedures were performed from 2014 to 2019 and evaluated. Data from several surgical osteotomies were collected and analyzed. Hallux valgus angle and intermetatarsal angle were measured preoperatively to determine the severity of the deformity and aid in surgical planning, then again during the final follow-up after the selected surgical procedure had been performed.The metatarsal protrusion distance was measured to assess the amount of residual shortening of the 1st ray and relative metatarsal protrusion. Charts were then reviewed for the development of post-operative metatarsalgia, and responses were split into two groups based on the chi squared test of 4.68 mm. Analysis of the responses was then done using Excel. The data collected was analyzed via the STATA analysis program.

Results
Average pre-op metatarsal protrusion distance was 2.9 mm. Post-operative metatarsal protrusion distance averaged 4.58 mm. Compared to pre-op measurements, there was a difference of +/- 3.8 mm. At follow up, 29 patients reported subsequent metatarsalgia with > 4.68 mm and 8 patients reported metatarsalgia < 4.68 mm.
Conclusion
It is believed that excessive shortening of the first metatarsal should be avoided during these procedures to decrease the occurrence of postoperative transfer metatarsalgia. The benefit of concomitant shortening of lesser metatarsal at index procedure is unknown.

Keywords: metatarsal protrusion, metatarsalgia, relative metatarsal length, hallux valgus

Levels of Evidence: 3

INTRODUCTION

One of the most popular operations in foot and ankle surgery is reconstructive first ray surgery for hallux abducto valgus deformity, degenerative joint disease, and hallux varus. Complications of first ray procedures include, but are not limited to, under correction, overcorrection, recurrence, elevation, excessive plantarflexion, shortening, and non-union. Shortening of the first metatarsal during hallux valgus restoration has long been thought to cause postoperative transfer metatarsalgia. In some cases, however, shortening can be useful for treating severe abnormalities or easing tight joints. The goal of this study is to see if surgical procedures cause metatarsal shortening and how much shortening of the first metatarsal may be tolerated from a biomechanical standpoint. It is expected that the excessive shortening of the first ray due to surgery or from a naturally short first metatarsal will significantly alter the metatarsal parabola, causing metatarsalgia and other secondary pains due to modified gait biomechanics. [1-7]

METHODS

The study was approved by the institutional review board of the New York College of Podiatric Medicine/Foot Clinics of New York. Between 2014 and 2019, a total of 99 first ray procedures were performed, 25 were lost to follow-up. Exclusion criteria included prior 1st or lesser ray procedure(s), revisional procedure(s), history of trauma, infection, and Charcot neuropathy. These patients had a pre-operative diagnosis of hallux valgus, hallux varus, hallux limitus, or hallux rigidus deformity. There were 55 females and 19 males used for this study. The procedures included the Austin, Scarf, closing base wedge osteotomy, Reverdin Green, hemi-implant, Lapidus, Youngswick, Reverdin Laird Todd, Reverdin Laird, Akin, 1st metatarsophalangeal joint arthrodesis, 1st interphalangeal joint arthrodesis, Kalish, Keller and off-set V osteotomies. The hallux valgus angle and intermetatarsal angle were measured preoperatively and again during the final follow-up after the selected surgical procedure had been performed. All measurements included in this study were taken from radiographic images. The average preoperative metatarsal protrusion distance was calculated to be 2.9 mm. The pre-op Seiberg index averaged 0.08 cm. Patients were asked about their past medical history such as CAD, diabetes, autoimmune disease, hyperparathyroidism, CKD, chronic liver disease, and COPD. Their social history of tobacco, alcohol use and recreational drug use was taken into consideration. The charts were reviewed for the development of post-operative metatarsalgia. Patients were evaluated at follow up. The pain levels were self reported using a visual analog scale of pain ranging from 1-10 on the VAS Score. Diagnostic x-ray images were used to assess the 2nd metatarsal length. The metatarsal protrusion length was recorded for patients who presented with metatarsalgia and stated they had pain regardless of pain level indicated on the VAS Scale. The responses were split into two groups based on the chi squared test of 4.68 mm. This number reflected the metatarsalgia threshold postoperatively. Analysis of the responses was then done using Excel. The data collected was analyzed via the STATA analysis program, which incorporated the Excel data that was collected from the patient pool. The measurements were done using the program's defined reference points for metatarsal protrusion via AccVue Cloud.

RESULTS

The mean age of the patients was 51 years, and the female to male ratio was 3:1. The average pre-op metatarsal protrusion distance was 2.9 mm. Post-op metatarsal protrusion distance averaged 4.58 mm. Compared to pre-op measurements, there was a difference of +/- 3.8 mm. Post-op Seiberg index was also calculated to be an average of 1 mm. All measurements were calculated from weight bearing radiographic images. At follow up, 29 patients reported subsequent metatarsalgia with > 4.68 mm and 8 patients reported metatarsalgia < 4.68 mm. The time to onset after surgery ranged from 4 months to 3 years. The Chi-squared statistic for the collected data was 4.33 mm with a p-value 0.00067, therefore validating the findings and data as presented.

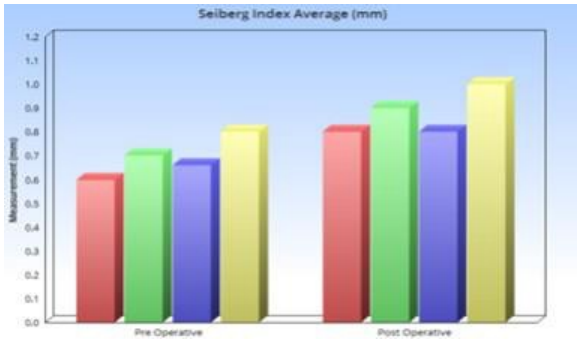


Figure 1: Seiberg Index Average in measured millimeters comparing preoperative vs post operative.

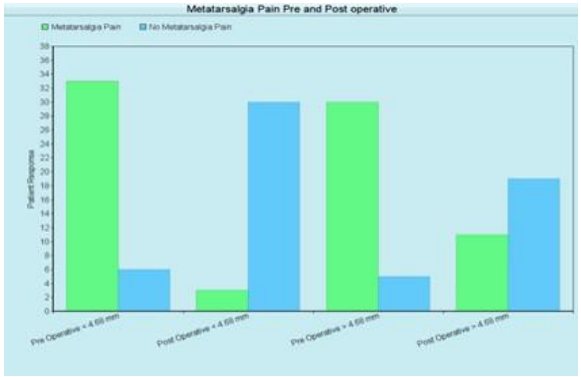


Figure 3: Patient measures of reported metatarsalgia pain, pre and post operatively regarding operative length.

DISCUSSION

The development of transfer metatarsalgia after first ray surgery presents a challenge to even experienced foot and ankle surgeons. This pathomechanical outcome is caused by loss of first ray function. [8,9] Several studies have reported on the development of transfer metatarsalgia due to first ray shortening, which varies depending on the procedure. [1,2,4,10] The amount of shortening tolerated can vary between patients, where some may tolerate more shortening than others based on their gait pattern. Evidence has shown that the metatarsal length is a critical variable within the third rocker, therefore these patients are more likely to develop central ray overload from 1st ray insufficiency.[11] Toth et al[10] reported on 240 patients and found a positive correlation between metatarsalgia and shortening of metatarsals 2, 3, and 4. The average shortening recorded was 3.8 +/- 1.8 mm. Ahn et al [2] reported on 185 feet and found that when shortening was less than 5.8 mm, no identifiable transfer problems arose. Nakagawa el al[1] reported that the upper limit of correction was 3 mm of shortening. On the contrary, Geng et al[4] reported that up to 6 mm of shortening can be considered safe. Our results depicted a similar trend, with the data suggesting a neutral middle ground between the previously reported literature. The data collected validated the hypothesis that the lesser the degree of shortening, the less likely the patient would develop metatarsalgia ($p < 0.05$).

LIMITATIONS

Limitations of the study include loss of patient population due to failure to follow up with the studies practitioner as well as a discrepancy in the varying length of time for follow up. Since no patients had a shortening lesser metatarsal osteotomy at the

time of the index procedure, a definitive recommendation cannot be ascertained as to whether to address the lesser rays prophylactically to minimize risk of metatarsalgia from expected shortening procedures. Further studies and data aggregation is vital to further understand this relationship and better treat patients.

CONCLUSION

Surgical osteotomies that cause shortening of the first metatarsal can develop transfer metatarsalgia depending on the surgical procedure and the total amount of shortening. This study and previous research report that 3 to 6 mm of shortening is considered safe enough to achieve biomechanical stability while also limiting the risk of complication of post-operative transfer metatarsalgia.

AUTHORS' CONTRIBUTIONS

D. Basaldua and E. Shafik, designed and conceptualized the study, conducted data collection and analysis, and drafted the manuscript. Both authors provided expertise in statistical analysis and helped with data interpretation, as well as contributed to manuscript revisions.
A. Ghali & A. Bastauross assisted in study design, data collection and analysis, and contributed to the writing and revision of the manuscript. Both authors assisted with study design, data analysis, and manuscript revisions.

All authors reviewed and approved the final version of the manuscript.

STATEMENT OF COMPETING INTERESTS

The authors have no conflicts of interest.

REFERENCES

1. Nakagawa, S., Fukushi, J. I., Nakagawa, T., Mizu-uchi, H., & Iwamoto, Y. (2016). Association of Metatarsalgia After Hallux Valgus Correction With Relative First Metatarsal Length. Foot & Ankle International, 37(6), 582–588. https://doi.org/10.1177/1071100716634792
2. Ahn, J., Lee, H. S., Seo, J. H., & Kim, J. Y. (2016). Second Metatarsal Transfer Lesions Due to First Metatarsal Shortening After Distal Chevron Metatarsal Osteotomy for Hallux Valgus. Foot & Ankle International, 37(6), 589–595. https://doi.org/10.1177/1071100715627350
3. Guidelines for reconstructing the metatarsal parabola with the shortening osteotomy. (1991). Journal of the American Podiatric Medical Association, 81(8), 406–413. https://doi.org/10.7547/87507315-81-8-406
4. Geng, X., Shi, J., Chen, W., Ma, X., Wang, X., Zhang, C., & Chen, L. (2019). Impact of first metatarsal shortening on forefoot loading pattern: a finite element model study. BMC Musculoskeletal Disorders, 20(1). https://doi.org/10.1186/s12891-019-2973-6
5. Liabakh, A., & Rudenko, R. (2020). Modern status of the problem of hallux valgus surgery HALLUX VALGUS (Review). Visnyk Ortopedii Travmatologii Protezuvannia, 1(104), 77–84. https://doi.org/10.37647/0132-2486-2020-104-1-77-84
6. Dominic, G., Munuera, P. V., & Lomas, M. (2009). Metatarsal Protrusion Angle. Journal of the American Podiatric Medical Association, 99(1), 49–53. https://doi.org/10.7547/0980049
7. Liabakh, A., & Rudenko, R. (2020). Modern status of the problem of hallux valgus surgery HALLUX VALGUS (Review). Visnyk Ortopedii Travmatologii

Protezuvannia, 1(104), 77–84. https://doi.org/10.37647/0132-2486-2020-104-1-77-84
8. Scioli MW. Complications of hallux valgus surgery and subsequent treatment options. (1997). Foot Ankle Clin, 2, 719-39.
9. Lehman DE. (2003). Salvage of complications of hallux valgus surgery. Foot Ankle Clin, 8, 15-35.
10. Toth K., Huszanyik I., Kellermann P., Boda K., Rode L. (2007). The Effect of First Ray Shortening in the Development of Metatarsalgia in the Second through Fourth Rays After Metatarsal Osteotomy. FAI, 28(1), 61-63.
11. Maceira E., Monteagudo M. (2014). Transfer Metatarsalgia Post Hallux Valgus Surgery. Foot Ankle Clin N Am, 19, 285-307.

Stem cell based therapy for peripheral arterial disease: A Literature Review

Ajay Patel BS; Caroline Downs, BS; Taylor Furtado, BS

ABSTRACT

Introduction

Peripheral arterial disease (PAD) is associated with systemic atherosclerosis, which most commonly affects the lower extremities. There is a high level of mortality and morbidity that accompany the disorder. Consequences of PAD include pain, ulceration, gangrene, and amputation. The current treatment options are mainly revascularization, either endovascularly or surgically, to reconstruct blood circulation. The problem with current therapies is a lot of patients are not eligible for the treatment due to variant anatomy, cost, recurrence of disease post treatment or various other comorbidities.[4] For this reason, other promising strategies are being researched to provide an alternative for more effective treatment. In this literature review, we plan to evaluate the use of stem cell therapy as a treatment option for peripheral arterial disease. We evaluated different studies and their use of progenitor cells, growth factors, cytokines, and other stem cell associated technology to promote angiogenesis. We assessed all aspects of the procedure from the type of stem cell used, administration to the patient, safety aspects and overall effectiveness of the treatment.

Most of the studies evaluated the success of the procedure based on ankle brachial index (ABI), pain at rest and decreased risk for amputation. Overall, we are hoping to show a comprehensive evaluation of the current state of research in this field and any possible obstacles associated with implementing the treatment going forward.

Methods

A PubMed database search was conducted using “stem cell” AND “cell therapy” AND “peripheral artery disease”. Inclusion criteria were added as: English, RCTs, Meta-Analysis, Systematic Review, Human Subjects, and Published within 5 years. Lastly, exclusion criteria were applied to studies not using stem cells and studies not specific for peripheral artery disease.

Results

From the studies reviewed, it was determined that various methods of stem cell therapies resulted in significant improvements in both ABI and TcPO2 levels when compared to control groups. Improvement was also reported regarding severity of symptoms and rate of wound healing in the treatment groups, along with improvement in pain level post-treatment when compared to patients’ pain level prior to treatment. However, there was no evidence of significant change in angiogenesis via various types of imaging between the different treatment and control groups. It should be noted that there was data that reported an improvement in flow scores in the treatment group via MR angiography, and that co-administration of JH4 with human adipose tissue-derived mesenchymal stem cells (ASCs) limited apoptosis of the ASCs, therefore increasing tissue reperfusion.

Conclusion

The findings from the studies analyzed in this literature support the conclusion that stem cell therapy in patients with PAD can improve patients' symptoms and quality of life. There is mixed evidence on whether stem cell therapy has the capability for angiogenesis and improvement of flow in occluded arterial vessels.

Key Words: Stem cell, PAD, ABI, TcPO2, ulcer, ischemia, pain, angiogenesis

Level of Evidence: 4

INTRODUCTION

Peripheral arterial disease (PAD) is an atherosclerotic disease affecting all the noncoronary vasculature, especially the peripheral arteries of the lower extremity.[1, 2] PAD has become a major healthcare issue, affecting more than 8 million people in the United States and more than 236 million people worldwide, as of 2015.[3] Peripheral arterial disease (PAD) is characterized by occlusion of arterial blood flow in the lower extremity facilitated by atherosclerotic plaques, which are composed of excess cholesterol, free fatty acids, and calcium. These plaques subsequently harden the arteries and cause stenosis of the arterial walls, ultimately decreasing overall blood flow to the distal limb[3]. Severe occlusion of lower extremity arteries with PAD can lead to critical limb ischemia. This can manifest as intermittent claudication, pain at rest, ulcerations of the lower extremities and gangrene. Pain is a common symptom that occurs with PAD due to narrowing of the blood vessels and the hostile environment that occurs in the setting of low tissue perfusion. Pain initially develops while walking and is relieved at rest, but can worsen to pain at rest with increasing severity of the disease. Controlling pain in PAD patients is an important treatment that can greatly increase the patient's quality of life. Eventual consequences of PAD may also include limb amputation. There are several risk factors associated with PAD that have been reported, including age, diabetes mellitus, smoking, hypertension, hypercholesterolemia, and elevated C-reactive protein.[1] PAD can be diagnosed in an office setting by calculating the ankle brachial index (ABI). This is done by measuring blood pressure at the arm and ankle. A normal ABI value is 1.0 to 1.2, while the diagnostic ABI value for PAD is anything below 0.9. Due to Kortokoff sounds being quiet or inaudible in the lower extremity with a stethoscope, ABI is typically measured with a doppler.[1]

Current conservative treatments for PAD include statins, ACE-inhibitors, antiplatelet agents, and other anticoagulants. These drugs have been shown to reduce severity of PAD along with morbidity and mortality of upstream cardiovascular events. However, a major drawback to these treatments is that the drugs themselves have little to no effect on the symptoms of PAD localized to the lower extremity.[5] The main treatment specified for the lower extremity related to PAD is revascularization of the affected arteries. Classically, by utilizing surgical and endovascular approaches such as angioplasty and arterial bypass grafting. These methods are widely accepted and practiced, however 20-40% of symptomatic patients are not candidates for these procedures due to variant anatomy, cost, recurrence of disease post treatment or various other comorbidities.[4] The ineffectiveness of drug therapies and the multiple complications associated with the surgical approach has driven the progression of a new type of therapy focused on utilizing the angiogenic properties of stem cells to treat the lower extremity focused symptoms of PAD.

The overarching category of stem cells that have been used in clinical trials to treat PAD are mainly mesenchymal stem cells (MSCs). These cells can be seen in many diverse tissues, such as umbilical cord blood, adipose tissues, dental pulp and virtually all postnatal tissues[3]. Certain stem cells have been clinically tested over the years, while others have only more recently entered clinical trials. Previously, there was a focus on progenitor stem cells from bone marrow or peripheral blood. The progenitor cells that have been studied are bone marrow-derived

mononuclear cells (BMMNCs) and peripheral blood mononuclear cells (PBMNCs). Sub-distinctions of these cells are granulocyte colony-stimulating factor mobilized PBMNCs, expanded BMMNCs and enriched CD34+ BMMNCs. Circa 2013, there was a pivot toward studying the efficacy of placenta-derived mesenchymal stromal cells.[1] Other studies have also made use of adipose tissue-derived mesenchymal stem cells (ASCs) to improve vascular perfusion.[3]

The overall objective of stem cell therapy for treatment of PAD is to achieve therapeutic angiogenesis. Therapeutic angiogenesis is the growth of novel, non-pathologic blood vessels using stem cells that distribute blood flow around the atherosclerotic artery and into the target tissue (lower extremity).[1] These stem cells, specifically ASCs, release angiogenic factors, such as vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), insulin-like growth-1, and extracellular vesicles. These factors stimulate both angiogenesis and arteriogenesis, making ASCs favorable options for treatment. ASCs also possess the ability to differentiate into cardiovascular lineages.[3] Other growth factors, including fibroblast growth factor (FGF) and hypoxia-inducible factor-1 (HIF-1), have also been evaluated for their angiogenic effects and furthermore their revascularization capability.[1] The intention with use of these factors in treatment of PAD is to increase overall perfusion of tissues and to deliver oxygen to the affected ischemic extremities.

Byproducts of reactive oxygen species, such as H2O2, are released into the environment in the setting of oxidative stress, such as with PAD. These byproducts induce apoptosis by damaging DNA, lipids, and proteins within the cell. A protein that works interdependently with the oxidative stress response is Lamin A/C. Lamin A/C leads to chromatin condensation and nuclear shrinkage, seen in apoptosis. A novel chemical compound, JH4, was found to act as an inhibitor of Lamin A-progerin binding. The utilization of this compound in combination with human adipose tissue-derived mesenchymal stem cells (ASCs) may improve the efficacy of treatment.[3]

This paper is a review of multiple studies that assess the efficacy of stem cell therapy for the treatment and management of peripheral arterial disease.

METHODS

A PubMed database search was conducted using “stem cell” AND “cell therapy” AND “peripheral artery disease.” It yielded 584 articles. Inclusion criteria were applied as: written in English, RCTs, Meta-Analysis, Systematic Review, Human Subjects, and Published within five years, yielding 27 articles. Lastly exclusion criteria were applied as studies not using stem cells and studies not specific for peripheral artery disease, yielding eight articles used for this literature review.

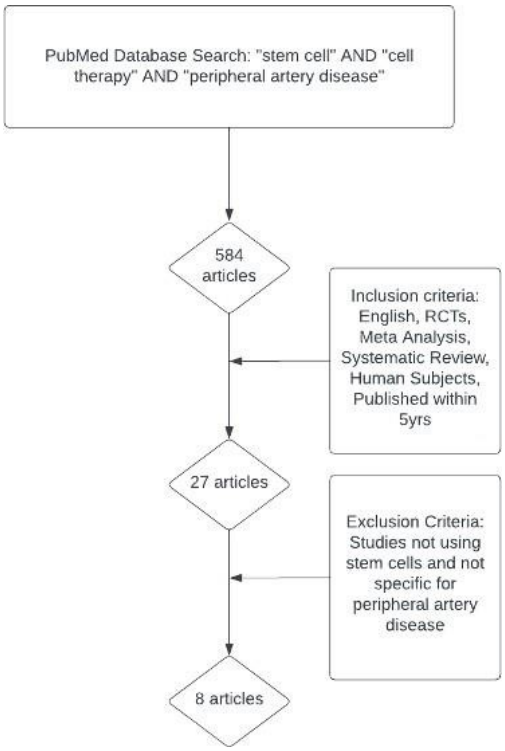


Figure 1. Summary of articles obtained after inclusion and exclusion criteria were applied on PubMed.

RESULTS

The Therapeutic Angiogenesis using Cell Transplantation (TACT) study conducted by Tateishi-Yuyama et al. in 2002, was one of the first studies done looking at bone marrow mononuclear stem cells (BMMNC) as a means of treating limb ischemia and therefore PAD. This study began with a pilot study that consisted of 25 participants with chronic conditions of critical limb ischemia who did not qualify for revascularization. The study focused on unilateral ischemia with the inclusion criteria of an ankle brachial index (ABI) of less than 0.6, pain at rest and/or non-healing ulcers. The group was injected with BM-derived mononuclear cells ($1.6 +/- 0.6 \times 10^9$) at 40 points in the gastrocnemius of their ischemic limb. The same participants were injected in the less ischemic leg (ABI >0.6) with saline solution to serve as the control. The results showed improved ABI, transcutaneous oxygen pressure (TcPO2) and rest pain.[6] The study was furthered with randomized control testing that looked at 22 patients with bilateral leg ischemia (ABI<0.6). The patients were randomly given the active treatment of BMMNC in one leg or unstimulated peripheral blood mononuclear cells which served as a placebo. The results showed the ABIs of the treatment group increased by 0.1 at four and twenty-four weeks, while no significant change occurred in the placebo group (p<0.0001). The other measures showed statistically significant improvements in transcutaneous oxygen pressure, rest pain and pain free walking when looking at the treatment group.[2]

Botham et al. performed a systematic review discussing 13 clinical trials of adult stem cell therapy for treatment of PAD. They selected studies using either BMMNCs or PBMNCs, each with a follow-up time frame ranging from 1 week to 12 months. The experimental patient counts ranged from 10 patients to 51 patients. The control patient counts ranged from 9 patients to 54 patients. They then put together a chart of the results of each trial they selected, categorized based on if they showed improvement in ABI, TcPO2 or limb salvage. Every study that they assessed had either shown improvement in ABI, improvement in limb salvage or improvement in both. Based on transcutaneous oxygen pressure (TcPO2), it seems to have not been studied as widely because only six studies out of the 13 had results on the effect on TcPO2. Of these 6 studies, 5 reported an increase in TcPO2 while 1 reported no effect.[1]

Takagi et al. conducted a study comparing the efficacy of controlled release fibroblast

growth factor (FGF) versus bone marrow mononuclear stem cell implantation (BMCI) for the treatment of PAD. A total of 25 patients were used all of whom were confirmed to have PAD with no prior surgical intervention. Along with this, the patients were classified as having severe PAD with risk of limb amputation at various hospitals. The patients were divided into a BMCI group (n=15) and a FGF group (n=10). Due to the patients having severe PAD and limb ischemia, the researchers deemed it unethical to use control patients receiving no treatment in the study. The FGF utilized in the study was in the form of a b-FGF-incorporated biodegradable hydrogel (600 ug) that was injected in 1mL saline solution at 20 injection sites under ultrasound guidance. The BMCI therapy was conducted by retrieving bone marrow from bilateral iliac bones. The bone marrow was then processed through a cell separator and a mononuclear cell fraction was sorted. 1mL injections containing ($0.4–5.1 \times 10^{10}$ cell) of stem cells were given in 3x3cm grids across both legs with a total of 70 injections per leg. Visual analog pain scale (VAS), ^{99m}technetium-tetrofosmin (Tc-TF) scintigraphy, transcutaneous oxygen tension (TcPO2), and ankle-brachial index (ABI) were evaluated before and 4 weeks after each treatment, and 2-year prognosis was determined. The results of the study showed a significant improvement in both VAS and TcPO2 scores. The VAS score decreased from 67 ± 15 to 4 ± 5 ($p<0.01$) in the FGF groups and 67 ± 42 to 5 ± 9 mm ($p<0.01$) in the BMCI group. TcPO2 levels showed a significant increase from 16 ± 14 to 47 ± 17 ($p < 0.01$) in the FGF group and from 13 ± 13 to 37 ± 21 mmHg ($p < 0.01$) in the BMCI group. Tc-TF and ABI had no significant change. Along with this the 2-year prognosis had no significant change after the 2 year follow up or between the 2 groups. This study concluded that FGF and indirectly BMCI both have therapeutic uses for the treatment of PAD symptoms. Along with this the efficacy and BMCI therapies have comparable efficacies and could be used interchangeably. A major drawback the authors state in the study is that treatment and group selection were not randomized due to ethical concerns. They stated that this affects the BMCI group more than the FGF group due to patients deemed to require additional surgical interventions such as wound debridement being placed preferentially in the BMCI group. Along with this the study is an open labeled which could affect the VAS score, however not the TcPO2, ABI, or Tc-TF values since they are measured by equipment.[8]

Similarly, Huang et al. studied cytokines as a way to avoid bone marrow aspiration. This study looked at how granulocyte colony stimulating factor (G-CSF) mobilized peripheral blood mononuclear cells (PBMNCs). The trial included 28 diabetic patients that were randomly assigned to treatment groups. The treatment group received G-CSF for five days in which Peripheral Blood Mononuclear cells (PBMNCs) were collected from circulation then delivered intramuscularly to the patient's ischemic limb. The control group received conventional wound care[6]. The results at 3 months showed that none of the patients in the treatment group underwent amputation while 36% of patients receiving conventional wound care had to undergo amputation ($P=0.007$).[2] Other parameters that showed improvement were pain-free walking, healing of diabetic foot ulcers and ABI. It is important to note that Huang et al. furthered their studies and concluded G-CSF-stimulated PBMNC may have a lower regenerative potential as compared to BMMNC.[6]

In a randomized control trial to compare bone marrow mesenchymal cells as a treatment for PAD, Lu et al. compared bone marrow mesenchymal stem cells (BMMSCs) and bone marrow mononuclear cells (BMMNCs). The trial consisted of 41 diabetic patients with bilateral leg ischemia that were randomly given BMMSC treatment, BMMNC, or a control placebo consisting of a saline solution. The results indicate at 24 weeks, the BMMSC and BMMNC groups showed a significant improvement in ABIs, TcPO2, and pain free walking as compared to the control. In addition, MR angiography showed significantly higher scores in treatment groups, with significantly greater improvements in the BMMSC group. Both treatment groups showed 100% ulcer healing in the 24 weeks, while the control showed an 80% healing rate. The BMMSC group healing occurred by week 8 and the BMMNC group healing occurred by week 12.[2]

A multi-part clinical study conducted by Heo et al. aimed to determine the efficacy of co-administration of JH4 with human adipose tissue-derived mesenchymal stem cells (ASCs). This was done to limit apoptosis of the ASCs and therefore increase tissue reperfusion. In the first part of the study, ASCs were treated with H2O2 at different concentrations for 48 hours, both with and without JH4. The H2O2 was used to mimic oxidative stress that would be present in the environment of ischemic tissue. ASC morphology was then observed using phase-contrast microscopy while ASC viability was measured using an MTT (tetrazolium dye) assay which is a colorimetric reduction assay. They first determined the appropriate concentration of JH4 to maximally decrease H2O2-mediated apoptosis, which was ~1μm. They then found that treating the ASCs with 1μm of JH4 resulted in significantly more viability in the presence of H2O2 than if the ASCs were transplanted alone. This was seen in their MTT assay with less than 50% survival rate of ASCs without JH4 and ~75% survival rate of ASCs with JH4, both in the presence of H2O2. Another part of this study utilized an ischemia model of a mouse hind limb to determine if JH4 aids in ASC-mediated tissue reperfusion and limb salvage. The limbs first had their femoral arteries ligated and were then treated intramuscularly with either salt solution, ASCs alone or ASCs with JH4. Laser doppler imaging was performed for 4 weeks after treatment to determine blood flow recovery and images were evaluated from day 28 after treatment. The necrosis score of each group was also measured on day 28. The limb treated with salt solution showed severe necrosis and amputation with no limb salvage. The necrosis score of this limb at day 28 was greater than 2. The limb treated with ASCs alone showed significant tissue reperfusion up until day 14, after which there was only a mild increase in blood flow. The necrosis score of this limb at day 28 was ~1.5. The limb treated with both ASCs and JH4 showed a further increase in tissue reperfusion throughout the course of the 28 days. The necrosis score of this limb at day 28 was ~0.5.[3] ABI was measured in 12/13 studies (all of which utilized BMMNCs and PBMNCs) showing an improvement in ABI in 8 of the studies and no significant change in 4. TcPO2 was measured in 13 of the studies discussed, of these 6 included results on TcPO2. Out of these 6 studies, 5 showed improvement of TcPO2 with treatment and 1 showed no effect.[3]

Szabó et al. conducted a randomized clinical trial measuring the efficacy and safety of peripheral blood derived autologous stem cells that are expanded in vitro (VesCell) in patients with severe PAD. Twenty patients

were injected with a proprietary product known as VesCell which consisted of autologous ACPs taken from a sample in the peripheral blood and expanded in vitro. The cells were injected into the gastrocnemius muscle of the ischemic limb 24 hours after the initial harvest. An initial intake, 3 month, and 2 year follow ups were conducted and the efficacy of the treatment was measured via recording of death rate, prevention of amputation, tissue perfusion parameters (ABI and TcPO2), pain levels, ulcer/gangrene presence and characteristics and angiogenesis via DSA. The results of the study were as follows: amputation rate at the 3 month follow up showed six major amputations in the control group and no major amputations and one minor amputation in the VesCell group. The difference in amputation rate was significant between the two groups ($p<0.01$). Along with this one patient that had an amputation in the control group died of a cardiac arrhythmia. At the 2-year follow up there were 6 more major amputations and one more death occurred due to diabetic coma. In the treated group there were 3 major amputations and 2 minor amputations. Overall, by the 2-year follow up, 70% of the treatment group was amputation-free while 40% of the control group was amputation-free. ABI in the control group showed an insignificant change at the 3 month follow up while the VesCell group showed a significant improvement of 0.36 ± 0.11 ($P=0.01$). At the 2-year follow up, there was further significant improvement in ABI measurement for the VesCell group. TcPO2 values showed a significant improvement in the VesCell group from baseline (6.6 ± 4.0 in the treated group and 3.5 ± 5.4 in the control group). There was further improvement at the 2-year mark in the VesCell group. Pain scores in the control group showed no change at the 3 months follow up and 50% of the VesCell group reported improvement. At the 2-year follow up there was no change in pain status in either group. At the time of the study a baseline was conducted for ulcer/wounds. In the control group seven patients had an ulcer while eight did in the VesCell group. At the 3 month follow up only one wound had healed in the control group while there were four partial wound healing and two complete healings in the VesCell group. Angiogenesis baseline was measured by DSA showing suprapopliteal occlusion in all patients. In both groups there was no significant changes or observation of new collateral arteries via angiogram.[7]

DISCUSSION

ABI

Ankle-Brachial Index (ABI) is a standard method for determining not only the presence of PAD but the severity of PAD symptoms based on the relative improvement of the ABI value. The majority of the studies reviewed included ABI in their methods to determine the efficacy of the various stem cell treatments. Most studies showed a statistically significant improvement in ABI scores at various time frames post stem cell treatment. This could indicate that stem cell therapy has the potential to decrease cardiovascular mortality and severity of symptoms with PAD. However, many more questions are required to further this claim. While all the studies listed do indicate if there was a significant improvement in ABI, not all the studies gave specific values for the improvement. Therefore, we are unable to determine if different types of stem cells used therapeutically are more efficacious for improving ABI, or the magnitude of increase in ABI values which can indicate the improvement of symptoms and change in cardiovascular mortality risk.

TcPO2

Transcutaneous oximetry (TcPO2) was measured as an indication of low tissue perfusion, which is common with PAD, making it a fair parameter of gauging PAD in patients. The TACT study, performed by Tateishi-Yuyama et al. and a study conducted by Lu et al. both revealed that there was a significant improvement of TcPO2 in patients treated with BMMNCs when compared to the control groups. This implies that both groups, one treated with fibroblast growth factor and another treated with bone marrow mononuclear stem cell implantation, displayed a significant increase in TcPO2 as well.[8] Similarly, a study by Szabó et al. reported that after 3 months, both the VesCell group and control group had an increase of TcPO2. But after 2 years, the group treated with VesCell showed significantly further improvement of TcPO2 than the control group.[7] The majority of studies discussed in this review lead to the conclusion that stem cell-based treatment correlates with increased TcPO2. This is clinically significant for PAD patients because an increase in TcPO2 relates to increased tissue perfusion, the main goal of PAD treatment. Increasing tissue perfusion can limit some of the complications that come with PAD, such as tissue necrosis, ulcer formation and limb amputation.

Limb Salvage and Ulcer Healing

Limb amputation is a great risk in patients with PAD, especially with a comorbidity of diabetes. Using limb salvage as a parameter allows one to judge the treatment's effect on patients' future morbidity and mortality. When evaluating the parameter of limb salvage, both Huang et al. and Szabó et al. reported a decrease in amputation in the treatment groups compared to the control. In Huang et al.'s study none of the patients in the treatment group needed to undergo amputation as opposed to the 36% in the control group.[2] Similarly in Szabó et al. reported at the 3 month follow up no major amputations and one minor amputation in the treatment group, as compared to the control group which 6 patients had underwent a major amputation. At the 2 year follow up 30% of the treatment group underwent amputations, while only 70% of the control group needed an amputation.[7] Furthermore, Heo et al.'s systematic review showed all ten trials that used BMMNCs or PBMNCs reported improved limb salvage.[3] These results show promising use of stem cells as a means of limb salvage in patients with PAD as 25% of patients with chronic limb ischemia undergo a major amputation in the first year after diagnosis.[2] This complication can furthermore lead to death. An important risk factor that leads to amputation is ulcers, which can become non-healing in patients with PAD as the tissue requires increased metabolic demand that cannot be met due to the decreased arterial flow.[2] Many trials showed the use of stem cells to treat PAD also improves the healing capacity of ulcers. Both Lu et al. and Szabo reported a significant improvement in ulcer healing and appearance in their treatment groups when compared to controls.[7] These improvements further support the use of stem cells to treat ulcers, thereby decreasing the need for amputation decreasing mortality risk.

Pain

Pain is a common symptom of PAD, therefore used as a measure in treatment potentials. In the TACT study, performed by Tateishi-Yuyama et al., it was found that treatment with BMMNCs showed a statistically significant improvement in

patients' rest pain and pain when walking.[2] Similarly, two additional studies, one conducted by Lu et al. and one conducted by Huang et al. also showed significant improvement in patients' pain free walking.[2,6] Takagi et al.'s study, which compared treatment with FGF versus treatment with BMCI, used the visual analog scale for pain (VAS score) to assess progression of patients' pain throughout the trial. Results revealed a statistically significant reduction in pain scores after BCMI treatment. Lastly, a clinical trial performed by Szabó et al. obtained pain scores from two groups, one treated with VesCell and one control group. It was found that after 3 months, 50% of the VesCell group reported improvement of pain while the control group reported no change in pain. But, at the 2-yearfollow up, neither group reported a change in pain status.[7] As seen through these studies, stem cell therapy greatly improved patients' pain; meaning that this treatment can be utilized both to physiologically treat the patient and also to improve patient wellbeing.

Angiogenesis

A steadfast method for determining if angiogenesis has occurred post-stem cell therapy is various types of imaging, specifically angiography. Lu et al. utilized MR angiography which showed a significant score improvement in the treatment group (BMMSC) when compared to the control, this indicates an increased perfusion rate and collateral vessels in the treatment group. Huang et. al reported an improvement of angiographic scores in the treatment group Takagi et. al used technetium-tetrofosmin (Tc-TF) scintigraphy to measure angiogenesis which showed no significant changes in either treatment group. In addition, Szabo et al. used digital subtraction angiography to visualize the patency of the suprapopliteal arterial vessels of the leg. Suprapopliteal and crural occlusions were shown before treatment in both groups, while post treatment revealed no significant changes in flow or observation of new collaterals.

Co-Administration

When it comes to treating PAD with human adipose tissue-derived mesenchymal stem cells (ASCs), it seems that the main limitation is poor survival of the transplanted cells secondary to a hostile ischemic environment. This environment consists of a hypoxic and nutrient-poor habitat with inflammatory reactions and oxidative stress. The study by Heo et al. aimed to determine if co-administration of JH4 with ASCs would decrease the incidence of apoptosis of the transplanted cells and increase the effectiveness of tissue reperfusion by blocking the progerin-lamin A interaction. Through their study, they found that co-administration of ASCs with JH4 significantly decreased the instance of apoptosis of the ASCs, as seen through their MTT assay and ASC morphology trial. There was ~25% increase in the viability of cells co-administered with JH4 in the presence of H2O2 than the cells that were administered on their own. Also in the ASC morphology, the co-administration of JH4 appeared to have spared the cells from H2O2 mediated breakdown. Another part of the study, using a mouse hind limb ischemia model, also found an improvement in tissue reperfusion and a decrease in necrosis score with utilization of JH4. All these results lead to the conclusion that co-administration of ASCs with JH4 will increase the cells' likelihood of survival by inhibiting apoptosis, therefore increasing tissue reperfusion and decreasing incidence of necrosis.[3]

While the individual studies did contain adequate sample sizes and appropriate selection of patients based on symptoms of PAD, further information is to be desired such as if there is a difference in the efficacy of treatment based on gender or if the quantity of stem cells being injected affects the outcomes symptom improvement. A limitation of this review is the lack of distinction of how the treatment affects different racial groups since there is a genetic component to developing PAD. Another limitation is none of the studies analyzed had a sample size larger than 50 participants per group, with most studies having around 20-30 participants in each the control and treatment groups. These small sample sides could hinder the results of the studies.

CONCLUSION

The majority of studies reviewed concluded that stem cell therapy has the potential to be an efficacious non-surgical option for treatment of PAD and its related symptoms. This improvement was quantified over the various studies by measurements such as ABI, TcPO2, pain scores (claudication and at rest), and rates of limb salvage and ulcer healing, all of which showed marked improvements over the various follow up times in most of the studies. All studies indicated that injection in multiple sites and in multiple continuous doses of the various types of prepared stem cells was the most efficacious method of delivery, along with this the majority of the injections were given in multiple doses. While the individual studies did contain adequate sample sizes and appropriate selection of patients based on symptoms of PAD, further information is to be desired such as if there is a difference in the efficacy of treatment based on gender or if the quantity of stem cells being injected affects the outcomes symptom improvement.

AUTHOR'S CONTRIBUTION

All authors had equal contribution to the formation of the topic, design of the review, and evaluation of the studies included in the final manuscript. All authors contributed equally to the formation of the final literature review and reviewing the final version for submission

STATEMENT OF COMPETING INTEREST

All authors declare they have no competing interests associated with this literature review.

REFERENCES

1: Botham CM, Bennett WL, Cooke JP. Clinical trials of adult stem cell therapy for peripheral artery disease. Methodist Debakey Cardiovasc J. 2013 Oct-Dec;9(4):201-5. doi: 10.14797/mdcj-9-4-201. Erratum in: Methodist Debakey Cardiovasc J. 2014 Apr-Jun;10(2):134. PMID: 24298310; PMCID: PMC3846073.

2: Gupta NK, Armstrong EJ, Parikh SA. The current state of stem cell therapy for peripheral artery disease. Curr Cardiol Rep. 2014 Feb;16(2):447. doi: 10.1007/s11886-013-0447-2. PMID: 24414120.

3: Heo SC, Kwon YW, Park GT, Kwon SM, Bae SS, Park BJ, Kim JH. Mesenchymal Stem Cell-Mediated Therapy of Peripheral Artery Disease Is Stimulated by a Lamin A-Progerin Binding Inhibitor. J Lipid Atheroscler. 2020 Sep;9(3):460-473. doi:

10.12997/jla.2020.9.3.460. Epub 2020 Sep 14. PMID: 33024737; PMCID: PMC7521968.

4: Lachmann N, Nikol S. Therapeutic angiogenesis for peripheral artery disease: stem cell therapy. Vasa. 2007 Nov;36(4):241-51. doi: 10.1024/0301-1526.36.4.241. PMID: 18357916.

5: Nikol S. Therapeutische Angiogenese mittels Gen- und Stammzellentherapie bei der peripheren arteriellen Verschlusskrankheit [Therapeutic angiogenesis using gene transfer and stem cell therapy in peripheral artery disease]. Dtsch Med Wochenschr. 2011 Apr;136(14):672-4. German. doi: 10.1055/s-0031-1274561. Epub 2011 Mar 29. PMID: 21448824.

6: Lawall H, Bramlage P, Amann B. Stem cell and progenitor cell therapy in peripheral artery disease. A critical appraisal. Thromb Haemost. 2010 Apr;103(4):696-709. doi: 10.1160/TH09-10-0688. Epub 2010 Feb 19. PMID: 20174766.

7: Szabó GV, Kövesd Z, Cserepes J, Daróczy J, Belkin M, Acsády G. Peripheral blood-derived autologous stem cell therapy for the treatment of patients with late-stage peripheral artery disease-results of the short- and long-term follow-up. Cytotherapy. 2013 Oct;15(10):1245-52. doi: 10.1016/j.jcyt.2013.05.017. PMID: 23993298.

8: Takagi G, Miyamoto M, Tara S, Takagi I, Takano H, Yasutake M, Tabata Y, Mizuno K. Controlled-release basic fibroblast growth factor for peripheral artery disease: comparison with autologous bone marrow-derived stem cell transfer. Tissue Eng Part A. 2011 Nov;17(21-22):2787-94. doi: 10.1089/ten.tea.2010.0525. Epub 2011 Aug 2. PMID: 21810028.

Suture Button Versus Screw Fixation for Syndesmotic Injuries in Ankle Fractures: A Literature Review

Laurin Larian, DPM

ABSTRACT

Introduction: The tibiofibular syndesmosis is imperative in maintaining the function and stability of the ankle joint. Disruption of this syndesmosis is commonly seen in ankle fractures. It is important to repair the syndesmosis to ensure proper ankle joint range of motion and positive clinical outcomes. Current treatment options for syndesmotic injuries include screw fixation or the use of suture button devices. This systematic review focused on the benefit of using one form of fixation over the other.
Study Design: Systematic Review of the Literature

Methods: A PubMed database search was performed to include the following terms in the title "(Ankle AND suture button AND screw) AND (Fracture OR Fractures)". Inclusion criteria were articles written in English. There were no exclusion criteria. All six articles yielded were used.

Results: Four of the six articles found that there was no significant difference between either fixation option. However, the article that conducted a meta-analysis/systematic review found that suture button fixation allowed for a significantly lower reoperation rate and a decreased tendency for malreduction.

Conclusion: The six articles analyzed showed that both screw fixation and suture button fixation are effective in reducing syndesmotic injuries. Future studies should include a larger sample size and a longer follow-up to see the long-term effects of the fixation options.

Level of Evidence: 1

Key Words: ankle fracture, screw fixation, syndesmosis injury, suture button

INTRODUCTION

Background

The distal tibiofibular syndesmosis is made up of the anterior inferior tibiofibular ligament (AITFL), posterior inferior tibiofibular ligament (PITFL), inferior transverse ligament, interosseous ligament, and interosseous membrane.[1] A syndesmotic injury occurs when an external force is applied to the foot. This may result solely in a ligamentous injury or with an associated fracture. These ankle fractures include pronation external rotation (Weber C), supination external rotation (Weber B) or proximal fibular fracture (Maissoneuve).[1]

Clinical Exam

On clinical exam, there is pain and tenderness anteriorly along the syndesmosis.[1] Specifically, there is pain along the AITFL, tenderness with AITFL palpation, pain with external rotation of the foot and pain with dorsiflexion.[2] Pain can also travel proximally. On gait exam, there is a noticeable heel-raise gait rather than the normal heel toe gait. This is because the heel-raise gait allows for avoidance of excessive ankle dorsiflexion, avoiding pain with push off. There may also be an antalgic gait with a shorter stance phase on the affected foot.[2] The squeeze test and external rotation test may help detect ligamentous syndesmotic injuries.[1] The squeeze test involves squeezing the tibia and fibula above the mid-calf, resulting in pain and separation of these two bones distally. The external rotation test involves externally rotating the foot with stabilization of the leg with the knee flexed to ninety degrees, resulting in pain over the syndesmosis.[1] The point test or palpating test involves palpating the distal tibiofibular syndesmosis and this elicits pain.[2] The dorsiflexion maneuver involves dorsiflexion of the foot and eliciting pain as the wide anterior aspect of the talus is pushed into the ankle mortise, resulting in separation of the tibia and fibula.[2] Lastly, the one-legged hop test consists of standing in the injured leg and hopping to excite pain. It is noted that this test should be used with caution so that further separation of the distal tibiofibular syndesmosis does not occur.[2]

Radiographic Exam

Radiographically, syndesmotic injuries are diagnosed with increased tibiofibular clear space, decreased tibiofibular overlap, and increased medial clear space.[1] Stress radiographs may assist in diagnosing latent syndesmotic injuries and for surgical purposes. Stress mortise views would illustrate lateral displacement of the fibula and a stress lateral view illustrates a posterior displacement of the fibula.[1] CT and MRI can also be used for additional guidance.

Treatment

Conservative treatment is recommended for syndesmotic sprains without associated fractures. Treatment includes rest, ice, compression, and elevation. Stabilization can be applied with a posterior splint and having the patient be non-weightbearing. Electrical stimulation and cryotherapy are additional modalities to test pain and inflammation. Strength training and an exercise program can be recommended after pain has subsided.[2] Ankle fractures with syndesmotic injury are usually treated surgically.[3] The fibula fracture is usually treated with hardware and the syndesmotic is reduced through various techniques. The main goal is to restore the correct length, alignment, and Rostov of the fibula in relation to the tibia at the distal tibiofibular joint.[3] The purpose of this paper is to compare screw fixation and suture button fixation in a syndesmotic injury in ankle fractures.

METHODS

A PubMed database search was performed to include the following terms "(((Ankle[Title]) AND (suture button[Title]) AND (screw[Title])) AND ((Fracture [Title]) OR (Fractures [Title]))". The search yielded six results. Inclusion criteria was English language. There were no exclusion criteria. All six articles were used. The figure below shows a summary of the methods for this paper.

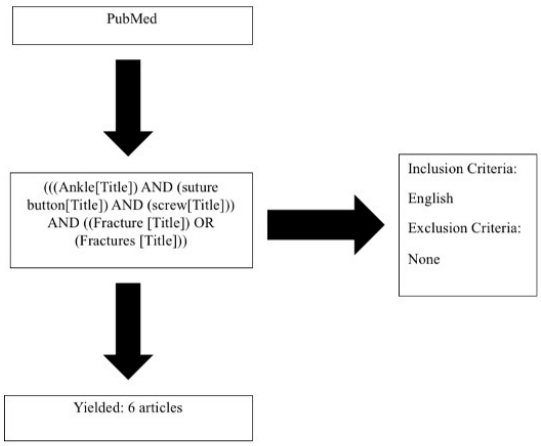


Figure 1. *Summary of Article Acquisition*

RESULTS

Kim and colleagues compared screw and suture button fixation for treating syndesmotic injuries in ankle fractures.[4] A retrospective and prospective study was performed on 44 patients who received surgery for a syndesmotic injury after already having an open reduction internal fixation of their ankle fracture. Syndesmotic injury was demonstrated by movement of over 3mm with lateral fibular distraction, over 6mm of tibiofibular clear space, over 6mm of medial clear space, and less than 6mm of tibiofibular overlap. Twenty-four patients received screw fixation and 20 patients received the Tightrope suture button fixation. The screw fixation group was studied retrospectively while the suture button group was observed prospectively. Outcomes included American Orthopedic Foot and Ankle Society (AOFAS) scores and a visual analog scale (VAS) score. Initially, arthroscopy was used for debridement and to detect syndesmotic injury before ankle fracture fixation. In the screw fixation group, syndesmotic fixation was performed by drilling 3 cortices from the fibular side so that a 3.5mm screw could pass to the inner cortical portion of the tibia. The screw was inserted in an oblique manner 25 to 30 degrees from posterolateral to anteromedial. Fixation was performed 2 to 6cm superior to the tibial plafond with reduction forceps maintaining the desired position. When necessary, a plate was used for fibular stability or 2 cortical screws for high impact injuries. In the suture button fixation group, reduction clamps were also used to hold the desired position and fixation was also placed 2 to 6cm above the tibial plafond. A hole was made in the 4 cortical bones and a screw was inserted at a 30-degree angle in the coronal plane. A metal plate was applied to the fibula and the suture button was inserted via the screw hole on the metal plate. A button was then used to fix the inner tibial aspect and the threads were hand-tied. Postoperatively, all patients were non weight bearing and wore a below knee cast for 1 week. Patients then wore ankle walker boots to begin exercise. Patients in the screw fixation group began partial weight bearing at 6 to 8 weeks while the suture button group began at 6 weeks. Clinical and radiological assessments were performed at 6 weeks, 6 months and 1 year postoperatively. Both groups had an improved tibiofibular clear space, tibiofibular overlap and medial clear space. There was a statistically significant improvement of only the tibiofibular clear space in the screw fixation group, but the authors note that the suture button group did recover with normal range of motion. Additionally, there was no significant difference between the two groups in terms

of the AOFAS and VAS scores. All patients had bone union achieved. However, postoperative complications were seen in five patients in the screw fixation group in which they had a broken screw at 1 year radiographic follow up. Therefore, the authors concluded that there was no difference in using screw fixation or suture button fixation for the syndesmotic injuries, although patients with a suture button can ambulate sooner and do not require suture button removal.[4]

In a study by Hemings and colleagues, they researched the postoperative alignment of syndesmotic fixation using suture button or syndesmotic screw fixation in ankle fractures with additional 3D imaging.[5] A retrospective case control study was used and consisted of 47 patients. Inclusion criteria were unilateral syndesmotic fixation with either screw or suture button, anatomical fracture reduction, uninjured ankle, and a postoperative CT 10cm proximal to the distal tibial plateau. All patients had anatomical fracture reduction and osteosynthesis. Syndesmotic stabilization was then performed with a syndesmotic screw (18 patients) or Tightrope suture button (29 patients). The authors did not describe the method of placement of the fixation devices for either group. CT scans were performed three days postoperatively and were taken at least 10cm proximal to the distal tibial plafond. 3D imaging software was used to measure the tibiofibular clear space, translation angle (dorsal translation of fibula compared to tibia), and vertical offset (fibularis shortening) compared to the normal side of the patient. The authors found that both groups had mild diastasis after stabilization and slight dorsiflexion of the fibula on the tibia. In addition, the fibula to tibia length ratio did not differ between the two groups. Overall, syndesmotic malreduction in the sagittal and coronal planes was 32%, of which 39% was from the screw fixation group and 28% was from the suture button group. Again, the authors concluded that there were no significant differences in immediate alignment postoperatively between suture button and screw fixation of syndesmotic injuries.[5]

A study by Yawar and colleagues also assessed suture button and screw fixation for syndesmotic injuries.[6] This was a retrospective cohort study consisting of 53 patients who had ankle fractures and distal tibiofibular syndesmotic injury which was diagnosed Intraoperative lay and radiographically. Thirty-four patients received suture button fixation while 19 received screw fixation. The outcomes included comparing reoperation rates, complications, time to weight bearing and post-operative radiographic analysis. As in the previous paper, the specific surgical techniques were not discussed. The authors found that 21% of patients in the screw fixation group required reoperation due to screw backout or screw pain; 9% of patients in the suture button group required reoperation due to pain, infection, or other screw removal. Radiological fixation was better than the screw fixation group but was not statistically significant. General outcomes for both groups included ankle joint stiffness and pain. Similar to the previous papers, the authors recommend that both suture button and screw fixation allow for good outcomes.[6]

Lehtola and colleagues evaluated suture button and screw fixation for syndesmotic injuries in pronation external rotation (PER) ankle fractures. This was a randomized control trial with 43 patients.[7] After osteosynthesis, 22 were placed into the screw fixation group and 21 were put in the suture button group. Patients were skeletally

mature and had PER 4/Weber C ankle fractures with preoperative or intraoperative syndesmotic instability. Outpatient visits were performed for an average of 7.1 years. Both groups had their fibular fractures stabilized with a semi tubal plate (with/without lag screw). Individuals with high fibular fractures only had syndesmotic fixation performed. Medial malleolus fractures were fixed with two 3.5mm partially threaded cancellous screws. Dislocated posterior malleolus fractures which were over 25% of the joint area were reduced and fixed with two 3.5mm partially threaded cancellous screws. The suture button group was then treated with the Tightrope suture button. The screw fixation group was fixed with a 3.5mm fully threaded tricortical screw. Intraoperative CT was used to assess reduction and fixation was corrected if malreduction was detected. Both groups wore a below knee cast and partial weight bearing was permitted for six weeks. Recovery was checked in clinic 2, 6 and 12 weeks postoperatively in addition to ankle radiographs. Outcomes were maintenance of syndesmotic reduction via CT, osteoarthritis grade using Morry & Wiedeman classification, and functional outcomes using Olerud-Molander Ankle score (OMAS) and RAND-36 Item Health Survey for Quality of Life (RAND-36). The authors found that there was no difference in OA severity between the two groups. The OMAS and RAND-36 scores were also similar between the groups and the OMAS scores were mainly good to excellent in both groups. They also did not find any difference between both groups in maintaining the syndesmotic reduction after a follow up of six years. As with the previously discussed papers, both fixation methods have comparable rates.[7]

A study by Xu and colleagues determined the efficacy of suture button or screw fixation on syndesmotic injury seen in ankle fractures.[8] They did a single center, case control, retrospective study of 76 patients who had an ankle fracture with concurrent syndesmotic injury. The suture button group had 34 patients and the screw fixation group had 42 cases. All malleolar fractures were fixed first. In the suture button group, a 3.5mm guidewire was used to drill from the fibula to the tibia through 4 cortices and angled 25 to 30 degrees, parallel to the ankle joint surface: the suture button was then placed. In the screw fixation group, the syndesmosis was reduced and fixed with a 3.5mm cortical bone screw also at a 25-to-35-degree angle, parallel to the ankle joint surface. The screw was placed 2 to 3cm above the posterolateral fibula. Patients were 6 weeks non-weight bearing with active range of motion. They then began partial to full weight bearing rehabilitation. Syndesmotic screws were removed 8 to 12 weeks postoperatively, although the reason for removal was not stated. Follow up occurred at 1, 2, 3, 6, 9, 12 and 24 months. Outcomes consisted of operation duration, time to full weight bearing, tibiofibular overlap and tibiofibular clear space, complications, and ankle function using OMAS. The authors found that there was no statistically significant difference in tibiofibular overlap and tibiofibular clear space pre and postoperatively between groups. Complications in the suture button group were irritation, diastasis, deep vein thrombosis and infection. Complication in the screw fixation were irritation, screw breakage, diastasis, and deep vein thrombosis. However, there was no statistically significant differences between the 2 groups. The OMAS score was significantly higher in the screw fixation group, but it was not statistically significant 12 months postoperatively. Lastly, the time to full weight bearing was significantly lower in the suture button group. The

authors concluded that both fixation devices are similar in postoperative efficacy.[8]

The final study was by Schmal and colleagues which was a systematic review and meta-analysis on using suture button or screw fixation for syndesmotic injuries in ankle fractures.[9] The review consisted of patients with closed growth plates who had an ankle fracture with syndesmotic injury and had surgery within three weeks of the injury. Studies consisted of suture button and cortical screw fixation comparison. Six studies were chosen and consisted of two randomized control trials, two prospective and retrospective cohort studies which resulted in a total of 275 patients. All studies first fixed the malleolar fractures followed by syndesmotic reduction. Syndesmotic reduction was performed on patients with a Maissoneuve fracture. Screw fixation was done through three or four cortices with 3.5mm or 4.5mm syndesmotic screws. Not all suture buttons were the same, but surgeons did use similar approaches. This included pulling the suture button medially with a needle through a hole through 4 cortices. After the suture button passed through the medial tibial cortex, the suture was tightened using the free ends on the lateral fibula. All the studies placed the syndesmotic fixation devices 2 to 2.5cm superior to the tibial plafond but one study used 2 screws and 2 suture buttons for the patients. Four studies used fluoroscopy intraoperatively. Five of the studies had similar postoperative treatment which consisted of initial ankle immobilization followed by partial weight bearing or non-weight bearing. Outcomes of interest were AOFAS scores, Olerud-Molander (OM) scores, malreduction, reoperation rate and time to pre-injury activities. Three of the studies saw a significant difference in AOFAS scores from final follow-up. Three studies evaluated malreduction radiographically, out of which one found that the suture button group had significantly lower malreduction at 6 and 12 months follow-up. However, another study found no significant difference at 2 years follow up, which may have been due to the different criteria used to diagnose malreduction. Additionally, in all the studies, reoperations were performed more in the screw fixation group. Lastly, three of the studies found that the suture button grouphad a faster return to work and full weight bearing time. A meta-analysis was also completed using 2 of the randomized control trials. There was no statistically significant difference in the lower amount of malreduction in either of the groups; malreduction diagnosis was performed at different times. Through the meta-analysis it was also found that the risk for reoperation was statistically significant in that the suture button group had a lower risk for reoperation. From this analysis, the authors of the study were unable to make a final conclusion on which fixation devices is superior based on functional outcomes.

Table 1. Variables Assessed by Articles

Article Authors	Number of Patients	Groups	Outcome Measures
Kim (2016)	44	Screw vs Tightrope suture button fuxation	AOFAS scores VAS scores Clinical assessment Radiological assessment
Hemings (2021)	47	Screw vs suture button fixation	3D imaging assessment
Yawar (2021)	53	Screw vs suture button fixation	Reoperation rate Complications Time to weight bearing Postoperative Radiographic analysis
Lehtola (2021)	43	Screw vs suture button fixation	CT analysis Osteoarthritis grading OMAS scores RAND-36 scores
Xu (2022)	76	Screw vs suture button fixation	Operation duration Time to full weight bearing Tibiofibular overlap and clear space Complications OMAS scores
Scholars (2019)	275	Screw vs suture button fixation	AOFAS scores OMAS scores Malreduction Reoperation rates Time to pre-injury activities

DISCUSSION

The distal tibiofibular syndesmosis stabilizes the tibia, fibula, and ankle joint and is sometimes disrupted in ankle fractures. Restoration of the syndesmosis is necessary to ensure proper ankle joint motion and function. Fixation for the syndesmosis include screw fixation and suture button fixation, both of which are widely used. Kim and colleagues (2016) found that there was screw failure in some patients. Additionally, Yawar and colleagues (2021) and Schmal and colleagues (2019) found that a higher percentage of patients who received screw

fixation needed reoperation. Ultimately, the literature has shown that both fixation devices reduce the syndesmotic disruption radiographically and functionally.

CONCLUSION

From this literature review, it can be concluded that both screw fixation and suture button fixation are safe and effective methods for restoring the distal tibiofibular syndesmosis. Further research is necessary to clinically assess ankle joint range of motion and gait after each fixation device. Additional studies should include more participants and randomized controlled trials. The studies should also specify the surgical technique used for syndesmotic reduction. Moreover, a longer follow-up time would be beneficial to see the long-term effects of these fixation devices and help hone in on the unique values of each fixation device.

AUTHORS' CONTRIBUTION

One author contributed to this article.

STATEMENT OF COMPETING INTERESTS

There are no competing interests.

REFERENCES

1. Zalavras C, Thordarson D. Ankle syndesmotic injury. J Am Acad Orthop Surg. 2007;15(6):330-339.
2. Lin CF, Gross ML, Weinhold P. Ankle syndesmosis injuries: anatomy, biomechanics, mechanism of injury, and clinical guidelines for diagnosis and intervention. J Orthop Sports Phys Ther. 2006;36(6):372-384.
3. Bava E, Charlton T, Thordarson D. Ankle fracture syndesmosis fixation and management: the current practice of orthopedic surgeons. Am J Orthop (Belle Mead NJ). 2010;39(5):242-246.
4. Kim JH, Gwak HC, Lee CR, Choo HJ, Kim JG, Kim DY. A Comparison of Screw Fixation and Suture-Button Fixation in a Syndesmosis Injury in an Ankle Fracture. J Foot Ankle Surg. 2016;55(5):985-990.
5. Hennings R, Souleiman F, Heilemann M, et al. Suture button versus syndesmotic screw in ankle fractures - evaluation with 3D imaging-based measurements. BMC Musculoskelet Disord. 2021;22(1):970. Published 2021 Nov 22.
6. K, Khan AM. Suture-Button Versus Syndesmotic Screw Fixation of Ankle Fractures: A Comparative Retrospective Review Over One Year. Cureus. 2021;13(9):e17826.
7. Lehtola R, Leskelä HV, Flinkkilä T, et al. Suture button versus syndesmosis screw fixation in pronation-external rotation ankle fractures: A minimum 6-year follow-up of a randomised controlled trial. Injury. 2021;52(10):3143-3149.
8. Xu Y, Kang R, Li M, et al. The Clinical Efficacy of Suture-Button Fixation and Trans-Syndesmotic Screw Fixation in the Treatment of Ankle Fracture Combined With Distal Tibiofibular Syndesmosis Injury: A Retrospective Study. J Foot Ankle Surg. 2022;61(1):143-148.
9. McKenzie AC, Hesselholt KE, Larsen MS, Schmal H. A Systematic Review and Meta-Analysis on Treatment of Ankle Fractures With Syndesmotic Rupture: Suture-Button Fixation Versus Cortical Screw

Fixation. J Foot Ankle Surg. 2019;58(5):946-953.

The significance of bacterial diversity and foot ulcer localization in younger and older individuals with diabetes

Shauna-Kay Rhooms, BS; Devondra Pitt, MS; Betty Kim, BS

ABSTRACT

Introduction

Infections of diabetic foot ulcer (DFU) is commonly associated with gram-positive organisms such as *Staphylococcus aureus, Enterococcus*, and gram-negative organisms such as *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella species*. Infected diabetic foot ulceration is the most common cause of non-traumatic lower limb amputation; approximately 15-20% of infected DFU results in amputation [(1)]. Controlling infected DFU spread is important for early diagnosis and critical treatment care for both the foot and the metabolic system. Understanding the diversity and population of bacterial microbes serves as a central component in the critical treatment and care of patients with infected DFU. The purpose of this literature review is to analyze the relevant differences in the bacterial diversity between species in younger and older age groups with diabetic foot ulcer localization.

Study Design: Systematic Review of Literature

Method

PubMed database searches were performed to include the terms "bacterial diversity and foot ulcers," "pseudomonas and foot ulcers," "s. aureus and foot ulcers," and "strep and foot ulcers.**"** Inclusion criteria included clinical trials, randomized control studies, and reviews. We also included studies with young and older patients, type 1 and type 2 diabetes, studies that focused on *Pseudomonas*, Streptococcus and *Staphylococcus aureus.* In addition, all studies utilized were from 2000 to 2022 and resulted in 4 articles that were reviewed for this study.

Results

There was a significant difference found within the age ranges of individuals with diabetic foot ulcer (DFU). The frequency of *Pseudomonas* and *Staphylococcus aureus* was found to increase with age. With patients experiencing ischemic or deep wounds, gram negative species were more likely to be found in their ulcerated foot. Incidence of diabetic foot ulcer localized to plantar side were most associated with Enterobacteriaceae, while diabetic foot infections localized to the forefoot and plantar side were most associated gram positive species. [1]

Conclusion

Based on our review, given the spectrum of bacterial diversity in diabetic foot ulcer patients, it was found that the dominant species was gram positive species. Increase in age was associated with an increase in *Staphylococcus aureus*, *Streptococcus* and *Pseudomonas aeruginosa*. Foot ulcer localization also influences bacterial diversity in infected diabetic foot ulcers.

Key words: Bacterial diversity, Foot ulcer localization, Diabetic foot ulcer, S. aureus, Pseudomonas aeruginosa, Streptococci

INTRODUCTION

Diabetes and its associated complications is a serious public health issue. The four common complications of diabetes include retinopathy, foot-associated issues, heart attack and stroke, and kidney-associated issues[9]. Such complications have contributed to the global healthcare burden. The mortality and morbidity in both developed and underdeveloped countries. Diabetic foot ulcer (DFU) is not only a common medical complication but patients must also face the social, psychological, and economic implications that come with it. Examining the complications of an infection of the diabetic foot ulcer (DFU) and how it affects patient lives is central to their care and treatment. Infected DFU can be one of the most traumatizing events for a diabetic patient; following the infection they are at a 2.5-fold increased risk of cardiovascular mortality compared to diabetic patients without foot ulcers[5]. Studies have also shown that more than 50% of DFU can become infected with non-traumatic lower limb amputation as the leading complication of infected DFU because these infections are often hard to control [5].

Approximately 9.1 to 26.1 billion people will develop DFU every year, according to the International Diabetes Federation [6]. One of the main challenges of DFU is the increased vulnerability to different potential pathogens such as gram-positive organisms (*Staphylococcus aureus, Enterococcus*), and gram-negative organisms (*Pseudomonas aeruginosa, Escherichia coli,* and *Klebsiella species*). The susceptibility to such pathogens and the biofilm-forming ability of certain bacteria has been associated with increased antibiotic resistance and chronic recurrent infections.

Studies have shown that there are differences in bacterial diversity in DFU patients' between different populations based on socioeconomic, geographical, and climatic differences. In more developed countries such as Canada and France, infected diabetic foot ulcers were primarily caused by aerobic gram-positive cocci, while gram-negative species like *Enterobacteriaceae* were the dominant pathogen spectrum in the Middle East. Antibiotic treatment, which included the time duration and depth of the ulcer also had an impact on the expected pathogen spectrum. *Staphylococcus aureus* was seen in shorter lasting diabetic ulcers which are easier to treat, while longer-lasting and deep ulcers often contained gram-positive, gram-negative, and anaerobic bacteria [7].

A recent study has shown that the bacterial spectrum in DFU has changed within the last few years. There is an increase in neuro-ischemic diabetic foot infections (+ 10.1%), an increase in *Enterobacteriaceae* (+ 14.7%), and an increase in *Pseudomonas aeruginosa* (*P. aeruginosa*, + 4.6%). There was also an increase in *S. aureus associated* with an increase in age. It is also important to note that the rate of methicillin-resistant S. aureus (MRSA) was reported to be 15–35%[8].

Diabetic foot ulcer infections are polymicrobial and complications of DFUs can be minimized by understanding the diversity and population of bacterial microbes to better control these infections. Detecting specific pathogens and their susceptibility pattern is vital in starting therapy earlier with the appropriate antibiotics to prevent dissemination of infection. The purpose of this literature review is to analyze the relevant differences in the bacterial diversity between species in younger and older age groups with diabetic foot ulcer localization.

METHODS

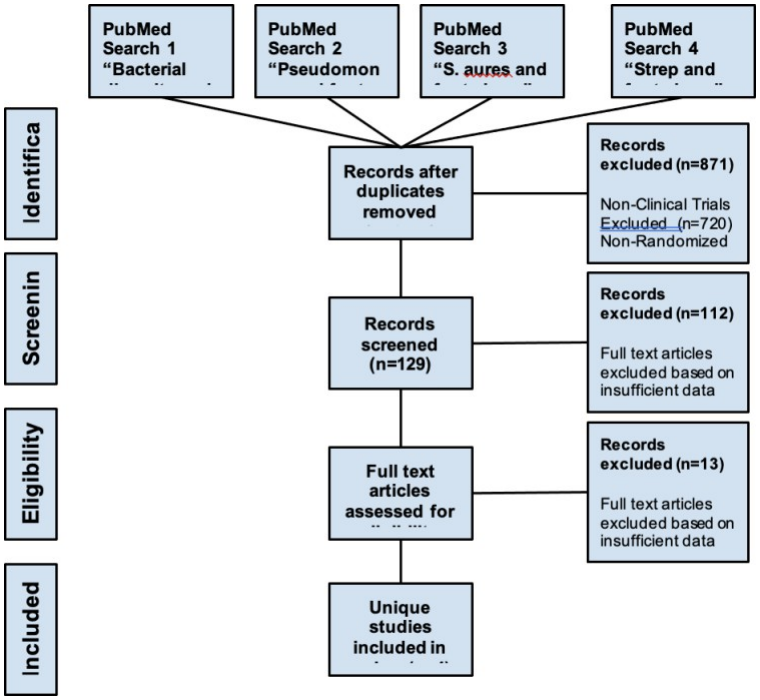


Figure 1: Study Selection Process

RESULTS

Xie et al. conducted a retrospective study that assessed the bacterial profile and antibiotic resistance patterns in diabetic foot ulcers (DFUs) of 405 inpatients from Sun Yat-sen Memorial Hospital from Jan. 1, 2010, to Dec. 31, 2015. They found higher amounts of Gram-negative bacteria (GNB) compared to Gram-positive bacteria (GPB) (54.1% versus 45.9%). Their results also showed predominance of Enterobacteriaceae (73.2%) and Staphylococcus (65.2%).[7]

Dorr et al. conducted a prospective study that assessed bacterial diversity in diabetic foot infections (DFIs) within 12 months from October 1, 2018, to September 30, 2019. They found that the majority (61.5%) of DFIs was caused by gram-positive germs, first and foremost S. aureus, followed by *Enterococci, Streptococci*, and Corynebacteria. In addition, the most common gram-negative species were P. aeruginosa, Enterobacter, Proteus, E. coli and Klebsiella.[1]

Macdonald et al. conducted a retrospective cohort study to compare the local microbiological profile and investigate potential relationships between the microbiological results for 12 months of the year 2017 from seventy-three patients (56 males and 17 females) from one multidisciplinary diabetic foot outpatient clinic, Scottish tertiary hospital. They found that Among the monomicrobial results (n =

77), most were Gram positive isolates (96.1%) and the most frequently isolated bacteria was S. aureus (84.4%). In addition, the prevalence of S. aureus in DFIs may be associated with increasing patient age.[8]

Patel et al. conducted a study that investigated four antibiotics from different categories for both the planktonic and biofilm phase and determined their resistance pattern and their effectiveness in inhibiting PA01 biofilm formation and eradication. They found ofloxacin proved to be the most effective even at lower concentrations. Tobramycin was most effective at
higher concentrations for eradicating and inhibiting PA biofilms.

Table 1: Key Findings of Article Review

Author	Key Findings
Xie et al.	**Key Finding** - Gram-negative bacteria (GNB) was higher than Gram-positive bacteria (GPB) (54.1% versus 45.9%), in which Enterobacteriaceae (73.2%) and Staphylococcus (65.2%) were predominant respectively - Neuro-ischemic ulcer (N-IFU) was more susceptible to GNB infection. - GPB isolated in ischemic foot ulcer (IFU) showed more resistance than the N-IFU, while GNB isolates were on the opposite **Limitations** - +The lack of anaerobic culturing - Small number of included patients
Dorr et al.	**Key Finding** - The majority (61.5%) of DFIs was caused by gram-positive germs, first and foremost S. aureus, followed by Enterococcus, Streptococci and Corynebacteria. - The most common gram-negative species were P. aeruginosa, Enterobacter spp., Proteus spp., E. coli and Klebsiella spp.
Macdonald et al.	**Key Finding** - Among the monomicrobial results (n = 77), most were Gram positive isolates (96.1%) and the most frequently isolated bacteria was S. aureus (84.4%). - The prevalence of S. aureus in DFIs may be associated with increasing patient age - The odds of being infected with *S. aureus* exponentially increase every year such that the probability of having a *S. aureus* infected DFI goes from 0.15 to 0.43 from age 40 to age 80. **Limitations** - Limited sample size - Insufficient statistical power

	- Intrinsic bias because of individual patients contributing multiple results, although these most likely represented different infectious episodes from the same foot ulcer.
Patel et al.	**Key Finding** - Ofloxacin proved to be the most effective even at lower concentrations. Tobramycin was most effective at higher concentrations for eradicating and inhibiting PA biofilms

DISCUSSION

DFIs initially presented to the physician are diagnosed clinically if the diabetic foot ulcer presents with classic signs of inflammation such as redness, pain, swelling, warmth, or purulent discharge. DFIs ranging from local cellulitis to osteomyelitis and gangrene must be treated empirically. Modifications to these treatments based on swab cultures result in a more fine-tuned course of treatment than the initial antimicrobial treatment. However, there are many factors, including the rapid progression of DFIs and their high association with amputation, impaired healing process in diabetic patients, and the time it takes to get wound culture results, which is usually a week to three weeks if testing for anaerobic bacteria. This length of time is imperative that empirical treatment be broad-spectrum enough to address the polymicrobial nature of DFIs and prevent the risk of reinfection.

Dorr et al. study confirmed the need for broad-spectrum therapy when every DFU was found to harbor an average of 2.1 microorganisms with *S. aureus* and *Pseudomonas* as the most common Gram-positive and Gram-negative strains of bacteria, respectively. Dorr et al.'s study aimed to identify indicators outside of standard wound culture results in assessing choices clinicians can make to fine-tune antimicrobials prescribed for the first-time patient, while considering the severity of the patient infections, patient comorbidities, and history of infections and treatments.

Dorr et al.'s study confirmed what we know about the common pathogens found in DFIs. Dorr et al. went further to investigate whether or not routine bloodwork, HbA1c, WBC, CRP, and interleukin levels can provide further information to help inform treatment protocol. Although the study found no significant relationship between WBC and CRP levels as markers of pathogen specificity, it is interesting to note the effect climate has on prevalent pathogens. There was variation in dominant pathogens in warm versus cold weather climates. Given the environmental effect climate change has on pathogen dominance in DFIs, this information could help clinicians by serving as an additional treatment protocol and assessment tool.

DFI Categorization

DFIs in first-time patients can be categorized by several wound classification systems. A Wagner-Armstrong score and a SINBAD score can be used to classify a wound based on physical exam alone, while the diabetic foot classification relies on neurological and vascular testing with the use of a monofilament and tuning fork test, and a Doppler assessment. This "first sight" or first look of a DFI allows the physician to

determine the severity of the infection which can dictate surgical intervention or empirical antimicrobial treatment. Wagner-Armstrong combines two grading systems, a numerical and alphabetical grade, which are based on an ulcer's depth which is determined by a probe and the presence of osteomyelitis or gangrene. Wagner grades range from 0 to 5 with a grade of a 4 or 5 given to a DFI which presents with either localized or extensive gangrene of the foot. Armstrong grades are from A to D based on evidence of ischemia with a grade of C or D indicating partial or complete gangrene of the foot. For example, DFIs with a Wagner-Armstrong grade of 4C, 4D, 5C, and or 5D typically go straight to surgery without initial antibiotic intervention if the infection is severe enough.

The SINBAD score system takes into account the site, ischemia, neuropathy, bacterial infection and depth where components of classification can be added together to produce a score that is between 0 and 6. The limitations of using the SINBAD score are that it does not describe ulcer depth or the severity of an infection, but it is a score that should be reported for a wound and which is recognized by the IWGDF[10].

Xie et al. incorporates the IDSA/IWGDF classification system, a set of diagnostic criteria used in studies of DFI[11] and guidelines aimed to help clinicians in diagnosing and managing the diabetic foot by defining the presence of an infection, which should present with two or more classic findings of inflammation or purulence[12], and its severity which determines if a patient must be hospitalized for further imaging, surgical intervention, or amputation. IDSA/IWGDF was used to quantify the severity of a diabetic foot infection into categories of uninfected, mild, moderate, or severe. One last classification system Xie et al. considered was the classification of the diabetic foot into three types: an ischemic foot ulcer (IFU), neuropathic foot ulcer (NFU), and neuro-ischemic foot ulcer (N-IFU). An IFU is a DFU with peripheral arterial disease; an IFU with peripheral sensory neuropathy was defined as an N-IFU; a DFU with peripheral sensory neuropathy but no peripheral arterial disease was defined as an NFU.

Inflammation Markers

Erythrocyte sedimentation rate and c-reactive protein, in addition to procalcitonin and white blood cell count levels, are usually measured at baseline with a patient's blood work to monitor the response to antimicrobial treatment[12]. Both Xie et al. and Dorr et al.'s studies looked into inflammation markers as another way to characterize patient wounds and establish some pattern between bacterial profiles, marker levels, and classification of a DFI.

Xie et al. noted elevated serum c-reactive protein (CRP) and procalcitonin levels in increasing Wagner and IDSA/IWGDF grade wounds. Moderate to severe wounds showed a dominance in gram-negative bacteria particularly *Pseudomonas;* Dorr et al. showed that gram-positive species had higher CRP and WBC levels compared to gram-negative species. However, results in Dorr et al.'s study only counted for wounds with more than a "moderate" bacterial count, while Xie et al. included all patients with DFIs ranging from low grade to severe at Wagner grades 1, 2, 3, and 4. Xie et al. points out that an increasing Wagner and IDSA/IWGDF grade coincides with an increase in gram-negative bacterial infections which does not support Dorr et al.'s findings. Xie et al.'s gram-negative species showed a higher CRP compared to gram-positive species. Dorr et al. studies

show patients with gram-negative accentuated DFI had lower CRP and lower WBC levels as seen in older patients.

CRP more than WBC can indicate DFI because it is nearly always elevated above UNL but never dramatically elevated. Another theory as to why infected diabetic foot ulcers may show normal or only slightly elevated inflammation marker levels is that dysfunctional wound healing in diabetics is attributed more to a process involving the tissue's extracellular matrix and a dysfunction in growth factor levels.

Overall, neither study could establish a significant link between inflammation marker levels and the bacterial profiles of DFU types, especially between younger and older patients.

Microbial Patterns in Younger and Older Patients

Previous literature establishes *Staphylococcus aureus* as the most frequent and virulent pathogen isolated in DFIs[13]. The decision to which type of antimicrobial coverage to pursue takes into consideration the severity of the infection which can be classified by two widely used wound grading tools commonly used in evaluating first time patients. Xie et al. and Dorr et al. utilized both the Wagner-Armstrong and SINBAD scores in evaluating their study groups, but Xie et al. included two additional wound classification systems: IDSA/IWGDF and typing a diabetic foot with a neuropathic component, vascular component, or both.

Dorr et al. found 61.5% of DFIs were caused by gram-positive bacteria dominated by *Staphylococcus aureus* with an increase in age making a diabetic foot infected with *S. aureus* more likely. MacDonald presented supportive findings with *Staphylococcus aureus* accounting for 84.4% of monomicrobial infections not influenced by gender or wound location but with age.

Although Dorr et al. was the only study to have two age-separated groups defined as "younger" at 70 years of age and younger and "older" at 70 years of age and older, all the studies were able to establish a pattern between increasing age and an increase in *Staphylococcus aureus* infections. Dorr et al. found between the age groups a slight increase in *S. aureus* associated with increase in age and a slight decrease in *Streptococci*.

Wounds with ischemia saw a slight increase in gram-negative bacteria between the two studies. The most common gram-negative bacteria found in DFIs was *Pseudomonas, Enterobacteriacea, Proteus, E. coli,* and *Klebsiella.* Xie et al. found more gram-negative bacteria to gram-positive bacteria in 54.1% of DFIs; however, most of Xie et al.'s study group were patients between the ages of 50 to 80 years old with ischemia associated with DFIs. Both Xie et al. and Dorr et al. determined that older patients tend to present with higher Wagner-Armstrong and IDSA/IWGDF grades with gangrene of the foot usually dominated by gram-negative species. Gram-negative species are more than five-fold frequent than gram-positive species when gangrene is present[1]. Older patients are also more at risk to present with chronic DFUs as opposed to acute DFUs where the spectrum of a superficial diabetic foot infection is more likely due to a gram-positive pathogen such as *S. aureus* or *Streptococcus.* Chronic ulcers are deeper with a possible history of previous treatment and are therefore more polymicrobial in nature and more likely to involve *Pseudomonas* and Enterobacteriaceae.

Xie et al. showed *Streptococcus* was detected only in wounds with Wagner grades of 2, 3, and 4 and in IWGDF scores of 2, 3, and 4. However, Xie et al.'s study was limited by the small number of patients with IWGDF-1 and Wagner scores of 1. *Streptococcus* would not be detected in an IWGDF score of 1 because it is a score that classifies a wound as being uninfected with no inflammation or purulence while a Wagner score of 1 classifies a superficial uncomplicated ulcer usually dominated by *S. aureus.*

The localization of a wound can influence microbial patterns which can also be associated with age. Dorr et al. maintains that hindfoot ulcers usually contain more gram-negative bacteria in comparison to plantar and forefoot ulcers, and that with an increase in age ulcers move from hindfoot to the toes[2]. Gram-positive species more seen in forefoot lesions can explain why there might be an increase in *S. aureus* seen in DFIs of the older patient. Xie et al. classified Neuro-Ischemic foot ulcers (N-IFUs) to be more susceptible to gram-negative bacteria and a type of wound comparable to higher graded Wagner and IWGDF foot ulcers. But overall *Staphylococcus aureus* was the dominant pathogen in a polymicrobial infection.

MacDonald had a limited sample size and could make no associations between wound location and bacterial patterns.

LIMITATIONS

Xie et al. and Dorr et al. lacked anaerobic culturing, an important pathogen that is implicated in more severe DFIs involving gangrene and higher wound grade scores. All studies had limited patient size.

CONCLUSION

In conclusion, gram positive species mostly S. aureus and Enterococcus, Streptococci and Corynebacteria contribute to the spectrum of bacterial diversity in diabetic foot ulcer patients. As individuals get older, not only do they develop the risk of complicated foot infections that result in foot ulcers but a strong association with an increase in *S. aureus, Streptococcus,* and *Pseudomonas aeruginosa*. Foot ulcer localization also influences bacterial diversity in infected diabetic foot ulcers.
Xie et al. and Dorr et al. determined that older patients presented with higher Wagner-Armstrong and IDSA/IWGDF grades with gangrene of the foot usually dominated by gram-negative species.

AUTHORS' CONTRIBUTION

All authors equally made substantial analysis, interpretation, and contribution to the production of this article. All authors participated in all revisions and approved the final draft for submission.

REFERENCES

1. Dorr et al., S., Freier, F., Schlecht, M. *et al.* Bacterial diversity and inflammatory response at first-time visit in younger and older individuals with diabetic foot infection (DFI). *Acta Diabetol* 58, 181–189 (2021).
2. Dorr et al., S., Schlecht, M., Chatzitomaris, A., Weisser, G., Lucke-Paulig, L., Friedl, A., Joachim, R., Lobmann, R. Predictive Effect of Inflammatory Response and Foot Ulcer Localization on Outcome in Younger and Older Individuals with Infected Diabetic Foot Syndrome. Exp Clin Endocrinol Diabete. 2021; 129: 878–886 https://doi.org/10.1055/a-1149-8989

3. Patel, D., Sen, P., Hlaing, Y., Boadu, M., Saadeh, B., & Basu, P. (2021). Antimicrobial resistance in pseudomonas aeruginosa biofilms. *Journal of Pure and Applied Microbiology*, *15*(4), 2520–2528. https://doi.org/10.22207/jpam.15.4.79
4. Selva Olid, A., Solà, I., Barajas-Nava, L. A., Gianneo, O. D., Bonfill Cosp, X., & Lipsky, B. A. (2015). Systemic antibiotics for treating diabetic foot infections. *Cochrane Database of Systematic Reviews*, *2015*(9). https://doi.org/10.1002/14651858.cd009061.pub2
5. Skrepnek GH, Mills JL Sr, Armstrong DG (2015) A diabetic emergency one million feet long: disparities and burdens of illness among diabetic foot ulcer cases within emergency departments in the United States 2006–2010. PLoS ONE 10:e0134914
6. Armstrong D, Boulton M, Bus S. Diabetic foot ulcers and their recurrence. *N Engl J Med* (2017) 376(24):2367–75. doi: 10.1056/NEJMra1615439
7. Xie X, Bao Y, Ni L, Liu D, Niu S, Lin H (2017) Bacterial profile and antibiotic resistance in patients with diabetic foot ulcer in Guangzhou (Southern China): focus on the differences among different Wagner's Grades, IDSA/IWGDF grades, and Ulcer types. Int J Endocrinol. https://doi.org/10.1155/2017/8694903
8. Macdonald KE, Jordan CY, Crichton E et al (2020) A retrospective analysis of the microbiology of diabetic foot infections at a Scottish tertiary hospital. BMC Infect Dis 20:218. https://doi.org/10.1186/s12879-020-4923-1
9. EmmaHook. (n.d.). Complications of diabetes. Diabetes UK. Retrieved January 1, 2023, from https://www.diabetes.org.uk/guide-to-diabetes/complications
10. Hamilton Em, Scheepers Jo, Ryan H, Perrin B, Charles J, Cheney J, Twigg S., Australian Guideline on Wound Classification of diabetes-related foot ulcers. 2021, from https://www.diabetesfeetaustralia.org/wp-content/uploads/2021/03/Wound-Classification-Supplementatary-Doc-V1.0.pdf
11. Lipsky B, Berendt A, Cornia P, Pile J, Peters E, Armstrong D, Deery H, Embil J, Joseph W, Karchmer A, Pinzur M, Senneville E 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. Clinical Infectious Diseases, 15 June 2012, Volume 54, Issue 12, Pages e132–e173, https://doi.org/10.1093/cid/cis346
12. Weintrob A, Sexton D. Clinical Manifestations, diagnosis, management of diabetic infections of the lower extremities (UpToDate) [Internet]. Available from: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-management-of-diabetic-infections-of-the-lower-extremities.
13. Selva Olid A, Solà I, Barajas-Nava LA, Gianneo OD, Bonfill Cosp X, Lipsky BA. Systemic antibiotics for treating diabetic foot infections (Review). Cochrane Database of Systematic Reviews. 2015, Issue 9. Art. No: CD009061. DOI: 10.1002/14651858.CD009061.pub2

The Difference in Dermatological Manifestations Between Kaposi Sarcoma and Diabetic Foot Ulcerations: A Literature Review

Faiyaz Mohammad Rahman, BA; Jason Singh, BA; Harman Manj, BA; Muhammad Abdulla, BA

ABSTRACT

Introduction:
Kaposi sarcoma (KS) is a low-grade vascular tumor with an endothelial cell lineage in the lining of blood and lymph vessels. KS is usually found in the lower extremities, nasal region of the face, oral and genital mucosa. More than 95% of the lesions caused by Kaposi sarcoma is due to an infection with a gamma herpes virus, human herpes virus 8 (HHV-8). KS may present as painless, non-pruritic, and violaceous (sometimes red or brown) nodules, patches, or plaques on the skin. This paper evaluates the current literature on the differences between lesions formed by Kaposi sarcoma and by foot ulcerations formed in patients with diabetic distal neuropathy.

Study design: Qualitative systematic review of literature

Methods: A literature search was performed using PubMed with the query "Kaposi sarcoma AND diabetic foot ulcer." After applying the inclusion criteria for filters composed of articles that involved human subjects and published in English between 1/01/2012 and 10/17/2022, the query yielded ten articles. Exclusion criteria removed articles not discussing Kaposi sarcoma or diabetic foot ulceration in the title or in the abstract. After applying the inclusion and exclusion criteria, a total of four articles were selected for review.

Results: Amongst the four articles selected for review, one article was an in-depth analysis of a rare ulcerative variation of Kaposi sarcoma. The articles were analyzed with an emphasis on comparing typical diabetic foot ulcerations with Kaposi sarcoma lesions.

Discussion and Conclusion:
KS shares characteristics of several lesions including diabetic neuropathic foot ulcerations. Because KS is rare, it is difficult to draw reliable conclusions differentiating KS lesions and diabetic neuropathic ulceration. In these cases, a proper clinical biopsy is essential for confirmation of KS. Although rare, it is important to correctly diagnose KS due to possible systemic or fatal complications, especially within the pulmonary tract.

Keywords: Kaposi sarcoma, diabetic foot ulcer, human herpesvirus-8, lower extremity

Level of evidence: Level 4

INTRODUCTION

Background

Kaposi sarcoma (KS) is a low-grade vascular tumor with an endothelial cell lineage in the lining of blood and lymph vessels.[1] KS is usually found on the lower extremities, nasal region of the face, and oral and genital mucosa.[2] KS constitutes approximately 1% of all worldwide diagnosed cancers.[2] Although it is commonly regarded as a complication of AIDS, five subtypes of KS have been identified, several of which are not associated with an immunocompromised state. The five subtypes are as follows: classic KS, African endemic KS, immunosuppression-associated KS, AIDS-associated KS, and non-epidemic gay-related KS.[2] In immunosuppression-associated KS, Kaposi sarcoma may be transmitted following organ transplantation if a patient is in an immunosuppressed state for an extended period. Classic KS is a rare and indolent cutaneous disease, most often reported in the Mediterranean population as slowly progressing, chronic lesions that are limited to the skin without systemic effects. This form of KS predominantly affects males (15:1) over 50 years of age.[3] However, in addition to the cutaneous effects of Kaposi sarcoma, non-epidemic gay-related KS patients have extra-cutaneous systemic spread in the oral cavity, gastrointestinal tract, and respiratory tract. Non-epidemic gay-related KS cases have also been largely associated with HPV infection.[1] The presentation for non-epidemic gay-related KS is similar to classical KS but also uniquely presents on the extremities and on the genitalia. These patients may often also have an HIV infection or AIDS that is associated with Kaposi sarcoma.[2] This form of KS is 20,000 times more common than the general population of individuals with diagnosed Kaposi sarcoma and it is reported 300 times more often than other immunosuppressed patient cases. Most of the reported KS subtypes have been reported in homosexual males or elderly Jewish males or males of Mediterranean descent.[1] Classic Kaposi sarcoma (KS) is rare and is not often included as a differential diagnosis in a patient with diabetic neuropathic foot ulceration.[4] It is critical that attendings and clinicians remain observant regarding the distinct similarities and differences in the clinical presentation of classic KS lesions that can also ulcerate and to those of diabetic foot ulcers (DFUs).[3] There are two categories of DFUs: either neuropathic or neuroischemic. Neuropathic ulceration occurs on the weight-bearing surfaces of the foot such as the plantar metatarsal heads. Important features that can differentiate neuropathic ulceration from neuroischemic ulcerations are the presence of pain and the surrounding wound margins. Neuropathic ulcerations are painless with a well-defined, often hyperkeratotic wound margin.[4] This peri-wound hyperkeratosis is a definitive characteristic of neuropathic foot ulcerations.[3] Abnormalities in gait biomechanics can result in mechanical stress-induced calluses to specific regions of the foot, that can potentially ulcerate if the underlying etiology is not addressed for an extended period. Neuroischemic ulcerations, on the contrary, tends to be painful and located on the foot edge, the distal aspects of the toes and on the posterior aspect of the heel. The neuroischemic foot type often presents with absent pulses, atrophy of the skin, absence of pedal hair and coolness from the compromised peripheral arterial blood circulation. When a suspected DFU does not improve with local wound care, other etiologies, including KS, should be considered.[4]

Classic KS lesions commonly present in the soles and arches of the foot prior to progression into the ulceration.[4] As previously mentioned, local wound care management is not the solution to control and resolve the KS lesions since they are tumors of viral origin.[4] In contrast to diabetic foot ulcerations, which are typically symmetrical, KS lesions are generally asymmetric, without the presence of peri-wound hyperkeratosis. Initial evaluation of a suspicious lesion can follow the ABCDE and CUBED diagnostic protocols.[3] The ABCDE protocol is used to identify a potential melanoma. With this protocol, the lesion is assessed for asymmetry, irregular border, multiple colors, diameter greater than 6mm, and elevation. The CUBED protocol assesses the multiple color of the lesion, diagnostic uncertainty, bleeding, enlargement of the lesion and any delay in healing. If a foot lesion demonstrates two or more CUBED criteria, then a biopsy is advised.[4]

In 1994, a link between KS and a potential transmissible agent was identified.[1] More than 95% of Kaposi sarcoma lesions are from a gamma herpes virus, human herpes virus 8 (HHV-8). KS may present as painless, non-pruritic, and violaceous (sometimes red or brown) nodules, patches, plaques on the skin.[1] These cutaneous manifestations of KS may also be mistaken for bruising, varicose veins, or telangiectasia.[3] Kaposi sarcoma lesions present symmetrically as elliptical or linear lesions along the cutaneous tension lines without necrosis of the skin or structures beneath the skin.[1] Kaposi sarcoma is important to monitor because it may appear similar to benign skin conditions or other common pathologies such as diabetic foot ulcers. Diabetic foot ulcers are exposed sores or wounds that usually appear on the plantar aspect of the foot. Approximately 15% of diabetic patients develop foot ulcers, of which 6% of patients may require hospitalization. These ulcers are formed due to multiple factors: foot deformities, trauma, venous insufficiency, lack of circulation, and numbness in the feet. The severity of these risk factors is increased if the patient has had diabetes for a significant period.[3] Peripheral neuropathy is a common result of diabetes and may lead to poor blood flow in the extremities which may lead to ischemia, especially the lower extremities. It is important to closely monitor diabetic foot ulcers because they are painless and can often go undetected by the patient due to a lack of noticeable symptoms. Diabetic foot ulcers may often be confused with other infections, such as Kaposi sarcoma or other related infections, due to the similarity in their symptoms.[3] Although rare, Kaposi sarcoma, if left untreated, may progress to systemic pathologies, which can be prevented if identified early.[3]

Treatments

Kaposi sarcoma treatment focuses on supportive care, halting the progression of the disease, and shrinkage or removal of tumors and lesions to reduce edema, organ damage, and psychological stress. It is important to have a high index of suspicion of KS if there are rapidly progressing lesions in areas of the lower extremity, such as the plantar aspect of the foot.[2] Highly active antiretroviral therapy (HAART) is commonly prescribed for AIDS-related KS.[1] A patient is treated more aggressively if the KS is rapidly expanding, if a low CD4 count is present, if there is a high viral load of HIV or if the patient is generally immunocompromised. Apart from HAART, local therapies may be used for cosmetic management, such as intralesional chemotherapy (i.e. liposomal doxorubicin also known as Doxil), topical alitretinoin, or radiation therapy. These therapies, however,

do not prevent the development of new lesions. Highly specific treatment against HHV-8 is also not widely currently available.[1]

Objective

This paper evaluates the current literature on the differences between KS and neuropathic and neuroischemic ulceration in patients with diabetes mellitus.

METHODS

A literature search was performed using the PubMed database with the query "Kaposi sarcoma AND diabetic foot ulcer" yielding ten articles for the initial search. Inclusion criteria included articles that involved human subjects and publication in the English language between 1/01/2012 and 10/12/2022. After applying the inclusion criteria, the search query yielded seven articles. Exclusion criteria removed articles not discussing Kaposi sarcoma or diabetic foot ulcerations in the title or in the abstract. After applying the inclusion and exclusion criteria, four articles were selected for review.

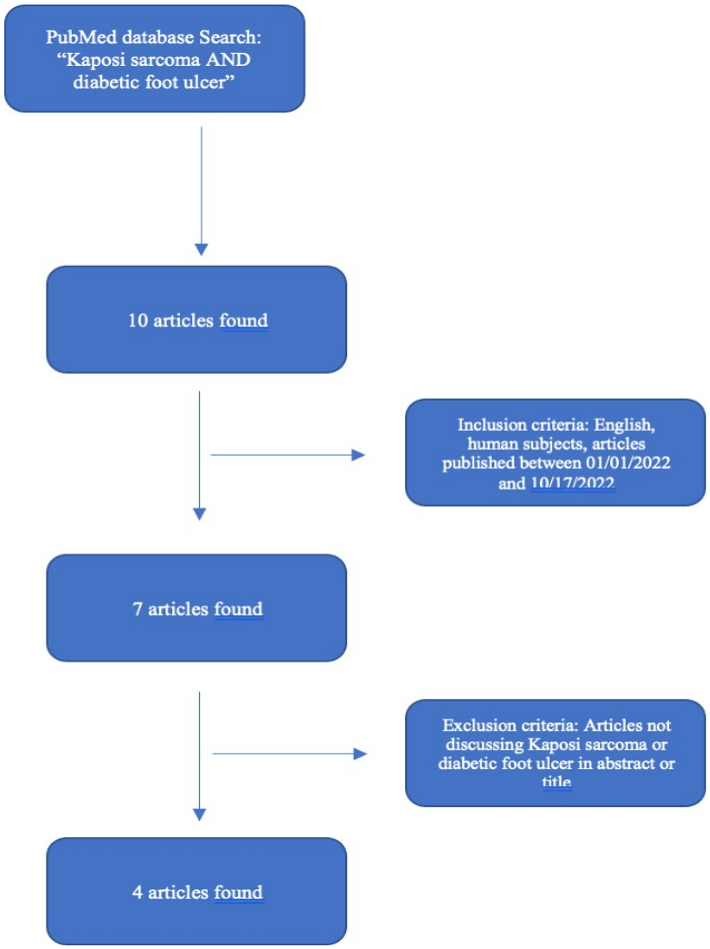


Figure 1: Articles obtained after inclusion and exclusion criteria applied

RESULTS

Table 1. Summaries of Articles Reviewed

Title, Publication Year	Authors	Relevant Results
Red flags and alarm bells: an atypical lesion masquerading as a diabetic foot ulcer, 2012[3]	Koo E et al.	In a case study for a diabetic individual presenting with unidentified lesions, several punch biopsies of approximately 4mm by 4mm were collected from different lesion sites from the patient who left his painless lesions untreated. They were identified as positive for HHV-8 and classic Kaposi sarcoma. Due to the loss of sensation from peripheral neuropathy from diabetes, the patient did not feel pain and his lesions were left untreated for an extended period. He sought medical assistance when the lesion on the right foot became ulcerated and increased with size. The misdiagnosis of neuropathic foot ulcer could have been detrimental for this patient if the biopsy was not taken and identified as KS. Other methods may also be employed visually such as asymmetry, border irregularity, color variation diameter and evolution of lesion to help confirm the diagnosis.
A case of mistaken identity: classic Kaposi sarcoma misdiagnosed as a diabetic foot ulcer in an atypical patient, 2019[4]	Torrence GM et al.	Diabetic patients are vulnerable to infection and tumor growth because high levels of blood glucose contribute to the lytic gene expression of HHV-8 leading to active Kaposi sarcoma lesions. Classic KS is rare in African American males who are HIV-negative and heterosexual population. Despite this rarity, it is important to be aware that the association between diabetic patients and Kaposi sarcoma may occur in any background and any variation of Kaposi sarcoma should not be immediately ruled out due to the background of the patient.

An interesting case of 'diabetic foot ulcer' in an HIV-positive patient, 2015[5]	Sivaprakasam V et al.	Kaposi sarcoma may appear similar to diabetic foot ulcers and require further testing to differentiate. The ulcers created in both conditions may be foul and may have infestations by organisms such as maggots, especially in the plantar foot. The cutaneous manifestation of the KS lesions may be pronounced in diabetic patients with foot ulcers because they are more susceptible to develop new ulcers and infection by HHV-8. In AIDS-related Kaposi sarcoma, antiretroviral therapy may relieve the cutaneous symptoms of Kaposi sarcoma and reduce the likelihood of systemic effects of Kaposi sarcoma in the pulmonary tract, which has the highest mortality associated with Kaposi sarcoma. Due to its high coincidence in patients with HIV infections or AIDS, it is important to have individuals diagnosed with Kaposi sarcoma also be tested for HIV/AIDS to consider other infections due to their increased immunocompromised state.
Human Immunodeficiency Virus-Negative-Associated Lymphangioma-like Kaposi's sarcoma with Variable Clinical Presentations, 2017[6]	Kotzias et al.	Lymphangioma-like Kaposi sarcoma (LLKS) is a rare variation of KS (5%) which is often associated with the lower extremity lesions that resemble exophytic ulcerated cauliflower lesions and no systemic involvement. Diabetic patients with foot ulcers may have worsened cases due to their increased likelihood of developing ulcers and leaving them untreated due to lack of sensation. However, LLKS also involves dilated lymphatics, spindle cell hemangioma, lymphangioendothelioma, neurofibroma, low grade angiosarcoma, leiomyoma and inflammatory pseudotumor. This is another case where KS should not be ruled out even if the patient is HIV negative.

DISCUSSION

The pathologies related to KS in patients with diabetes mellitus and foot ulcerations is complex and varies in its manifestation in the patient. Koo et al. reports that the cutaneous features of ulcerated lesions from KS strongly resemble the ulcers that a patient exhibits if he or she has diabetes mellitus with distal sensory neuropathy.[3] The multiple purple ulcerated lesions also resemble untreated neuropathic ulceration. There may also be satellite lesions of with irregular nodules that present in KS. Koo et al. suggests that the ulcerated lesions present in KS may also resemble lesions formed in pyogenic granuloma, nodular melanoma, melanocytic nevi, or arteriovenous malformation.[3] Due to its shared features with other skin infections and conditions,

the most currently reliable method of confirming KS is through a biopsy of the suspected lesion. The lesions are assessed based on the asymmetry, border irregularity, color variation, diameter (if greater than 6mm) and evolution of the lesion (i.e. elevation or enhancement of size). Suspected KS lesions are also observed for any bleeding, which includes chronic granulation tissue or any delay in healing.[3] Unlike benign lesions or diabetic foot ulcers, which usually present in symmetrical pattern, Kaposi sarcoma lesions in the case report by Koo et al. illustrate an asymmetrical growth pattern without the "peri-wound callous formation" that is usually associated with neuropathic foot ulcers in diabetic patients. The KS lesions described by Koo et al. were also not on a weight bearing surface (i.e. metatarsal heads) but rather on the non-weightbearing plantar surface of the foot, which is a common problem site for cutaneous manifestation of Kaposi sarcoma (i.e. heel or plantar metatarsal heads).[3] It is important to understand the specific differences between Kaposi sarcoma lesions and diabetic foot ulcers because they may appear in similar body parts but they may also have very different effects on the rest of the body. While Kaposi sarcoma may involve systemic infection, lesions like diabetic foot ulcers may be more limited to one region. Both cases require unique and specific treatments that are different from one another. In patients with a known prior history of diabetes mellitus type 2, it is critical to identify key characteristic differences in lesions formed by Kaposi sarcoma and foot ulcers because clinicians may often overlook other underlying factors due to its rarity, especially in diabetic patients who are prone to developing foot ulcers. Because there is a reported correlation between Type 2 diabetes mellitus and Kaposi sarcoma, African American populations may be more susceptible to KS.[4] Torrence et al. describes the case of an 80-year-old African American male with stabbing pain in the fifth digit of the right foot after stubbing it two months prior. His digit was reported to have a granulomatous mass in the medial aspect of the fifth digit with two distinct cyanotic papules. KS lesions in individuals with a darker skin complexion are more difficult to identify because KS lesions are usually purplish and may blend with normal skin.[4] Local wound care, which is the typical treatment of choice in diabetic foot ulcers, was not sufficient for this patient who required higher doses of topical retinoid therapy to relieve Kaposi sarcoma symptoms, and intralesional therapy with Doxil. Surgery and radiation may also be used to improve the cosmetic appearance and psychological health of the patient, which may also be a contributing factor to the frequency of manifestations of Kaposi sarcoma related lesions.[4] Due to this case of KS being present in a darker skinned, HIV-negative heterosexual man, KS was not the primary suspect as it is more prevalent in the homosexual population, which also has a higher incidence of HIV. Another form of Kaposi sarcoma that is not AIDS related but is a rare variant is lymphangioma-like Kaposi sarcoma (LLKS).[6] Kotzias et al. reports a 63-year-old diabetic Haitian man with numerous slowly progressing, ulcerated and poorly demarcated lesions on the left lower extremity. LLKS is frequently associated with lower extremity lesions resembling exophytic ulcerated cauliflower lesions and no systemic involvement.[6] Kotzias et al. reports LLKS is alarming because it may expand beyond the edges of the lesions it forms and affects the internal organs more readily than other variations of Kaposi sarcoma.[6] Upon histological evaluation, LLKS is described to have ectatic vascular channels lined with endothelial permeating

the dermis without spindle cell proliferation.[6] LLKS is associated with dilated lymphatics, spindle cell hemangioma, lymphangioendothelioma, neurofibroma, low grade angiosarcoma, leiomyoma and inflammatory pseudotumor. Detailed biopsy techniques such as shave, punch, curette, incisional and excisional biopsy along with identification of dilated lymphatic vessels in histopathology of the lesion are critical in identifying LLKS as opposed to other KS. Similar to diabetic foot ulceration, this variation of KS has a significant malodor and appearance of pus. Early diagnosis may lead to better long-term prognosis with optional resections and radiotherapy.[6]

Kaposi sarcoma is often reported in patients that are also infected with HIV. In 2010, 162 out of 172 UK cases of Kaposi sarcoma reported HIV as a coinfection as opposed to just an infection by HHV-8 which causes Kaposi sarcoma.[5] Venkat et al. describes a case of a 70-year-old British male who was a HIV positive with Kaposi sarcoma. In addition to the general appearance of classic KS, individuals with AIDS-related Kaposi sarcoma also suffer from other infections that may complicate the region where the Kaposi sarcoma lesion may be found, such as oral candida. There may be genitalia ulcerations, such as in the case of this man, who had ulcerations in the glans of the penis causing a stenosed meatus.[5] The left foot of the patient had nodules, which resembled a diabetic foot ulcer because it was violaceous and covered with slough on the plantar surface extending to the dorsum surface of the foot. The histopathology of this individual depicted lobular proliferation of the dermis with cellular, well-formed vessels between spindle cells without disruption of the skin. The foot lesions could not definitively be confirmed to be caused by Kaposi sarcoma until a biopsy was obtained and the tissue tested for HHV-8 because of the shared features between Kaposi sarcoma lesions and diabetic foot ulcerations.[5]

Kaposi sarcoma is an important complication in several patient populations based on ethnicity, sexual practices and immunocompetence. KS form lesions that resemble many benign conditions, however, it shares many features with diabetic foot ulcers, and it often targets diabetic patients due to their immunocompromised state. Although often reported with an HIV co-infection or AIDS, Kaposi sarcoma is not limited to one population or one form of lesion.

The literature states the continuous importance of having a broad differential when evaluating patients with plantar ulcerations. Koo et al. suggests the clinical findings of Kaposi sarcoma often resemble lesions also formed in nodular melanoma, pyogenic granuloma, melanocytic nevi, or arteriovenous malformation. Furthermore, in a case report by Koo et al., Kaposi sarcoma lesions present in asymmetrical growth pattern without a peri wound callus formation which is usually indicative of a neuropathic foot ulcer found in diabetic patients.[3] The lesions relating to Kaposi sarcoma described by Koo et al. was not on weight bearing surfaces such as the metatarsal heads, but rather they were on the plantar surface of the foot.[3] These findings indicate the importance of location in distinguishing between Kaposi sarcoma and diabetic foot ulcerations. Torrence et al. further reported that local wound care which is the treatment of choice for diabetic foot ulcer was not an adequate treatment regimen for a patient with Kaposi sarcoma. A patient with lesions resembling Kaposi sarcoma would require topical retinoid treatment and intralesional therapy.[4]

Kaposi sarcoma is often reported with patients infected with HIV or suffering from AIDS. Torrence et al. states that it is imperative to be aware that the association

between diabetic patients and Kaposi sarcoma may occur in any background and should not be ruled until an adequate diagnosis is made.[4] Sivaprakasam et. al reports the ulcerations of Kaposi sarcoma lesions and diabetic foot cannot be distinguished until a pertinent medical history and biopsy of the lesions is obtained.[5] Sivaprakasam et. al also suggests that although the skin is a common site of Kaposi sarcoma lesions, extracutaneous lesions may also occur in the gastrointestinal tract and lungs.[5] A comprehensive medical history, physical examination and biopsy evaluation are key components in identifying KS lesions and ruling out DFU. This is essential in the determination of a proper treatment course for the patient which can otherwise result in systemic or fatal complications, especially within the pulmonary tract, if there is a delayed diagnosis for Kaposi sarcoma.

CONCLUSION

Current research contrasting diabetic foot ulcer or other skin lesions from Kaposi sarcoma is limited. Although diabetic foot ulcers tend to resemble KS lesions if they ulcerate and remain open for long periods of time with their purplish and prominent color, diabetic foot ulcers tend to be symmetrical without callus forming around the wound and appear on weight bearing surfaces. In contrast, KS wounds are found on non-weight bearing surfaces and throughout the body as expected since it is due to a systemic infection. The medical history, progression of the lesions and biopsy techniques used to extract lesions are critical in determining the pathology related to Kaposi sarcoma. Further research should explore lesions between subtypes of Kaposi sarcoma to better differentiate Kaposi sarcoma lesion from diabetic foot ulcers and to inform our ability to have an earlier and more accurate prognosis for patients.

LIMITATIONS

The limitations to this literature review were that many of the articles selected were primarily case reports. Due to the rarity of KS, it is difficult to draw reliable conclusions about the different stages of the lesions and how they may differ between subtypes and diabetic neuropathic foot ulcerations. The studies referenced in the literature were also limited to the articles published within the last ten years. Current literature comparing lesions of KS to diabetic neuropathic foot ulcerations is lacking as the scope of this literature review was primarily able to encompass four articles relating to the topic.

AUTHORS' CONTRIBUTION

All authors contributed equally to this literature review. All authors drafted and reviewed the final manuscript.

STATEMENT OF COMPETING INTERESTS

The authors state that there were no competing interests in completing this manuscript.

REFERENCES

1. Phavixay L, Raynolds D & Simman R. Non AIDS Kaposi's sarcoma Leading to Lower Extremity Wounds, Case Presentations and Discussion. *Journal of the American College of Clinical Wound Specialists*. 2012;4(1): 13-15.
2. Schmidt BM & Holmes CM. Classic Solitary Kaposi sarcoma of the Foot in an Immunocompetent Patient: A

Case Report. *Index Wounds*. 2016;28(9): E35-E40

3. Koo E, Walsh A, Dickson H. Red flags and alarm bells: an atypical lesion masquerading as a diabetic foot ulcer. *Journal of Wound Care*. 2012;21(11): 550-552.
4. Torrence GM & Wrobel JS. A case of mistaken identity: classic Kaposi sarcoma misdiagnosed as a diabetic foot ulcer in an atypical patient. *Clinical Diabetes and Endocrinology*. 2019;5(8).

5. Sivaprakasam V & Chima-Okereke C. An interesting case of 'diabetic foot ulcer' in an HIV-positive patient. *International Journal of STD & AIDS*. 2015;26(4): 285-287.

6. Kotzias G, Modupe A, Isaac L & Khaladj M. Human Immunodeficiency Virus-Negative-Associated Lymphangioma-like Kaposi's sarcoma with Variable Clinical Presentations. *Journal of the American Podiatric Medical Association*. 2017;107(5): 461-466.

The Efficacy of Resveratrol on Wound Healing

Sebastian Sukdeo, BS; Naila Habeeb, MS; Nikki Hammond, MA; Bryant Tufino Flores, BA

ABSTRACT

Introduction
Diabetics in the US is a consistently growing population group, which brings with it issues relating to chronic wounds and wound healing. While there are numerous therapies, drugs, and combinations of both; many fall short in their ability to respond to the various pathways involved when it comes to wound healing. However, Resveratrol shows promise as a result of its various properties that allows it to tackle the complexity that is wound healing, making it a worthwhile drug to further assess and compile the current knowledge base available . This review serves to understand the efficacy of Resveratrol's synergistic properties and highlight its importance in diabetic wound healing.

Study Design: Qualitative Systematic Review of Literature

Methods
A literature search was performed on PubMed with the aim of looking at the relationship between Resveratrol, wound healing, and skin. The search yielded 48 articles, and after applying a date restriction and inclusion criteria, seven articles met the criteria .

Results
PubMed database search yielded 48 articles initially. Once the inclusion and exclusion criteria was applied, 7 articles met these criteria and were thus analyzed in this literature review. Resveratrol reduces oxidative stress, upregulates collagen formation and increases endothelial cell proliferation all of which contribute to enhanced wound healing.

Conclusions
Each of the included publications emphasize Resveratrol's synergistic ability to work with other structures to bring about stable wound healing in diabetic subjects. Resveratrol showcases itself as a versatile compound that improves the wound healing process in a variety of treatment plans and should be considered in protocols that deal with diabetic patients. Additional research to expand upon the clinical relevance of Resveratrol should be conducted on a large sample of human diabetic patients. This study should determine a clinical dose and track the full progress of the wound healing process to help determine a more standardized clinical use of Resveratrol.

Keywords: Resveratrol, Wound healing, Diabetes, Antioxidant, Anti-inflammatory, Chronic wounds, Grapes, polyphenol

INTRODUCTION

In the United States there are over 130 million adults who have diabetes and billions of dollars are spent every year due to this chronic disease.[1,2] Complications that arise from diabetes include, but are not limited to, hyperglycemia, neuropathy, cardiovascular disease, and renal failure.[2-7] Due to the complications associated with diabetes, diabetics have impaired wound healing.[2,4,5] The wound healing process is highly regulated and must follow a certain succession in order for a wound to heal successfully. This process comprises four phases: hemostasis, inflammation, proliferation, and tissue remodeling.[2,4-7] Chronic wounds experienced by diabetes are due to the non-resolving inflammation phase.[2,4,6,7] The danger of chronic wounds is that they might get infected and cause further complications.[4,6,7]

There are multiple techniques currently being used to help diabetics progress past the inflammatory stage of healing. Debridement is regularly performed and involves removing dead skin from the wound which reduces the bacterial burden.[2] Other treatment strategies include dressings, oxygen therapy, negative pressure therapy, off-loading, grafts, and stem cell therapy.[2,4] These treatment strategies decrease inflammation, target ulcers, and reduces pressure in certain areas of the foot. [2,4] Growth factor therapies, hydrogels, and matrices are further curated treatments to encourage wound healing.[2,4,7] Growth factor therapies encourage wound healing in all of its phases, and hydrogels and matrices are often used in combination to promote both wound healing and the synthesis of collagen.[2] Together, depending on the severity and symptoms of the patient, each treatment plays a specific role in healing a wound. However, these methods are not entirely personalized to the mixed pathology of an individual's wound. They are rather restricted and generalized to all diabetic wound-healing patients. An understanding of the pathophysiology and the cells directly involved are still under heavy research, which will be important in catering treatments to each individual.[7] As a result, issues involving the targeting of appropriately timed treatments, chronic wound healing, and multi-molecular pathways are still prevalent.[2] Diabetic populations especially require a focus on physical and mechanistic factors behind their wounds, many of which current treatments are unable to tackle.[2,4] With the variety of different methods that exist, each have the ability to compensate for the patents diminished ability to heal, but the issues may remain without correct supervision and application of each treatment. Thus, modern-day methods provide the means to handle wounds in diabetic populations, but often lack specificity and the ability to handle the various molecular pathways that are impacted by the combination of diabetes and wounds.

Resveratrol is a natural polyphenol component of many plant species, such as grapes' skin, seeds, and food sources such as red wine, peanuts, and soy.[8] Its main role in plants is to protect from harmful environmental influences such as UV radiation, ozone exposure, and other toxins.[9] Additionally, it provides protection from fungal, bacterial, and viral infections. Due to these effects seen in plants, Resveratrol has been classified as having anti-oxidant, anti-inflammatory, and pro-angiogenic properties.[10] Most recently, in humans, suppressive effects have been seen during all stages of carcinogenesis including initiation, promotion, and progression with the use of Reservatrol.[10] In turn, Resveratrol can influence wound healing by reducing oxidative stress, promoting cell proliferation

and migration, influencing neovascularization, and inducing vascular endothelial growth factor (VEGF) expression, among other pathways and mechanisms.[9,11] Resveratrol has the potential to be researched further due to its impact in creating an environment beneficial to the wound healing process.

METHODS

A PubMed database literature search was performed to include the following terms "Resveratrol" AND "Wound Healing" AND "skin". The search was then filtered for publications after 2012. The inclusion criteria consisted of papers written in English, those mentioning diabetes, and both preclinical and clinical research. The exclusion criteria included papers that were not related to our topic and were not accessible. This yielded a total of 7 papers.

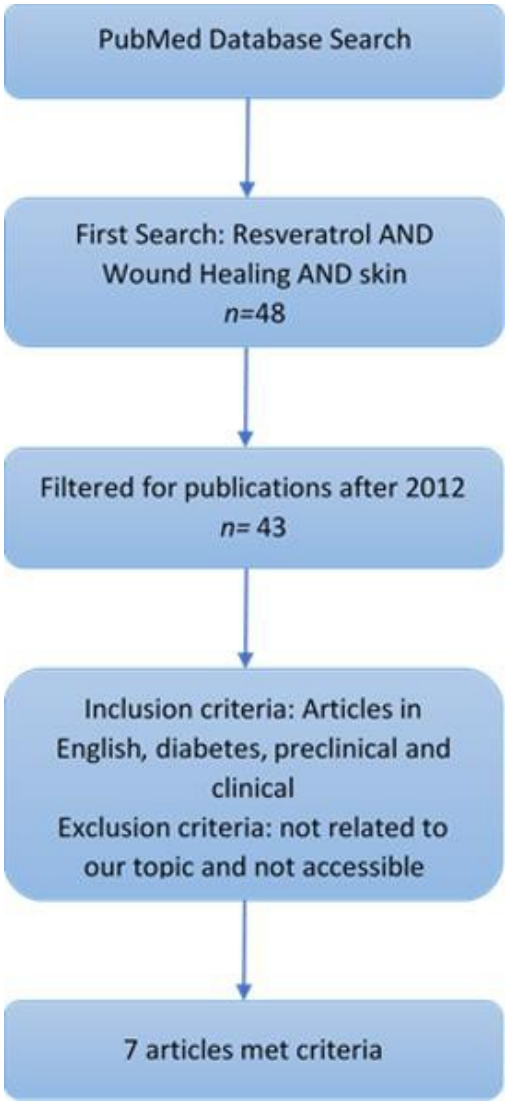


Figure 1. *Summary of how articles were acquired through inclusion and exclusion criteria*

RESULTS

Subject Type	Procedure	Effect on wound healing	Effect of Resveratrol	Conclusion	Reference
Mice Cell Lines	Varying amounts of H_2O_2 (10-100 μM) were added to simulate oxidative stress among fibroblasts. Then varying amounts of Resveratrol were added to the cell lines (1-100 μM). Following the setup. Oxidative stress levels and fibroblast migration were analyzed.	In the only H_2O_2 cell lines, the cells were hypertrophic and vacuolated and had other cell damage. The overall structural integrity of the cells was concerning. Overall, impeding wound healing.	The Resveratrol treated cell lines had a better-preserved structure in the nucleus, nucleolus, mitochondria, and normal junctions. Compared to the H_2O_2 only cell lines there is comparatively less vacuolization.	Overproduction of free oxygen species causes cellular oxidative stress and is associated with impairment of the wound healing process. In the process of inducing oxidative stress and using varying amounts of resveratrol it demonstrates the potential to improve wound healing to a certain extent. Future studies should be done with combinations of other substances.	Kaleci et al., 2020
Human Dermal Fibroblast Cells	Through the process of spray drying, Resveratrol was added into microparticles containing dipalmitoylphosphatidylcholine (DPPC) as well as hyaluronic acid (HA). Oxidative stress studies were done to evaluate effectiveness.	Promoted angiogenesis in wound healing and increasing DNA synthesis.	The presence of Resveratrol addicted the degradation time. There is increased cell proliferation and decreased oxidation in cells.	Demonstrates that Resveratrol can be encapsulated within HA and DPPC microparticles. Shows that it contains antioxidant activity and is dose dependent. However, this specific relationship has a synergistic effect, as result of Resveratrol only trials not being effective. This relationship shows promise for diabetic wound healing.	Erogl et al., 2014
Male Type 2 Diabetic Mice	Full thickness 6-mm punch biopsy on dorsal skin. Trans-resveratrol (5 micromol/L) and hesperetin (5 micromol/L) were added topically every day for 16 days.	Faster wound closure time compared to the control. Increase in capillary formation on treated wounds.	Increases GLO1 transcriptional activity	Overexpression of GLO1 in tissue accelerates wound healing and restores angiogenesis in type II diabetics	Li et al., 2019
Type 1 Diabetic Male Sprague-Dawley Rats	Rats were given an IP injection of sodium citrate containing STZ solution to induce Type I diabetes. An 8-mm diameter wound was created on the animal's back of full thickness. Wounds were covered by a conditioned medium of mesenchymal stem cells (MSC-CM) and some subjects also received 300 microM of resveratrol.	Animals treated with MSC-CM + Resveratrol had higher rates of wound healing as well as angiogenesis.	Promoted new collagen fiber formation. Increased Col-I and Col-II expression Downregulated proinflammatory cytokines (IL-1Beta, IL-6, and TNF-alpha). Upregulated antiinflammatory cytokines (IL-4, and IL-10)	Resveratrol treated MSC-CM promoted wound healing and angiogenesis.	Hu et al., 2022
Human Umbilical Vein Endothelial Cells (HUVECs)	Extracellular Vesicles (EVs) of rat MSC treated with resveratrol (SRT501) were isolated. Cell- counting Kit-8 Assay, Transwell, scratch test, tube formation and immunohistochemical assay were done to determine the effect of SRT501-EVs on HUVECs	N/A	Increases the proliferation, migration, and tube formation of HUVECs. The expression of the vascular marker CD34+ was increased.	Resveratrol promotes the enhancing effect of MSC-EVs on migration, proliferation and angiogenesis of HUVECs.	Hu et al., 2022
Human Umbilical Vein Endothelial Cells (HUVECs)	HUVECs underwent RT-qPCR to analyze miR-129 levels from SRT501-EVs and MSC-CM EVs	N/A	Expression of miR-129 was increased	Resveratrol promotes angiogenesis by increasing the transfer of miR-129 by MSC-EVs	Hu et al., 2022

Human Umbilical Vein Endothelial Cells (HUVECs)	HUVECs underwent RT-qPCR and western blot analysis of TRAF6 expression with MSC-EVS or SRT501-MSC-EVs	N/A	Decreased expression of TRAF6	EVs from Resveratrol treatment causes a downregulation of TRAF6	Hu et al., 2022
Type 1 Diabetic Male Sprague-Dawley Rats	Rats were given an IP injection of sodium citrate containing STZ solution to induce Type I diabetes. An 8-mm diameter wound was created on the animal's back of full thickness followed by sh-TRAF6 or sh-NC treatment.	sh-TRAF6 increased wound healing and angiogenesis	N/A	Silencing of TRAF6 caused the same effects as resveratrol and promotes skin wound healing and angiogenesis in type I diabetics	Hu et al., 2022
Human Umbilical Vein Endothelial Cells (HUVECs)	SIRT1 was deleted in HUVECs by siRNA transfection. The cells were then serum starved in low glucose DMEM for 12 hrs and then treated with high or normal glucose with or without 10uM resveratrol for 72 hrs. HUVECs underwent semi-quantitative RT-PCR, western blot analysis, TUNEL staining, and immunofluorescence	N/A	Increased expression of SIRT1 and inhibition of FOXO1	Under high glucose conditions, resveratrol acts as an agonist of SIRT1 and stimulates c-Myc expression through promoting FOXO1 degradation ultimately improving endothelial survival.	Huang et al., 2019
Type II Diabetic Mice (db/db)	Resveratrol was administered at a 50 mg/kg/day dose to the 8-week-old mice for 4 weeks. Endothelial dysfunction and wound healing were explored via TUNEL staining, immunofluorescence, and photography in-vivo	Endothelial cell proliferation was promoted whilst apoptosis of endothelial cells was alleviated in wounds of db/db mice	Resveratrol lowered fasting blood glucose and insulin levels as well as promoted endothelial cell proliferation in-vivo.	Resveratrol accelerated wound healing by diminishing the overexpression of FOXO1	Huang et al., 2019
Human Umbilical Vein Endothelial Cells (HUVECs)	The cells were starved of serum for 18 h, and then treated with 0-800 μM of H_2O_2 or pretreated with 1-1000 nM of resveratrol shortly followed by 100 μM of H_2O_2. An MTT assay was then performed. A scratch assay was performed to assess wound rate closure among each treated cell group. An intracellular reactive oxygen species (ROS) kit was used to evaluate ROS levels.	The close rate of the scratched wound was smaller than the control group	Resveratrol protected HUVECs from oxidative-induced injuries. 100 nM of Resveratrol administration worked the best	Resveratrol is a key candidate for reducing oxidative stress in chronic wounds	Zhou et al., 2020
Male Diabetic Rats	Wound beds were created with a size of 1 cm in diameter per rat. The size was observed daily and imaged throughout 2 weeks. During this time, the wound of each control group was washed with saline every day while that of the Resveratrol group was washed with saline and Resveratrol every day.	Wound bed size significantly decreased along with a more complete skin structure and lower inflammatory response	Nrf2 and Mn-SOD expression was upregulated and H_2O_2 induced ROS production was reduced	Resveratrol treatment accelerated wound healing. Caused by Resveratrol, under Nrf2 regulation, Mn-SOD upregulation may be one of the factors in the acceleration of wound healing.	Zhou et al., 2020
Dermal Matrix	Via lyophilization, a collagen-laminin porous dermal matrix was created. Hyaluronic acid (HA) dipalmitoylphosphatidylcholine microparticles (DPPC) loaded with Resveratrol was added to the matrix	N/A	The matrix with the Resveratrol added revealed increased antioxidant activity	The larger size of the microparticles due to the matrix allowed for a significantly higher impact on wound healing due to how macrophages were less likely to phagocytize them	Gocke et al., 2017
Male Rats with induced Diabetes	Two thick round wounds were made via excision with a dermal punch biopsy of 6 mm and then the matrix was applied. After 14 days, skin tissue samples were taken	Matrix provided anti-inflammatory and antioxidant properties	Enhanced the synthesis of collagen and laminin during the proliferation stage	The matrix provided optimal water uptake which provided an ideal moisture level for wound healing. Including Resveratrol in the matrix created a synergistic effect that improved tissue reconstruction.	Gocke et al., 2017

DISCUSSION

Effect of Resveratrol on Wound Healing

Resveratrol has proven to be beneficial for wound healing in a number of ways.[11-17] Diabetic patients often struggle with having adequate blood flow to their extremities, which is essential for wound healing. Through the use of HUVECs testing, it was observed that Resveratrol has the ability to promote angiogenesis, thereby accelerating wound healing.[14] This has been seen in

animal subjects. Type 1 diabetic male rats with an 8-mm diameter wound were administered topical resveratrol for 16 days and experienced a significant increase in wound closer. The same study also saw an increase in new collagen formation and angiogenesis in these treated rats.[14] Resveratrol increases the stability of the wound while healing by increasing antioxidant activity, allowing for improved wound healing.[16] A similar trend has been seen in Type II Diabetic Mice models where wound healing is accelerated and angiogenesis is restored.[13] In addition, Type II diabetic mice who received subcutaneous injections of resveratrol had lowered resting blood glucose and increased endothelial proliferation.[15] One way in which resveratrol may be able to increase endothelial proliferation is by decreasing oxidative stress which is commonly seen in diabetic patients.[11,16] The administration of Resveratrol to Diabetic animal models and HUVECs accelerates wound healing.[13-17] The research on resveratrol's ability to improve wound healing in diabetic patients is lacking, but by analyzing animal and cell models, we would expect to see a similar trend of improved wound healing.

Mechanism of Resveratrol

What allows Resveratrol to be an effective compound for wound healing is its role in a variety of mechanisms of action. A key component of Resveratrol is its ability to reduce oxidative stress. By simulating oxidative stress in mice cell lines and using varying amounts of Resveratrol, one can determine that oxidative stress decreases with increased Resveratrol amounts.[11] This is further supported by structural analysis of the cells in which they were shown to be healthier than those of the control groups. Another potential route that Resveratrol has on reducing oxidative stress is through the upregulation of the Nrf2 and Mn-SOD pathway, which minimizes the effects that oxidative stress has on cells.[16] While in a study using punch biopsy and topical Resveratrol, GLO1 transcriptional activity is shown to be overexpressed.[13] Studies show that increased GLO1 transcriptional activity accelerates the wound-healing process, demonstrating another pathway in which Resveratrol affects wound healing.[13] Resveratrol even affects the cellular integrity of organisms, which correlate to improved wound healing results. Studies involving diabetic mice with wounds that were treated with a conditioned medium of mesenchymal stem cells in combination with Resveratrol showed great promise. Analysis showed that there was an increase in Col-I and Col-III expression.[14] Collagen formation is effective for wound healing as it speeds up the process and provides a supportive structural foundation for wound healing.[11] Furthermore, in the previously mentioned study, there was a downregulation of proinflammatory cytokines (IL-1Beta, IL-6, and TNF-alpha) and also an upregulation of anti-inflammatory cytokines (IL-4, and IL-10).[14] These cytokines play a key role in the steps of wound healing, as inflammation plays a major part in the healing process.[13] Resveratrol is also a silent information regulation 1 (SIRT1) agonist. A specific study of this known mechanism highlights the fact that increased expression of SIRT1 is a result of the inhibition of FOXO1. This

promotes endothelial cell proliferation, which furthers the wound-healing process.[15] Resveratrol presents itself as a prominent compound in a variety of mechanisms, ranging from oxidative stress reduction, collagen upregulation, endothelial cell proliferation, and much more; all of which help to improve the wound healing process in patients and emphasizes its versatility.

Synergistic Effect of Resveratrol

A key feature of Resveratrol that further supports its beneficial role in wound healing is its synergistic effect. By collaborating with various proteins and substances, Resveratrol enhances the environment required for optimal healing. When added to the HA-DPPC matrix, it provides an ideal moisture level for wound healing in diabetic rats.[17] In combination with this matrix, Resveratrol has also been shown to enhance antioxidative properties when observing microparticles.[12] Another effect of the application of Resveratrol is how it influences the further synthesis of collagen and laminin in the collagen-laminin dermal matrix in diabetic rats.[17] By collaborating with matrices that are natural to an individual, adding Resveratrol vastly improves tissue reconstruction and illustrates its synergistic importance. It is necessary to address that the dosage of Resveratrol may play a role in its ability to impact these matrices. For instance, in one study, 100 nM of Resveratrol was found to be optimal in wound healing for HUVECs, whereas higher and lower numbers varied.[16] This should be investigated further as many current studies do not deeply explore the relationship between Resveratrol dosage and synergism.

Literature is lacking in the effect of Resveratrol on human diabetic patients. Future studies should consider looking into the progression of wound healing in human diabetic patients receiving topical or injectable resveratrol. Understanding the exact impact of Resveratrol on human diabetic patients will help integrate its use in regular practice.

CONCLUSION

This literature review analyzed the effectiveness of Resveratrol in enhancing wound healing in diabetics in cell and animal models. Resveratrol's ability to promote angiogenesis, collagen fiber formation and increase anti-inflammatory cytokines makes it a great option to use on diabetic patients. Further research needs to be conducted on human diabetic patients to be able to assess the extent of effectiveness of Resveratrol.

REFERENCES

1. Centers for Disease Control Prevention. National diabetes statistics report: estimates of diabetes and its burden in the United States, 2022. Atlanta, GA: US Department of Health and Human Services. 2022;2022.
2. Burgess JL, Wyant WA, Abdo Abujamra B, Kirsner RS, Jozic I. Diabetic Wound-Healing Science. Medicina (Kaunas). 2021;57(10).
3. World Medical Association. Newsroom Fact Sheets Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes. Published 2022. Updated September 16, 2022. Accessed November 26, 2022.

4. Okonkwo UA, DiPietro LA. Diabetes and Wound Angiogenesis. Int J Mol Sci. 2017;18(7).
5. Schmidt AM. Highlighting Diabetes Mellitus: The Epidemic Continues. Arterioscler Thromb Vasc Biol. 2018;38(1):e1-e8.
6. Ko KI, Sculean A, Graves DT. Diabetic wound healing in soft and hard oral tissues. Transl Res. 2021;236:72-86.
7. Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin Wound Healing: An Update on the Current Knowledge and Concepts. Eur Surg Res. 2017;58(1-2):81-94.
8. Salehi B, Mishra AP, Nigam M, et al. Resveratrol: A Double-Edged Sword in Health Benefits. Biomedicines. 2018;6(3).
9. Hecker A, Schellnegger M, Hofmann E, et al. The impact of resveratrol on skin wound healing, scarring, and aging. Int Wound J. 2022;19(1):9-28.
10. Pignet AL, Schellnegger M, Hecker A, Kohlhauser M, Kotzbeck P, Kamolz LP. Resveratrol-Induced Signal Transduction in Wound Healing. Int J Mol Sci. 2021;22(23).
11. Kaleci B, Koyuturk M. Efficacy of resveratrol in the wound healing process by reducing oxidative stress and promoting fibroblast cell proliferation and migration. Dermatol Ther. 2020;33(6):e14357.
12. Eroğlu İ, Gökçe EH, Tsapis N, et al. Evaluation of characteristics and in vitro antioxidant properties of RSV loaded hyaluronic acid-DPPC microparticles as a wound healing system. Colloids Surf B Biointerfaces. 2015;126:50-57.
13. Li H, O'Meara M, Zhang X, et al. Ameliorating Methylglyoxal-Induced Progenitor Cell Dysfunction for Tissue Repair in Diabetes. Diabetes. 2019;68(6):1287-1302.
14. Hu J, Liu X, Chi J, et al. Resveratrol Enhances Wound Healing in Type 1 Diabetes Mellitus by Promoting the Expression of Extracellular Vesicle-Carried MicroRNA-129 Derived from Mesenchymal Stem Cells. J Proteome Res. 2022;21(2):313-324.
15. Huang X, Sun J, Chen G, et al. Resveratrol Promotes Diabetic Wound Healing via SIRT1-FOXO1-c-Myc Signaling Pathway-Mediated Angiogenesis. Front Pharmacol. 2019;10:421.
16. Zhou X, Ruan Q, Ye Z, et al. Resveratrol accelerates wound healing by attenuating oxidative stress-induced impairment of cell proliferation and migration. Burns. 2021;47(1):133-139.
17. Gokce EH, Tuncay Tanrıverdi S, Eroglu I, et al. Wound healing effects of collagen-laminin dermal matrix impregnated with resveratrol loaded hyaluronic acid-DPPC microparticles in diabetic rats. Eur J Pharm Biopharm. 2017;119:17-27.

Incidence of Lower Extremity Injuries Occurring on Athletic Turf Versus Natural Grass: A Literature Review

Emil Gulman, BS; Muhammad Umair Husain, MPH; Nikolay Igdalov, MS; Rodion Savelyev, BS

ABSTRACT

Introduction

Non-contact injuries are common lower extremity injuries seen while playing on turf fields. The severity of an injury varies from mild sprains and turf toe to torn ligaments in the knee. Football, which is one of the most commonly played sports in America, is generally played on turf and many players suffer non-contact sports injuries. The National Football League (NFLPA) conducted a study which reported a 28% increase in lower extremity injury occurring on artificial turf compared to conventional grass, as well as a 32% increase in knee injuries and a 69% increase in foot and ankle injuries all occurring on turf fields. These injuries may be due to the increased force absorbed by the lower extremity when performing dynamic such as cutting and running, as turf fields absorb less force than regular grass fields. These numbers will likely increase due to the cheaper upkeep and sustainability of these fields. Playing on artificial turf can lead to acute injuries, which may progress into chronic injuries, like arthritis. Overall, this presents a serious issue, as many sports require grass or a grass-like alternative and the incidence of athletic injuries continues to rise in sports like football, soccer, and lacrosse.

Study Design: Systematic Literature Review

Methods

In order to conduct this literature review, we conducted a Pubmed search with the terms “non contact sport injury” or “turf” AND “grass”. 702 articles were reported, and after applying the inclusion criteria of randomized control trials, meta-analysis, and systematic reviews, and the exclusion criteria of articles more than 10 years old, and articles not relevant to our review, we had a total of 6 articles.

Results

From the 6 articles in our literature review, 4 articles reported an increased risk of injury in games played on turf compared with natural grass while 2 articles did not find a difference in injury rate. None of the articles stated the existence of a decreased risk of injury in games played on artificial turf.

Conclusion

Turf fields have been shown to have the potential to cause serious lower extremity injury in athletes that play on them. All of the articles utilized in our review shared one common factor, which was the field type that was played on. There is need for additional evidence and further research to be conducted, in order to more definitively state whether turf fields are the main reason for non-contact sports injuries. There are still many variables like training regime, field type, and cleat type, which can all possibly help cause an increase in the incidence of injuries to athletes. More research still needs to be done to determine ways we can circumvent non-contact injuries, as we still don't know the full cause of this pathology. New research should focus on pathology and cause of the pathology to help decrease burden on the medical system.

Level of Evidence: 4

Keywords: Lower extremity injury, sports, non-contact, artificial turf, grass

INTRODUCTION

Are turf fields leading to avoidable sports injuries? Artificial turf fields were introduced to the world of sports in the mid 1960's and quickly gained popularity due to the low cost and ease of maintenance compared to natural grass. Artificial turf has now become a controversial topic of discussion in the world of sports. As sports fans we have seen our fair share of some of our favorite players leave the field after suffering serious non-contact injuries. There is an ever-increasing belief among athletes that turf fields are directly leading to significantly higher rates of injuries than their natural grass counterparts. According to former player and current president of the NFLPA, JC Tretter, injury data collected by the NFL from 2012-2018 showed players have a 28% higher rate of non-contact lower extremity injuries on turf compared to natural surfaces. This data includes a 32% increase of non-contact knee injuries and a 69% higher rate of non-contact foot/ankle injuries on turf compared to grass. These numbers are staggering and yet 14 out of the 30 professional football stadiums still continue to use turf.

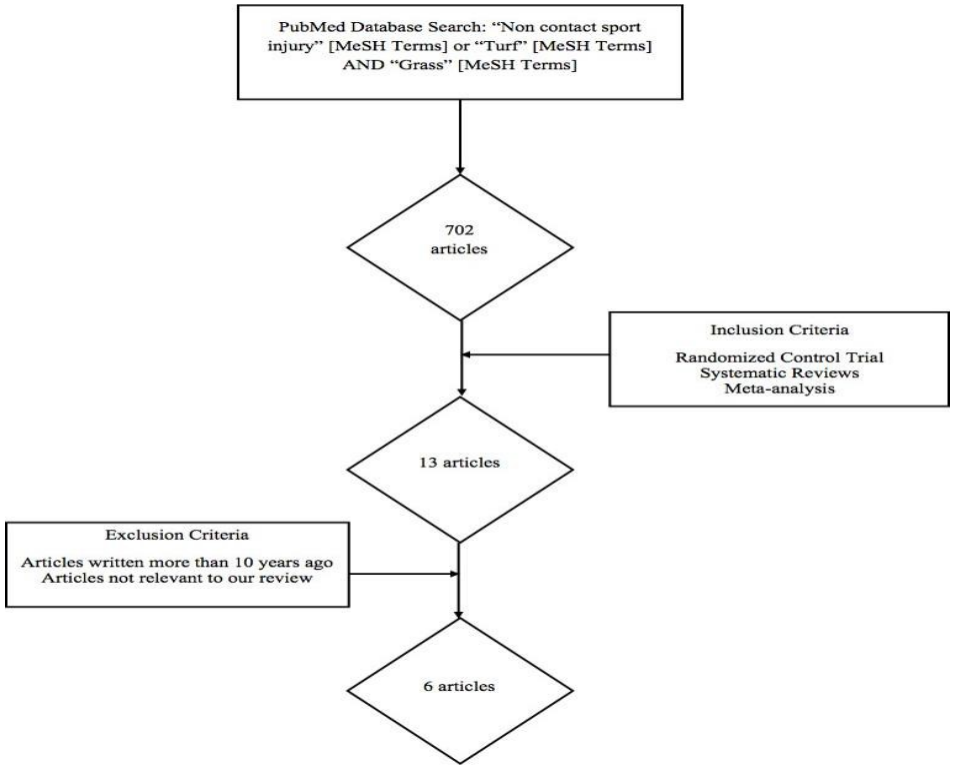
For completeness we examined other factors such as age, gender, BMI, choice of foot wear, warm up before engaging in activity, and training regimens of the athletes. This discussion centers specifically on non-contact injuries that occur while an athlete is running, stopping, or changing direction. We have considered the anatomy and biomechanics of the lower extremity and what effect, if any, different training regimens have on preventing injury. 4 out of the 6 papers that met our criteria point to validity in the athletes' claims of higher rates of injury of turf and support our hypothesis.

Although efforts are being made by some to transition to safer playing surfaces, the majority of stadium owners and schools are still reluctant to address the issue and incur the high costs involved without more concrete data. We feel strongly that the existing literature on non-contact lower extremity injuries related to playing surfaces in a variety of sports and levels already shows that a correlation is present. Our hope is this paper will shed some more light on this growing issue and will ultimately lead to the owners and operators of these fields and stadiums to reexamine their commitment to continued use of these dangerous playing surfaces.

METHODS

The Pubmed database was used to conduct a literature search. Utilizing Pubmed advanced search builder, we input our search terms to conduct an all fields search. Our search terms included "non contact sport injury" or "turf" AND "grass"; this search provided 702 articles. To further narrow our search, we implemented inclusion and exclusion criteria. The inclusion criteria for our review relied on literature from randomized control trials, systematic reviews and meta-analysis, bringing the count to 13 articles. Furthermore, the exclusion criteria excluded any articles published more than ten years ago, as well as articles that were not in alignment with

our research topic. This brought the final search yield to a total of 6 articles.



RESULTS

A total of six articles published between 2015 and 2022 were selected for study inclusion. All studies compared rates of injuries in football and soccer players who practiced on turf as opposed to grass. These articles also analyzed how factors like age, sex, type of artificial turf, type of cleats used, and moisture level can contribute to injury rates.

A systematic review by Silva et al. included 23 articles. Nine studies analyzed performance and 14 studies analyzed injury risk while using cleats on artificial turf and natural grass. Mechanical devices analyzed forces applied to the ankle and knee during practice on both natural grass and artificial turf. Injuries on artificial turf were attributed to an increased rotational traction, peak torque, and stiffness compared to natural grass. Increased rotational traction was associated with increased ankle and knee joint loading, which could potentiate a higher incidence of injury.[4]

In another study, a special injury prevention program was implemented for soccer players to reduce the number of ACL

injuries. 61 National Collegiate Athletic Association men's soccer teams were analyzed over the course of one soccer season. At the end of the study, no difference was found in ACL injury rates in the control group versus the intervention group that played on grass versus turf.[1]

A systematic review and meta-analysis by Xiao et al. looked at seven articles comparing ACL injuries in soccer players on artificial turf versus natural grass specifically, whether the injuries were more prevalent in male versus female players. Pooled ACL incidence rate ratios showed a significantly increased risk of ACL injuries for female players on artificial turf as opposed to male players. This result was explained by the fact that women are two to nine times more likely to sustain an ACL injury compared to males.[2]

A randomized control trial by Hägglund et al. set out to look at risk factors for ACL injury in female youth football players. 96 injuries were recorded, 21 of which were ACL injuries. The ACL injury rate was nine times higher during match play as compared to training. No difference in ACL injury rate was noted between artificial turf and natural grass, whether during training or match play. It was also observed that ACL injuries were more common in the non-dominant leg (n=11) compared to the dominant leg (n=6).[3]

Another article looked at injury risk on natural grass compared to old-generation and new-generation artificial turf. Injuries were subdivided into foot and ankle, knee, and hip injuries. Results indicated that old-generation turf was inferior to natural grass in terms of injury rates. However, new-generation turf studies showed no difference in injury rates when compared to natural grass. Furthermore, a majority of articles (12/25) on foot and ankle injury rates found artificial turf to produce more injuries, while a majority of articles (19/32) on knee injury rates showed no difference between artificial turf and natural grass. Finally, a majority of articles (13/26) on hip injury rates reported more injuries on artificial turf.[5]

A systematic review by Balazs et al. compared risk of ACL rupture on natural grass versus artificial turf. 322 studies were identified and ten of them were included in the systematic review. Seven studies compared natural grass to 3rd-generation artificial turf (synthetic turf with rubber infill), two compared natural grass to 1st-generation artificial turf (AstroTurf); and one compared natural grass to 1st- and 3rd-generation turf. Four of the studies found increased rates of ACL injury on artificial turf. In conclusion, an increased rate of ACL injuries was found in American football players playing on synthetic surfaces.[6]

Overall, a majority of the articles chosen (4/6) reported a significantly increased risk of injury in games played on artificial turf compared with natural grass, while two articles reported no difference in injury rate.

DISCUSSION

The incidence and rates of non-contact lower extremity injuries vary based on playing surface as the findings of our literature review have suggested. Although

these findings align with our initial hypothesis, the reality suggests a grave future for many athletes if changes are not made to decrease the risk of said injuries occurring. Gould et al. stated that the risk of foot and ankle injuries is higher on new-generation turf when compared to grass, while an increased risk of injury overall was noted to occur on old-generation turf. Earlier generation artificial turf consisted of densely woven nylon fiber carpets, which were placed on shock-absorbent padding.[6] When it came to the limitations assessed by Gould et al., they found that some teams continuously and consistently report injuries to their athletes, while some teams inadequately document injuries and under-report the statistics. This poses a significant risk for athletes at the pre-collegiate level as schools may not find it necessary to employ athletic trainers or physicians who are properly trained to alleviate the burden of risk that is posed upon these athletes. As a result, there may be an increase in the number of non-contact injuries that occur at this level of sports. It is also important to note that one of the biggest reasons fields are constructed with artificial turf is due to their cost effectiveness in regard to maintenance and upkeep.[6] Although this decision is economically motivated, it may not be the best option when it comes to the benefit of the athletes themselves.

In the randomized control trial (RCT) carried out with youth female soccer players in 2009,[2] their study focused on multiple factors including onset of menarche, familial predisposition to knee injuries, BMI, and natural grass vs. turf playing surface. While examining these factors, a positive correlation was found between older age, higher BMI, and onset of menarche with knee injuries, while Hagglund and Walden found no correlation between turf playing surfaces and more injuries as compared with natural grass. This study, while using a very large data pool, is limited by the fact that it focused on only young non-professional female athletes playing one specific sport (soccer). A similar future study could include professional level athletes, as well as male athletes in order to properly determine the effect playing surfaces have on injuries.

Rates of non-contact lower extremity injuries are mainly affected by the surface used during practice and games. Nevertheless, other factors like warm-up and the sex of a player can play a big role. As stated by Silvers-Granelli et al., implementing the 15- to 20-minute FIFA 11+ injury prevention program resulted in a 4.25-fold reduction in the rate of incurring ACL injury.[1] Further research should be conducted to see how other injury prevention programs compare to the FIFA 11+ program. Additionally, another article by Xiao et al. intended to compare ACL injury rates on natural grass vs artificial turf. Artificial turf proved to be associated with more ACL injuries, however, only female players saw an increase in ACL injury rate.[2] Although these findings support our hypothesis, injury acquisition can be different in males and females, further suggesting the need for two separate groups: one for females and one for males.

Non-contact lower extremity injuries are the result of several factors, however,

our study tried to narrow it down to one, turf fields. More research needs to be done to definitively say that turf fields are the number one reason for non-contact sports injuries. As stated by Silva et al., things like cleat styles and surfaces can contribute to these injuries via a person's foot not sticking to the ground while playing. Still, the ground type seems to be more of a factor for injury, specifically, the comparison between grass fields and turf fields. In order to find out which factor contributes most to non-contact sports injuries, there should be an individualized study comparing different variables like field type, cleat type, weather conditions, training regimens, and level of competition. To say turf fields do not cause an increase in non-contact injuries is to disregard many injuries professional athletes have suffered; For example, Odell Beckham Jr.'s injury in the Super Bowl, which was played on a turf field. One can also consider Sterling Shepherd, who was injured while jogging on a turf field at Met Life Stadium.

CONCLUSION

As we evaluated the research, we concluded that turf fields pose a serious issue when it comes to an athlete's risk of lower extremity injury and lower extremity health. Most of the research pointed to a common theme, which demonstrated turf fields as the collective factor responsible for lower extremity injuries in athletes. As our introduction stated, biomechanics are very important when it comes to injuries on turf. Biomechanical studies provided by Gould et al. support the incidence of an increase in frictional force on artificial turf, which has the potential to increase risk of injury as compared to natural grass. This follows as there's an increase in force needed to release from the contact surface, which increases the load on the ACL causing a rupture. Another article by Silva et al. highlighted an additional variable associated with the biomechanics of non-contact injuries, cleat type. Aluminum cleats increase vertical forces and loading, which are associated with impact injuries on the lower extremity. Most non-contact injuries found include torn ACLs. As a group, we'd like to know how training regiments and the type of training regiment, can mimic real match play in an attempt to possibly decrease injury on artificial turf. As described by Hagglund et al., there is a nine times greater injury rate during match play as compared to training. If turf fields are not easily changed then training regiments need to simulate real game scenarios, which can possibly decrease the risk of injury. Some of our research findings proved contradictory to what we originally thought. Still, we can attribute these discrepancies to the age of the participants, level of play, and competitiveness (professional vs. amateur). More research is needed to fully understand the anatomical and biomechanical processes of these non-contact injuries on turf and grass. Specific studies can break down each variable and help organize which factors pose the greatest risk for causing non-contact injuries. As sports become more popular in general public, there will be an increase in people who play. It poses a problem if we don't fully understand why non-contact injuries occur and will inevitably lead to an increase in injuries in

people who play, causing a burden on the medical system as well as the person sustaining the injury.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to all aspects of this literature review. All authors have read and reviewed this version for submission.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

REFERENCES

1. Silvers-Granelli HJ, Bizzini M, Arundale A, Mandelbaum BR, Snyder-Mackler L. Does the FIFA 11+ Injury Prevention Program Reduce the Incidence of ACL Injury in Male Soccer Players?. Clin Orthop Relat Res. 2017;475(10):2447-2455. doi:10.1007/s11999-017-5342-5
2. Xiao M, Lemos JL, Hwang CE, Sherman SL, Safran MR, Abrams GD. Increased Risk of ACL Injury for Female but Not Male Soccer Players on Artificial Turf Versus Natural Grass: A Systematic Review and Meta-Analysis. Orthop J Sports
3. Med. 2022;10(8):23259671221114353. Published 2022 Aug 12. doi:10.1177/23259671221114353
4. Hägglund M, Waldén M. Risk factors for acute knee injury in female youth football. Knee Surg Sports Traumatol Arthrosc. 2016;24(3):737-746. doi:10.1007/s00167-015-3922-z
5. Silva DCF, Santos R, Vilas-Boas JP, Macedo R, Montes AM, Sousa ASP. Influence of Cleats-Surface Interaction on the Performance and Risk of Injury in Soccer: A Systematic Review. Appl Bionics Biomech. 2017;2017:1305479. doi:10.1155/2017/1305479
6. Gould HP, Lostetter SJ, Samuelson ER, Guyton GP. Lower Extremity Injury Rates on Artificial Turf Versus Natural Grass Playing Surfaces: A Systematic Review [published online ahead of print, 2022 May 20]. Am J Sports Med. 2022;3635465211069562. doi:10.1177/03635465211069562
7. Balazs GC, Pavey GJ, Brelin AM, Pickett A, Keblish DJ, Rue JP. Risk of Anterior Cruciate Ligament Injury in Athletes on Synthetic Playing Surfaces: A Systematic Review. Am J Sports Med. 2015;43(7):1798-1804. doi:10.1177/0363546514545864

Use of Deep Vein Arterialization for Treatment of End-Stage Lower Limb Arterial Damage

Devondra Pitt, MS and Shauna-Kay Rhooms, BS

ABSTRACT

Introduction

Peripheral arterial disease (PAD) is the narrowing of the arterial vessels that results in reduced blood flow, more commonly in the lower extremities. PAD clinically presents on a spectrum; from individuals with asymptomatic symptoms to intermediate claudication to more severe stages of critical limb threatening ischemia (CLTI) or end-stage lower limb arterial damage.[14] It has been well reported that patients with CLTI have extremely high rates of amputation, as well as an increased risk of morbidity and mortality.[6] Within the CLTI population, a subset of patients do not have the required outflow distal targets needed for revascularization. For these patients, deep vein arterialization (DVA) serves as the next best option, allowing them to keep their lower limbs rather than undergoing amputation. DVA is a surgical technique that involves creating a shunt from the arterial blood inflow to the distal deep veins outflow. While DVA is not a new concept, new approaches to this surgical technique continue to be improved upon. The purpose of this literature review is to provide an updated analysis of the current techniques and outcomes of DVA used for the treatment of end-stage lower limb arterial damage.

Study Design: Systematic Review of Literature

Methods

PubMed database searches were performed to include the terms “deep vein arterialization and foot ulcer,” and “deep venous arterialization and lower limb ischemia.” Inclusion criteria included clinical trials, randomized control studies, and reviews. In addition, all studies utilized were from 2000 to 2022. We excluded studies that lacked the reported primary or secondary outcomes of amputation, increased mortality, patency, or limb salvage. In addition, studies were excluded if they did not have sufficient details on the procedure used to restore or reestablish adequate blood flow. In addition, all studies utilized were from 2000 to 2022 and resulted in 16 articles that were reviewed for this study and 11 were in analysis of this study.

Results

This review focused on the percutaneous and open deep vein arterialization (DVA) techniques, patient selection for each technique, and the patient outcome for each.The open DVA surgical technique yielded ranges from 59% to 100% in the primary restoration of patency of arterial vessels over a 1-year follow-up, with limb salvage rates ranging from 25% to 100%. And pain resolution and wound healing rates also ranging from 25% to 100%. as did rest pain resolution and wound healing rates.[5,15] The percutaneous DVA surgical technique yielded ranges from 19% to 40% in the primary restoration of arterial vessels throughout a 6 and 10-month follow-up.

Limb salvage rates increased slightly, and rates of major amputation slightly decreased in reported cases of percutaneous DVA.

Conclusion

All studies showed a significant increase in rates of lower limb salvage, regardless of the surgical technique. More specifically, open deep vein arterialization had the greatest increase in wound healing rate compared to percutaneous DVA. However, percutaneous deep vein arterialization offered the most minimally invasive options for patients. Overall, both percutaneous and open deep vein arterialization (DVA) were effective and efficient techniques for patients with end-stage lower limb arterial damage, who are not candidates for the traditional procedures.

Key words: Peripheral arterial disease, deep vein arterialization, chronic lower limb ischemia, limb salvage

INTRODUCTION

Critical limb ischemia (CLI) is considered to be the end stage of peripheral artery disease (PAD), it is characterized by chronic pain and tissue loss.[6,14] This can lead to a very poor prognosis without timely and effective intervention. The prevalence of both PAD and CLI is predicted to increase with the aging of the American population, as we see an increase in obesity, diabetes, hypertension and cardiovascular diseases. These conditions can contribute to the progression of PAD to CLI along with age and end stage renal disease.[6] In addition, CLI is associated with an impaired quality of life and a 50–60% 5-year mortality rate.[6,14]

Despite revolutionized technical approaches for conventional angioplasty or bypass, a significant number of patients are still not candidates. It often ends with limb amputation. Deep vein arterialization (DVA) is a surgical technique that involves creating a shunt to connect arterial blood inflow to the distal deep targets, in conjunction to disrupting the vein valves of the foot. There are many approaches to this technique including: open, percutaneous and hybrid. This approach provides arterialized blood in significant volumes compared to before and enough pressure to the plantar venous arch to promote healing of the ischemic tissue.

While DVA is not a new concept, new approaches have been continually improved on this surgical technique. Francois-Frank performed femoral arteriovenous anastomosis first in dogs, but then in humans in 1794.[5, 12] The results were poor rates of wound healing and limb salvage.[5] Halstead and Vaughn described venous arterialization in 1912; however, at that time it was not considered practicable due to the high morbidity and mortality following the procedure. Only one patient successfully had pulsation after the procedure [3,16]. In 1977, Sheil described the modern version of the procedure. The great saphenous vein was anastomosed to the dorsal venous arch of the foot in six patients with critical limb ischemia, with resolution of rest pain and healing of wounds in five of six patients.[5,7]

The purpose of this literature review is to provide an updated analysis of the current techniques and outcomes of DVA used for the treatment of end-stage lower limb arterial damage.

METHODS

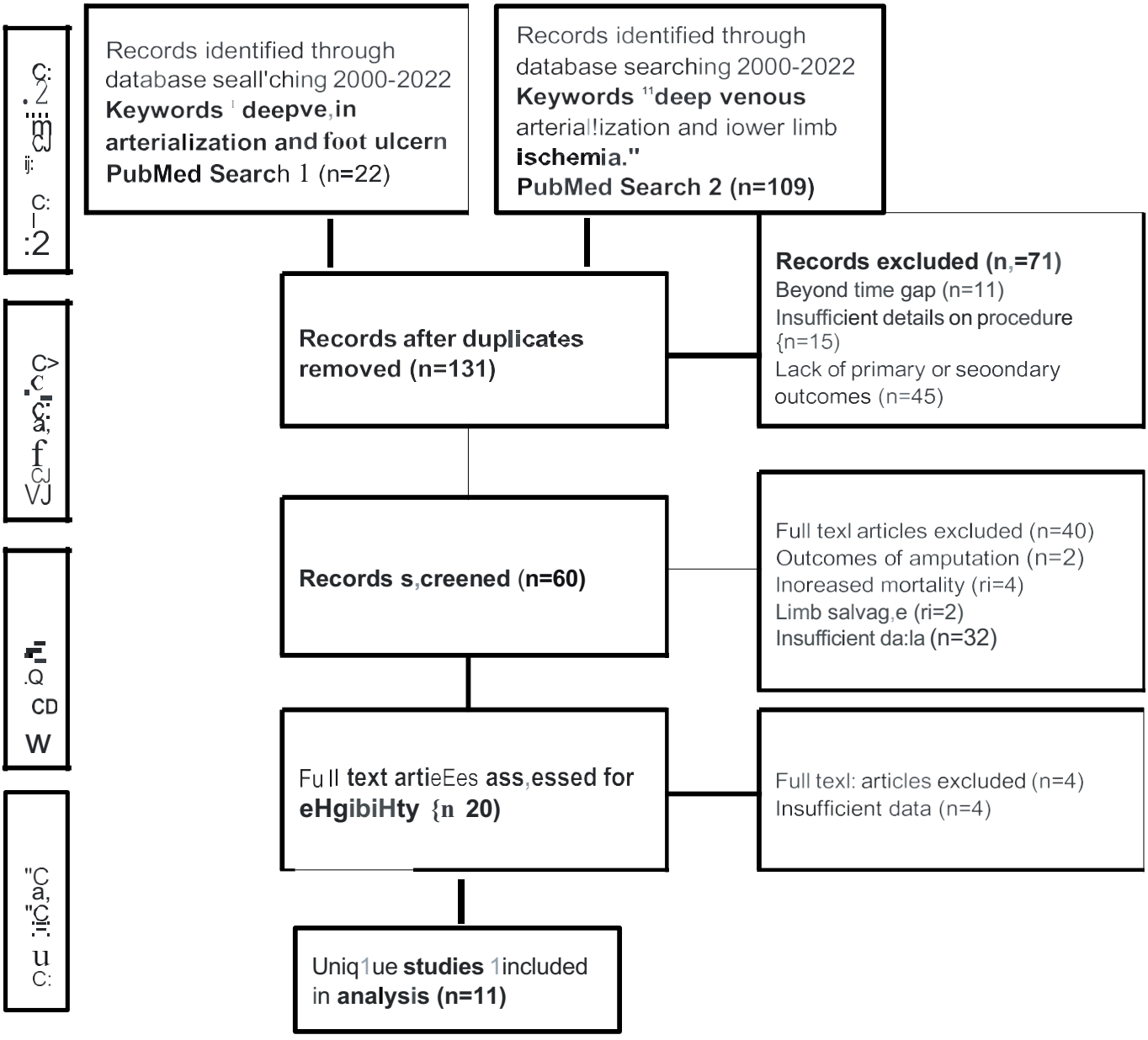


Figure 1: Study Selection Process

RESULTS

Deep Vein Arterialization Open Procedure Surgical Approach:

According to Ho et al., patients were selected for deep venous arterialization surgical approach based on being categorized in Rutherford class 5 or class 6 or Fontaine stage III-IV and not being viable candidates for open arterial revascularization.

Preoperatively, angiography and venography are performed to determine the optimal distal anastomosis and anatomy of the lower extremity arterial and venous system. It is important to identify valves that must be broken in order to allow for sufficient blood flow. Possible venous channels include the great saphenous vein and cephalic vein. The proximal arterial arteries include the common femoral artery, proximal tibial arteries, superficial femoral artery, and popliteal artery. Distal veins considered include venae comitantes of the posterior tibial vein and dorsal venous arch.[7]

Factors such as patency, inflow, and outflow of vessels are extremely important when choosing the vein and artery of choice. The preselected vein is harvested, reversed, and directly tunneled. The surgical incision of the preselected distal venous target vessel is then performed; the techniques include the use of a retrograde balloon catheter, valvulotome, dilators, direct valvotomy, and cutting balloons to break the valves.[7] The most commonly performed open DVA is an "end-to-side anastomosis", which is performed at the level of the posterior tibial vein at the ankle (target deep vein).[7]

Follow-up procedures are done to ensure reduced pressure and prevention of cardiac overload and vascular blood being shunted away from the foot.[7]

Based on the published results of the open DVA surgical approach, there are wide variations in the outcomes of this procedure. As referenced in the table data set, the primary 1-year patency outcome ranged from 59% to 100% (at 6 months), while the secondary patency was recorded in one study. The limb salvage rates also had a wide range from 42.7% to 100%, with wound healing ranging from 30% to 100%. Major amputation ranged from 0% to 70% of the cohorts in respective studies. Mortality rates ranged from 5.6% to 24%. According to Ho et al., similar studies published on the outcome of open deep vein arterialization also confirm the wide variation in outcomes of the open DVA surgical approach. Various factors such as the extent of arterial damage, the patient's anatomy, and the level of procedural techniques can contribute to the wide variation in open DVA.[7]

Percutaneous Vein Arterialization Open Procedure Surgical Approach:

Patients were selected for the percutaneous venous arterialization surgical approach based on categorization in Rutherford class 4 to 6 and if they were not viable candidates for open arterial revascularization.

According to researchers, the percutaneous LimFlow System was developed to optimize the deep vein arterialization procedure with the benefit of offering more consistent

results.[2] The LimFlow system enables artery-to-vein crossing and stent deployment with a more straightforward approach and fewer complications. The LimFlow procedural steps are summarized as follows: arterial access in the common femoral artery, venous access in the lateral plantar vein, artery-to-vein crossing, valvotomy, extension stent graft deployment, and crossing stent graft deployment.[2]

Based on the published results of the percutaneous DVA surgical approach, the posterior tibial vein served as the distal target vein for the majority of the cases. As referenced in the table data set, the primary 1-year patency outcome ranged from 19% to 90% (from 1 to 6 months), while the secondary patency was recorded in one study. The limb salvage rates were more consistent in their ranges from 60% to 87%, as wound healing ranged from 23.8% to 100%. Major amputation ranged from 0% to 38.1% of the cohorts in respective studies. Mortality rates ranged from 0 to 20%.[1,3,4,5,8,9,10,11,12,13,16]

Study	# of Patients	Criteria	Graft	Distal Anastomosis	Follow up (months)	Patency %	Limb salvage %	Wound healing %	Major amputation %	Mortality%
Engelke, 2001	18	Fontaine stage IV	Great saphenous vein (11) Cephalic (1) Small saphenous vein (2) polytetrafluoroethylene with vein (4)	Dorsal venous arch (14) Venae comitantes of Posterior tibial artery (4)	25	Primary: 66 Secondary: 72	83		16.7	5.6
Ozbek, 2005	7	Fontaine stages III (3) and IV (4)	Great saphenous vein	Distal Great saphenous vein	12	Primary: 100 at 6 months	100	100	0	
Mutirangura, 2011	26	Fontaine stages III (10) and IV (16)	Great saphenous vein	Posterior tibial vein (24) Anterior tibial vein (2)	12	Primary: 59	76	76	23.1	14.6
Djoric, 2012	30	Fontaine stages III (3) and IV (9)	Great saphenous vein	Medial marginal vein	6.1	Primary: 80	91.6	87.5	16.7	3.3
Houlind, 2013	10	Fontaine stages III (2) and IV (8)	Great saphenous vein (8) Great saphenous vein-	Dorsal venous arch (5) Venae comitantes of Posterior tibial	1-12	Primary: 80	30	30	70	10

			polytetrafluoroethylene spliced (2)	artery (3) Venae comitantes of Common Plantar Artery (2)						
Schreve, 2014	21	Fontaine stage IV	Great saphenous vein	Dorsal venous arch	12	Primary: 71	53		43	24.1
Arsenault, 2017	14	Rutherford classes 4 (2), 5 (10), and 6 (2)	Great saphenous vein or cephalic Distal	Great saphenous vein	1	Primary: 82	42.8	42.8	28.6	7.7

Table 1: Summary of Deep Vein Arterialization Open Procedure Surgical Approach.[1,3,4,5,8,9,10,11,12,13,16]

Study	# of Patients	Criteria	Distal Anastomosis	Follow up (months)	Patency %	Limb salvage %	Wound healing %	Major Amputation %	Mortality %
Del Guidice, 2018	5	Rutherford classes 4 to 6	Posterior tibial vein (4) Anterior tibial vein (1)	6	Primary: 40	60	40	20	20
Kum, 2018	7	Critical limb ischemia without candidacy for angioplasty or open bypass	Posterior tibial vein	10	Primary: 28.6	71	71.4	28.5	0
Mustapha,2019	10	Rutherford classes 5 to 6	Posterior tibial vein	6	Primary: 90 (1 month); 40 (6 months)	86	100	0	0
Saab, 2022	42	Rutherford classes 4 to 6	Posterior tibial vein (23) Plantar (13) Anterior tibial vein (5)	6	Primary: 19 (6 months) Secondary: 7.1	78.6	23.8	38.1	6

Table 2: Summary of Deep Vein Arterialization Percutaneous Procedure Surgical Approach.[1,3,4,5,8,9,10,11,12,13,16]

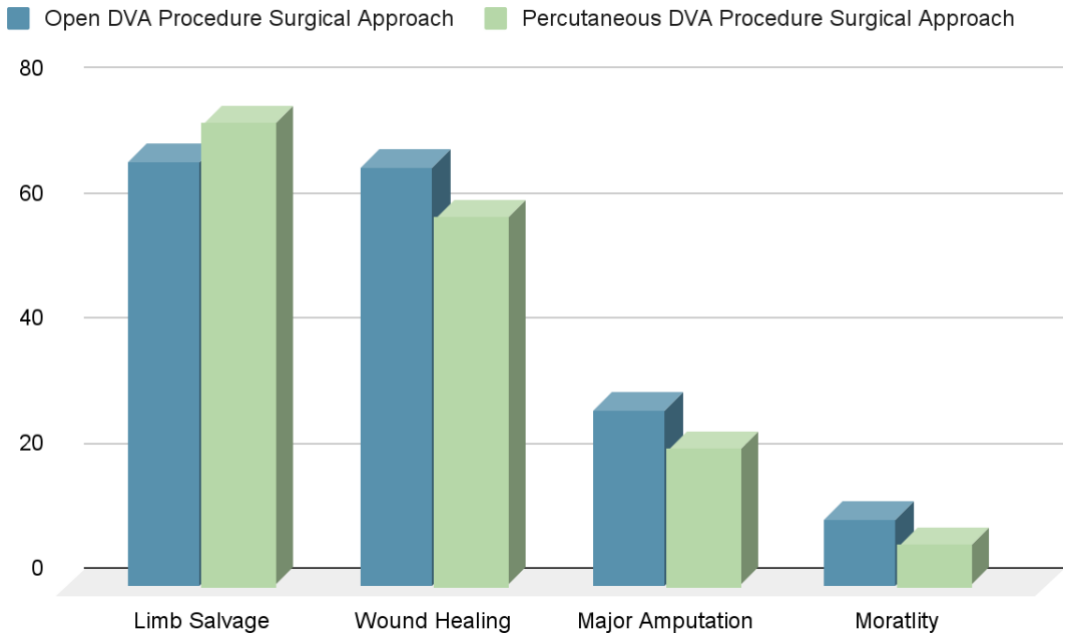


Figure 2: Summary percentages of Open and Percutaneous Deep Vein Arterialization procedure resulting in amputation, limb salvage, wound healing and mortality rates among patients.[1,3,4,5,8,9,10,11,12,13,16]

DISCUSSION AND LIMITATIONS

Based on the results shown in Figure 2, the outcomes of open and percutaneous DVA procedures were compared and the percutaneous arterialization surgical procedure consistently showed improved outcomes.[8] Limb salvage rates increased slightly and rates of major amputation slightly decreased in reported percutaneous DVA cases. There was also a decrease in mortality cases reported in percutaneous DVA procedures compared to open DVA. However, wound healing was not consistent, which could be the result of compounding factors.

According to numerous studies, the diagnostic criteria to determine end-stage peripheral disease has not been clearly established. Before peripheral DVA procedures, patients underwent institutional ultrasonic and angiographic testing, which entails arterial lumen obliteration, calcified obliteration, and occlusion of distal arteries. In some studies, traditional endovascular revascularization was also reposted. The lack of established diagnostic end-stage peripheral disease criteria could have contributed considerably to the variation of patient population selection within each study group.

This study was also limited in the data outcomes of both open and percutaneous DVA cases. For each study, the range of years varied in terms of wound care, vascular approach and revascularization approaches. The inconsistency in wound care contributed to various rates of wound healing in each study. Some studies focused on referring patients in their respective cohorts to specialized podiatric care familiar with the pDVA procedure, while others did not disclose this information.[1,9] Another factor that contributed to the inconsistency in wound care is the patients' access to specialized wound care centers. Saab et al. emphasize the importance of addressing wound care as it is extremely important in the patient outcome and success rate for limb preservation.

Ho et al. highlighted sample size as a limiting factor when comparing the significant outcomes of open percutaneous DVA surgical procedures. Certain sample sizes limited the ability to remove independent risk factors and comorbidities, including smoking status, hypertension, surgical history, and chronic kidney disease. There was also a limitation in percutaneous DVA procedural therapy compared with open DVA, which contributed to the difficulty in ascertaining the surgical outcomes.

CONCLUSION

In conclusion, deep vein arterialization is widely used for patients with end-stage lower limb arterial damage, specifically those in need of endovascular arterial revascularization, due to comorbidities such as peripheral artery disease or small arterial disease. According to the results, Percutaneous DVA proved to offer the most minimally invasive options for patients. The literature review confirms this by showing

limb salvage rates averaging approximately 68% for open DVA and 74% for percutaneous DVA. Overall, deep vein arterialization is deemed practicable and a last resort for patients who have no other option.

AUTHORS' CONTRIBUTION

Both authors conceived of the presented manuscript. Both authors equally made substantial analysis, interpretation, and contribution to the production of this manuscript. Both authors participated in all revisions and approved the final draft for submission.

REFERENCES

1. Arsenault K.A., Tse L.W., Gagnon J., Kelton D., Baxter K., Chen J. et al. Venous arterialization for non reconstructable lower extremity arterial disease: a multicenter case series. J Vasc Surg. 2017; 66: e68-e69
2. Clair DG, Mustapha JA, Shishehbor MH, et al. PROMISE I early feasibility study of the LimFlow System for percutaneous deep vein arterialization in no-option chronic limb-threatening ischemia 12-month results. J Vasc Surg 2021;74:1626–35.
3. Del Giudice C., Van Den Heuvel D., Wille J., Mirault T., Messas E., Ferraresi R. et al. Percutaneous deep venous arterialization for severe critical limb ischemia in patients with no option of revascularization: early experience from two European centers. Cardiovasc Intervent Radiol. 2018; 41: 1474-1480
4. Djoric P., Zeleskov-Djoric J., Stanisavljevic D., Markovic Z., Zivkovic V., Vuletic M., et al. Distal venous arterialization and reperfusion injury: focus on oxidative status. Eur Surg Res. 2012; 48: 200-207
5. Engelke C, Morgan RA, Quarmby JW, Taylor RS, Belli AM. Distal venous arterialization for lower limb salvage: angio- graphic appearances and interventional procedures. Radiographics 2001;21:1239-48.
6. Fereydooni, A., Gorecka, J., & Dardik, A. (2019). Using the epidemiology of critical limb ischemia to estimate the number of patients amenable to endovascular therapy. Vascular Medicine, 25(1), 78–87. https://doi.org/10.1177/1358863x19878271
7. Ho, V. T., Gologorsky, R., Kibrik, P., Chandra, V., Prent, A., Lee, J.; Dua, A. (2020). Open, percutaneous, and hybrid deep venous arterialization technique for no-option foot salvage. Journal of Vascular Surgery, 71(6), 2152–2160. https://doi.org/10.1016/j.jvs.2019.10.085
8. Houlind K., Christensen J.K., Jepsen J.M. Vein arterialization for lower limb revascularization. J Cardiovasc Surg (Torino). 2016; 57: 266-272
9. Kum S., Huizing E., Schreve M.A., Unlu C., Ferraresi R., Samarakoon

L.B., et al. Percutaneous deep venous arterialization in patients with critical limb ischemia. J Cardiovasc Surg (Torino). 2018; 59: 665-669

10. Mustapha J.A., Saab F.A., Clair D., Schneider P. Interim results of the PROMISE I trial to investigate the limflow system of percutaneous deep vein arterialization for the treatment of critical limb ischemia. J Invasive Cardiol. 2019; 31: 57-63
11. Mutirangura P., Ruangsetakit C., Wongwanit C., Sermsathanasawadi N., Chinsakchai K. Pedal bypass with deep venous arterialization: the therapeutic option in critical limb ischemia and unreconstructable distal arteries. Vascular. 2011; 19: 313-319
12. Özbek C., Kestelli M., Emrecan B.Özsöyler İ, Bayatli K., Yaşa H., et al. A novel approach: ascending venous arterialization for atherosclerosis obliterans. Eur J Vasc Endovasc Surg. 2005; 29: 47-51
13. Saab, F. A., Mustapha, J. A., Ansari, M., Pupp, G., Madassery, K., N'Dandu, Z., Wiechmann, B. N., Bernstein, R., Mize, A., & Pliagas, G. (2022). Percutaneous deep venous arterialization: Treatment of patients with end-stage plantar disease. *Journal of the Society for Cardiovascular Angiography & Interventions*, *1*(6), 100437. https://doi.org/10.1016/j.jscai.2022.100437
14. Sachs T, Pomposelli F, Hamdan A, et al. Trends in the national outcomes and costs for claudication and limb threatening ischemia: Angioplasty vs bypass graft. J Vasc Surg 2011; 54: 1021–1031.e1.
15. Sasajima T, Azuma N, Uchida H, Asada H, Inaba M, Akasaka N. Combined distal venous arterialization and free flap for patients with extensive tissue loss. Ann Vasc Surg 2010;24:373-81.
16. Schreve, C.G. Vos, A.C. Vahl, J.P.P.M. de Vries, S. Kum, G.J. de Borst, Ç. Ünlü, Venous Arterialisation for Salvage of Critically Ischaemic Limbs: A Systematic Review and Meta-Analysis,European Journal of Vascular and Endovascular Surgery, Volume 53, Issue 3,2017

Using Botulinum Toxin as a Non-Surgical Treatment for Diabetic Neuropathy: A Literature Review

Olivia Chandler BA; Christian Elder BS; Tommy Oliveri BS

ABSTRACT

Introduction
Botulinum Toxin Type A (BTX-A) is commonly known for its cosmetic applications, but recent studies have found another use for the potent and naturally occurring toxin. Diabetes mellitus (DM) is one of the fastest growing chronic diseases worldwide. Chronic diabetes often results in the development of neuropathy as a symptom of the condition. The goal of this systematic literature review is to determine if BTX-A is an effective treatment for diabetic neuropathy.
Study Design
Systematic Review of Literature
Methods
A search was done in PubMed using the query "Diabetic neuropathy and Botulinum toxin [MESH Terms]" that yielded a result of 38 articles. The inclusion criteria for this review included randomized clinical trials and systematic literature reviews. Exclusion criteria were as follows: animal models, and articles not written in English. After applying these criteria, 8 articles were applicable and included in this systematic review.
Results
Botulinum Toxin Type A has been demonstrated as an effective option for those suffering from intractable neuropathic pain, such as diabetic neuropathy.
Discussion/Conclusion
While diabetic neuropathy may be an inevitable symptom of chronic diabetes, the acute pain associated with the condition may be able to be addressed in a non-surgical manner. Studies analyzed in this literature review indicate that the use of botulinum toxin A can be an option in the pain management of these patients.

Keywords: botulinum toxin, diabetic neuropathic pain

Level of Evidence: 3

INTRODUCTION

Diabetes is an illness that has recently become a world health pandemic. Nearly 537 million people currently live with some form of diabetes. This disease has affected many aspects of global health, including the quality of life of those afflicted with the illness, as well as a very costly economic burden. Many individuals are at higher risk for developing this illness, including those who have dyslipidemia, obesity, hypertension, thyroid diseases, genetically predisposed individuals, and many other factors. Aside from the dysregulation of maintaining blood glucose levels, diabetic individuals must also deal with a vast array of comorbidities that result from having diabetes over a prolonged period. One of the major difficulties associated with diabetic individuals is Diabetic Peripheral Neuropathy (DPN). This condition affects the distal peripheral nerves responsible for both sensory and some motor functions.

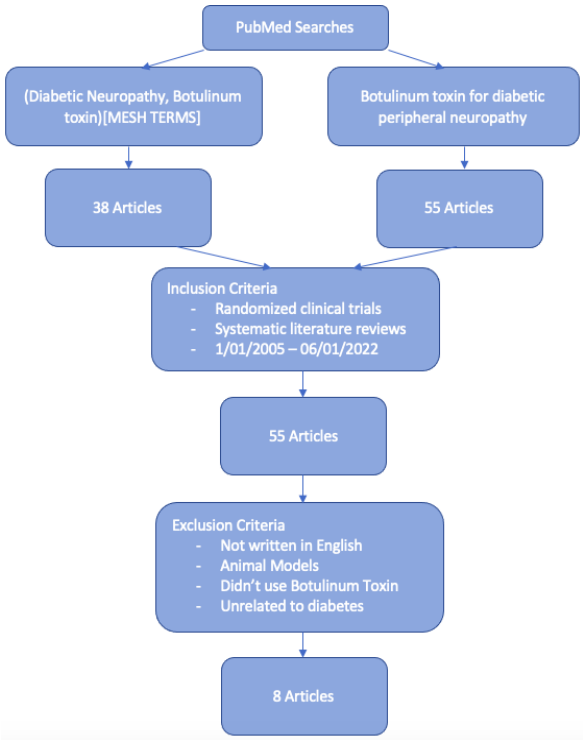
Of those diagnosed with type 2 diabetes, 8% have peripheral neuropathy; after 25 years, nearly 50% of those diagnosed with diabetes will progress to having Diabetic Peripheral Neuropathy (DPN). While those with DPN experience several unfortunate symptoms, one of the most detrimental, as well as prevalent symptom, is pain. Pain, and other sensory abnormalities such as allodynia, hyperalgesia, and tingling and burning sensations, are all associated with DPN. Currently, there are several options used to treat DPN. Many of them are systemic treatments such as gabapentin, opioids, pregabalin, and certain antidepressants. These treatment options can cause systemic adverse effects and are often not well-tolerated by the patients. In recent years, researchers have been experimenting with using botulinum toxin as an alternative treatment for symptoms associated with Diabetic Peripheral Neuropathy.

Botulinum Toxin A (BTX-A) is a naturally occurring protein produced by the bacterial species *Clostridium Botulinum*. Historically, this toxin has been known for its potency and, more recently, has been adapted for the cosmetic purposes of reducing and preventing wrinkles. BTX-A inhibits the release of acetylcholine at the neuromuscular junction, preventing muscle contraction. As a result, the muscle remains relaxed and does not respond or carry normal action potential stimuli. Additionally, acute pain sensation has been observed to be reduced after administration. The effect of BTX-A is reversible and non-permanent, requiring multiple treatments to maintain the effects. Newer research has delved into other opportunities for this toxin to be used to provide medical treatment for various conditions. BTX-A has been successfully used to treat migraines, post-surgical neuralgia, and cramps in diabetic cohorts. These studies have shown that administration of BTX-A for its various uses is safe, though dosages differ depending on the desired results.

Although limited, the research compiled over the past decade has shown promising results of BTX-A regarding the management of diabetic peripheral neuropathy. The studies evaluated in this systematic review measured the outcomes of BTX-A with similar, though slightly different, assessments. BTX-A has also been shown to affect multiple systems throughout the body, many of which coincide with those damaged by diabetic peripheral neuropathy. This review focuses specifically on diabetic peripheral neuropathy of the foot. The goal of this systematic review is to analyze the effectiveness of BTX-A as a viable treatment option for diabetic peripheral neuropathy.

METHODS

Our research began using PubMed, searching "Diabetic Neuropathy and Botulinum toxin [MESH TERMS]". This search yielded 38 results. The authors then applied the filters, "Randomized controlled trials" and "Systematic reviews" and published within January 2005 to June 2022 which then presented 6 results. Results that were based on animal models, those which were not written in English, and those who did not utilize botulinum toxin were excluded. Of the 6 articles remaining, two were excluded on the premise of not being written in English. A second search was performed, using the phrase "Botulinum toxin for diabetic peripheral neuropathy" with no MESH terms. The search yielded 55 results. The inclusion criteria for the second search remained the same as the primary search. This narrowed the result pool to 49 articles. Of the remaining 49 articles, 45 were excluded due to being irrelevant to the research topic or not meeting the inclusion criteria. In total, 8 articles were included in the systematic review.



RESULTS

Park et al. reviewed studies utilizing BTX-A therapy as a treatment for neuropathic pain. These studies encompassed many forms of neuropathic pain that utilized Botulinum Toxin as treatment, including but not limited to central stroke pain, diabetic neuropathy, occipital neuralgia, and phantom limb pain. These studies also included different forms of Botulinum Toxin A administration, ranging from intradermal to subcutaneous to chessboard injection. As per the guidelines of American Academy of Neurology, BTX-A is recommended for neuropathic pain associated with post-surgical neuralgia, diabetic neuropathy, and central post stroke pain (Level B). More research is required for BTX-A use for neuropathic pain associated with occipital neuralgias, complex regional pain syndrome, and phantom limb pain. BTX-A had minimal adverse irreversible medical effects. Overall, there was a need for more comparative studies inquiring as to the safest and most effective method of administration as well as minimum dosing required for effective results. These randomized control studies should be large, well designed and blinded to continue further research.[3]

Hastings et al. conducted a double blind, randomized clinical trial investigating the use of BTX-A to limit plantarflexion of the foot during gait, thereby reducing forefoot pressure. They hypothesized that the reduction in pressure on the forefoot would reduce subsequent ulcerations in this area. Seventeen subjects with type 2 diabetes mellitus, peripheral neuropathy and forefoot plantar ulcers were randomized into three groups (placebo, 200 unit, 300 unit). Subjects were predominantly male and obese. Plantarflexor peak torque and forefoot pressure were measured prior to treatment and two weeks post injection. No injection complications or adverse effects

occurred with the BTX-A administration. Hastings et al. found that there was no relationship between the amount of BTX-A administered and change in plantarflexor peak torque. Both plantarflexor peak torque and forefoot peak plantar pressure remained unchanged for placebo and the 300 unit group (0 ± 11, 0 ± 5 N/cm^2 respectively) but decreased in the 200 unit group (-4 ± 16 N/cm^2). This study was limited by small sample size and inequality in weight distribution in groups. Additional research is required to investigate physiologic changes specific to DM that may impact BTX-A's effectiveness to guide proper dosing for desired results.[4]

Wang et al. explored the idea of using BTX-A as a treatment for painful diabetic peripheral neuropathy (DPN). To achieve this, 263 articles were identified through a database search that resulted in four total studies used in their systemic review and meta-analysis. Of these four studies, 231 patients were included. The trial duration ranged from 3 to 12 weeks and the route of administration of the BTX-A was intradermal injection on the dorsum of both feet in three of the studies and injection in the sole of the foot in the remaining one. The dosage ranged between 50 to 150 units in each foot. This study showed a reduction in pain scores in comparison to the placebo treatment. This included hot, sensitive, and unpleasant sensations as well as deep and surface pain. One of the participants had a mild infection at the site of injection but was later deemed insignificant to the results.[5]

Larken et al. performed a meta-analysis on the effects of BTX-A for diabetic neuropathic pain. The two studies involved included a total of 58 patients. Of the two studies, one was a double-blinded crossover trial. This study administered 50 to 100 units of BTX-A intradermally across the dorsum of both feet. Overall, there was significant pain reduction and one adverse event of infection that was not statistically significant to the study. These researchers stated that the weakest aspect of their study was sample size, and that larger sample sizes are needed before therapy can become universally accepted.[1]

Yuan et al. conducted a double-blind crossover trial to evaluate BTX-A's effects on diabetic neuropathic pain. The study had a total of 20 patients, each required to have a 3-year history of diabetic neuropathy in both feet. This was diagnosed using DN4 exams and nerve conduction velocity tests. The BTX-A treatment showed an upward trend towards improvement after just a single week with its effects lasting for 12 weeks. After the crossover at week 12, researchers noticed a placebo effect in subjects when switching from placebo injections to BTX-A injections but did not reach statistical significance. Overall, BTX-A therapy improved neuropathic pain and sleep quality, but failed to improve quality of life. This trial indicated that injections are a safe and effective method for managing diabetic neuropathic pain, even though there was a single adverse event involving a mild infection at the injection site. Further studies can test optimal dose and precise course of therapy.[6]

Hary et al. created a systematic review of 10 randomized controlled trials that included 505 patients. Their goal was to assess the efficacy and safety of BTX-A as a treatment for peripheral neuropathic pain. At one-month and three-month post injections, the groups treated with BTX-A had lower mean differences in pain score: MD - 1.87 (CI - 2.91; - 0.83) and - 1.38 (CI - 1.95; - 0.81), respectively. The researchers conducted subgroup analysis, which identified greater efficacy for diabetic polyneuropathy, when compared against other neuropathy etiologies, i.e., post-herpetic neuralgia, post-surgical neuralgia, etc. The researchers found that the

groups treated with BTX-A had a significant effect in pain intensity reduction, present at one month, and persisting for up to three months. No major side effects were reported in any of the study participants, suggesting that BTX-A injections for neuropathic pain, are safe.[7]

Taheri et al. conducted a double-blinded, prospective randomized controlled trial to determine the efficacy of intradermal BTX-A injections in painful diabetic neuropathy patients. The study included 141 diabetic patients with diabetic polyneuropathy. The research team utilized a single center to carry out their RCT, at the Imam Hossein Medical Center pain clinic, in Tehran, Iran. The participants were randomly divided into treatment and control groups. The treatment group showed improvement in Visual Analogue Scale (VAS), pain intensity, sharp and hot sensation, and other neuropathic pain parameters, when compared with the control group. The researchers were able to support their claim that local injection with BTX-A is an efficacious treatment for diabetic polyneuropathy.[2]

Restivo et al. investigated the efficacy of BTX-A as a treatment for cramps in diabetic neuropathic patients. The researchers performed a single-centered, double-blind, placebo-controlled perspective study including 50 diabetic patients with peripheral neuropathy and cramps. The patients were divided into a treatment and control group, with the treatment group receiving intramuscular injections on both sides of the gastrocnemius or the small flexor foot muscles. The primary outcome of cramping pain intensity showed statistically significant improvement in the treatment group compared to the control group. Changes with respect to the cramping pain intensity baseline levels were significant after one week and persisted up to 14 weeks. No major side effects were noted in the study. Ultimately, the researchers found BTX-A injections to be an effective and safe procedure for obtaining a sustained amelioration of muscle cramps associated with diabetic neuropathy.[8]

DISCUSSION

In this systematic literature review, eight articles were analyzed to investigate the newfound use for an otherwise potent neurotoxin. A commonality across the articles demonstrated the real possibility of BTX-A being an alternative to surgical intervention for pain associated with diabetic peripheral neuropathy. The studies demonstrated statistically significant effects of the toxin on reducing sharp and acute pain associated with chronic disease.[2, 3] This research offers exciting new possibilities in the treatment of diabetic peripheral neuropathy. It can be administered to those unable to receive other known pain treatments such as opioids, capsaicin cream, and pregabalin. Across all studies, minimal adverse effects were reported. Success in this niche opens the door to expanding the scope of BTX-A as a treatment for other diseases that result in chronic neuropathic pain.

A recurrent theme throughout the studies included in this review was the need for more randomized control studies to be conducted. This is not limited to this systematic review but speaks to a greater challenge that all novel treatments undergo. While using BTX-A as a treatment is new and exciting, it is just that - new. There are limited studies at present discussing its therapeutic use, however more are expected to be on the horizon given the current studies' success.

There are many questions still unanswered regarding the use of Botox as a treatment in medicine. Future research will provide a better understanding of how to properly

utilize Botox in its therapeutic capacity. Particular focus on tolerance development to the toxin and long-term usage would be beneficial. Most studies are limited by short time frames, so adverse effects associated with lengthier use are still unknown. Furthermore, it is unlikely that patients will be able to self-administer this treatment due to the inherent dangers associated with neurotoxic injections. A specially trained physician would be required to monitor the patient for any potential adverse effects.

Additionally, more research needs to be conducted to investigate how obesity alters the body's physiological response to toxins. Obesity, while not an explicit risk factor for diabetic neuropathy, plays a substantial role in altering the synaptic pathways of those afflicted with this disease. Specifically, obesity is implicated in reducing the effects of previously administered Botulinum Toxin A.[4] Hastings et al. suspected the extra lipid accumulation acted as an insulator around the nerves, essentially blocking them from the effects of BTX-A. They believe a higher initial dose and subsequent maintenance doses might have been required to enter the proper therapeutic range. It is not yet evident if the dosing is based upon weight, but rather may be multifaceted and not as clear cut as researchers would hope. While remaining within what we know to be safe dosing for the toxin, future researchers might consider animal studies to investigate the potential correlation between dosage and obesity.

CONCLUSION

Botulinum Toxin A is gaining credibility as a viable treatment option for diabetic neuropathic pain. Based on the pool of findings from the multiple systematic reviews, meta-analyses, and randomized clinical trials, BTX-A injections in patients with diabetic polyneuropathy appear to be effective and safe. The most common parameter that showed significant improvement was decreased sharp pain sensations. There is not enough evidence at this point in time to show a significant increase in the quality of life in patients suffering from these ailments. One of the biggest concerns with this potential treatment option is that researchers have not discovered the optimal dosage of BTX-A to administer, due to the insufficient amount of data. However, as research advances and more clinical trials are conducted on BTX-A for the treatment of diabetic neuropathies, we may discover more accurate dosage requirements as well as key anatomical locations yielding the best results. The future of BTX-A treatment appears to be promising; not only for those with diabetic polyneuropathy but also for people suffering from other neurologic pathologies.

AUTHORS' CONTRIBUTION

The authors contributed equally to the initial research, writing, and editing process. All authors reviewed the final paper prior to submission.

STATEMENTS OF COMPETING INTERESTS

The authors had no competing interests for the duration of writing, editing, and submitting this systematic literature review.

REFERENCES

1. Lakhan SE, Velasco DN, Tepper D. Botulinum Toxin-A for Painful Diabetic Neuropathy: A Meta-Analysis. Pain Med. 2015;16(9):1773-1780. doi:10.1111/pme.12728

2. Taheri M, Sedaghat M, Solhpour A, Rostami P, Safarpour Lima B. The Effect of Intradermal Botulinum Toxin A injections on painful diabetic polyneuropathy. Diabetes Metab Syndr. 2020;14(6):1823-1828. doi:10.1016/j.dsx.2020.09.019

3. Park J, Park HJ. Botulinum Toxin for the Treatment of Neuropathic Pain. Toxins (Basel). 2017;9(9):260. Published 2017 Aug 24. doi:10.3390/toxins9090260

4. Hastings MK, Mueller MJ, Sinacore DR, et al. Botulinum toxin effects on gastrocnemius strength and plantar pressure in diabetics with peripheral neuropathy and forefoot ulceration. Foot Ankle Int. 2012;33(5):363-370. doi:10.3113/FAI.2012.0363

5. Wang C, Zhang Q, Wang R, Xu L. Botulinum Toxin Type A for Diabetic Peripheral Neuropathy Pain: A Systematic Review and Meta-Analysis. J Pain Res. 2021;14:3855-3863. Published 2021 Dec 16. doi:10.2147/JPR.S340390

6. Yuan RY, Sheu JJ, Yu JM, et al. Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial. Neurology. 2009;72(17):1473-1478. doi:10.1212/01.wnl.0000345968.05959.cf

7. Hary V, Schitter S, Martinez V. Efficacy and safety of botulinum A toxin for the treatment of chronic peripheral neuropathic pain: A systematic review of randomized controlled trials and meta-analysis. Eur J Pain. 2022;26(5):980-990. doi:10.1002/ejp.1941

8. Restivo DA, Casabona A, Frittitta L, et al. Efficacy of Botulinum Toxin A for Treating Cramps in Diabetic Neuropathy. Ann Neurol. 2018;84(5):674-682. doi:10.1002/ana.