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Podiatry is a dynamic field due to its increasing demand as both the diabetic and baby boomer soon-to-be geriatric populations exponentially grow. Because of this, there has never been a greater necessity for cutting edge research employing the principles of evidence-based medicine. The standards for current patient care and the advancement of podiatry relies on our duty towards the pursuit of innovative clinical research.

Through the dedication, hard work, and noble pursuit of original research topics, I have the distinct honor to present the latest volume of NYCPM’s annual Podiatric Medical Review. This journal would not be possible without the tireless work of our Senior Editors, Editors, student peer reviewers, and collaborative authors. As is the trend every year since its inception, we had a record number of abstract submissions and have diligently accepted only the most novel for this publication. We hope to continue this journal for many years to come and I am extremely proud to have been the Editor-in-Chief for this volume.

Without further ado, I present volume 26 of the Podiatric Medical Review.

Happy Reading,

[Signature]
Diltaj Singh
Editor-in-Chief
Podiatric Medical Review
Treatment Outcomes of Pediatric Spastic Equinus due to Cerebral Palsy: A Literature Review

Michelle Diaz, BS, HyunJi Boo, BS, Hussain Hussain, BS, Sanjna Sanghvi, BS

Abstract

Introduction: This literature review aims to showcase the most current invasive and non-invasive options for the treatment of pediatric spastic equinus due to Cerebral Palsy. The methods of treatment will be evaluated for effectiveness primarily through the measurement of ankle dorsiflexion. The procedures explored include gastrocsoleus recession, aponeurotic lengthening of the calf muscles, Mesh and Vulpius Achilles Tendon Lengthening (ATL), Z-lengthening, Tibialis Anterior Tendon shortening, shock wave therapy, and botulinum toxin A injection.

Study Design: Systematic Review of Literature

Methods: A PubMed search query including the terms “Cerebral Palsy” [MeSH] AND “Equinus Deformity” [MeSH] AND “Treatment Outcome” [MeSH] AND “Child” [MeSH] was performed with inclusion criteria of human subjects, English language, and published between 1/1/2010 and 5/1/2017. Six exclusion criteria were defined. First, papers structured as systematic reviews, studies including subjects with etiology of equinus deformity other than Cerebral Palsy and studies not evaluating treatment outcomes were excluded. Next, incomplete studies, papers not reporting outcome data with defined objective measurements, and studies in which authors did not distinguish results between treated and untreated limbs were also excluded.

Results: 22 articles were found with the initial search query when the inclusion criteria were applied. The application of exclusion criteria narrowed the results to the 12 articles reviewed in this paper.

Discussion and Conclusions: In this paper, six studies evaluated invasive procedures in the treatment of spastic equinus in children with diplegic or hemiplegic Cerebral Palsy. All six studies reported positive outcomes and were part of a multilevel surgery. Passively measured ankle dorsiflexion and 3D gait analysis showed improvement in all studies. Post-operative complications included recurrence and development of calcaneal gait. Of those studies, the paper exploring the efficacy of the Mesh ATL procedure was novel and showed that patients who underwent that procedure had no complications. Patients also had faster recovery time than patients who underwent the more commonly utilized Vulpius and Z-lengthening procedures. Six studies evaluated a variety of non-invasive treatments such as extracorporeal shockwave therapy and Botulinum Toxin-A injection. All six studies reported positive outcomes with no complications and short post-procedural protocol. A major limitation of all twelve papers was that reported follow-up measurements were not consistent. Overall, more research in this field is required to establish a clear clinical recommendation for the treatment of spastic equinus in children with Cerebral Palsy.

Key Words
Cerebral Palsy, spastic equinus, diplegia, hemiplegia, treatment, gait, pediatric, child

Level of Evidence: 4
INTRODUCTION

Cerebral Palsy (CP) is a neurologic and motor disorder that impedes cognition, movement, posture and gait. The exact cause of this neuromusculoskeletal disease is unknown, but a cerebral lesion occurs intrauterine or shortly after birth of premature infants.\(^1\) There are identified risk factors such as radiation exposure and hypoxia. Despite growing knowledge, the prevalence of CP remains at about 2 per 1,000 live births in developed nations with a greater tendency amongst males.\(^1,2\) CP is a heterogeneous disease involving multiple clinical conditions. This literature review will explore the effectiveness of invasive and non-invasive treatments in the pediatric population for one of these conditions: spastic equinus.

To understand the complexity of this static encephalopathy and its associated musculoskeletal pathologies it is important to learn the classifications of CP. Classification is based on various factors related to the severity and progression of disease or disability. Classifying CP based on movement, topographical distribution, and gross motor function is a first step in initiating a treatment plan.

Approximately 60-80% of children with CP have a spastic movement disorder.\(^1,2\) Spasticity is defined as a velocity-dependent increase in muscle tone with passive stretch presenting as exaggerated deep tendon reflexes and joint contraction.\(^1,2\) The topographical distribution of CP is defined as either unilateral or bilateral. Unilateral CP can involve monoplegia or hemiplegia. Bilateral CP either involves two limbs (diplegia), three limbs (triplegia) or all four limbs (quadriplegia).\(^1\) Typically, the lower extremities are affected in pediatric CP, thus the classification of topographic distribution is essential when choosing an appropriate treatment modality.\(^2\)

The Gross Motor Function Classification Scale (GMFCS) involves assessment of a child’s level of mobility on a scale from I- V. Stage V is most severe as voluntary mobility is restricted and all motor functions are limited. At GMFCS level I and II, children have mild limitations of complex gait function such as running but are able to walk independently. Level III is defined by the ability to walk with an assistive device such as a walker or wheelchair. Children eligible for treatment of spastic equinus secondary to CP are typically categorized into GMFCS Level I, II, or III. Children at a level of IV or V GMFCS typically have a spastic quadriplegia and have little to no means of independent mobility.\(^1\) Another commonly used classification of spasticity is the Ashworth Scale. The Ashworth Scale assesses components of muscle resistance in response to passive movement.\(^3\) The scale is defined from 1-4 with 1 indicating no increase in tone and 4 indicating a rigid limb in flexion or extension. A Modified Ashworth Scale (MAS) is similar to the original; however,
there is an additional 1+ score to indicate resistance through less than half of the movement. The MAS, along with GMFCS, allows for the determination of spasticity in the lower leg pre and post treatment, quantifying the success of treatment outcomes.

Children with CP and spastic hemiplegia can be further divided into four types based on severity of contracture. Type I involves foot drop during the swing phase of gait. Type II is an obvious equinus deformity in both stance and swing phase of gait. Type III involves equinus deformity impacting the knee. Type IV is more severe as the equinus deformity extends to the knee with co-contraction of the hamstrings and associated hip problems. In children with spastic diplegia, gait patterns can also be classified into four groups: true equinus, jump gait, apparent equinus, and crouch. True equinus describes the ankle in equinus with the knees and hips in fixed extension. In jump gait, the ankle is in equinus, with knees and hips in varying degrees of flexion. In apparent equinus, the ankle is plantigrade in relation to the tibia with knees and hips excessively flexed. Crouch gait involves the ankle within functional range and excessive flexion at the knees and hips.

Classification is essential to determining appropriate treatments and reducing post-treatment complications. Ineffective surgical intervention can result in complications such as recurrent equinus or overcorrection of the Achilles tendon, potentially leading to calcaneal or crouch gait. Calcaneal gait occurs when the calf muscles are weakened and unable to restrain the forward movement of the tibia over the foot during midstance and propulsion. Current options for conservative treatment of spastic equinus include botulinum toxin type-A injection (BoNT-A), custom ankle foot orthoses (AFO), casting, physiotherapy, and extracorporeal shock wave therapy.

Regarding BoNT-A injection, there is no standard protocol for dosage, formulation (Dysport or Botox) or injection location, but research has revealed a better understanding of the metabolism and distribution of BoNT-A in the treatment of spastic equinus in children with CP. Physiotherapy, casting, and AFOs are also common measures to increase ankle dorsiflexion (DF). In children with true equinus, for example, a hinged AFO is an effective way to improve gait. Shock wave therapy is a new non-invasive therapy that decreases spasticity and improves nerve conduction. While conservative treatments are relatively safe and effective for some patients, they often do not provide a permanent solution.

Some pediatric CP patients, generally those with a GMFCS classification of I, II, or III, with spastic equinus qualify for surgical intervention. Invasive correction of equinus involves lengthening of the posterior muscle group to improve ankle DF. To better understand the various surgical approaches, the gastrocsoleus can be considered as having three distinct zones.
Zone 1 is the area from the gastrocnemius origin on the popliteal surface of the femur to the most distal fibers of the medial gastrocnemius belly. Zone 1 surgical lengthening procedures are typically proximal or distal recessions of the gastrocnemius and soleus.\textsuperscript{1} Zone 2 is defined from the distal extent of the gastrocnemius muscle to the end of the soleus muscle fibers. Zone 2 procedures such as the Vulpius involve lengthening the combined gastrocnemius aponeurosis and soleus fascia.\textsuperscript{1, 13, 14} Zone 3 is the convergence of the superficial posterior leg muscles at the Achilles tendon.\textsuperscript{1} Zone 3 procedures lengthen the Achilles tendon. The heterogeneous nature of CP complicates treatment. There is no true solution for CP; thus, treatments aim to resolve the secondary problems such as spastic equinus.\textsuperscript{2} This literature review aims to explore the most current non-invasive and invasive options for the treatment of pediatric spastic equinus due to CP.

\textbf{METHODS}

A PubMed search query including the terms “Cerebral Palsy”[MeSH] AND “Equinus Deformity” [MeSH] AND “Treatment Outcome” [MeSH] AND “Child” [MeSH] was performed with inclusion criteria of human subjects, English language, and published between 1/1/2010 and 5/1/2017. Six exclusion criteria were defined. First, papers structured as systematic reviews, studies including subjects with etiology of equinus deformity other than CP and studies not evaluating treatment outcomes were excluded. Next, incomplete studies, papers not reporting outcome data with defined objective measurements, and studies in which authors did not distinguish results between treated and untreated limbs were also excluded. The search parameters are outlined in Figure 1.

\textbf{RESULTS}

(See Table 1 and Table 2 attached)

The initial search query with inclusion criteria returned 22 articles. The application of specific exclusion criteria refined the
search to 12 papers, which were included in this review. Based on common treatment modalities for spastic equinus related to CP in a pediatric population, papers were reviewed in two main categories—surgical and non-surgical interventions.

**Invasive Treatments**

**Surgical Intervention**

Dreher et al. explored the long-term effects of gastrocsoleus intramuscular aponeurotic recession as described by Baumann and Koch on 44 patients (82 limbs) with spastic diplegic CP. This was part of a multilevel surgery which included gastrocnemius lengthening, soleus lengthening, gastrocsoleus intramuscular aponeurotic recession, psoas over the brim lengthening, proximal rectus femoris recession, hamstring lengthening, distal rectus femoris transfer, Achilles tendon lengthening, femoral derotational osteotomy, tibial derotational osteotomy, and foot stabilization. The mean age of patients was 9.8 years at time of surgery. Indication for surgery included unsuccessful conservative management using botulinum toxin injections, casting, night splinting, and AFOs. The intraoperative goal was to achieve 15-20° of ankle DF while the knee is extended and flexed. If patients were unable to achieve adequate intraoperative ankle DF, a soleus muscle lengthening was performed. If further correction was required, a limited Achilles tendon lengthening was done with a distal approach. Post-operative management included four to five weeks of walking plaster casts, carbon fiber AFO, and night splint for one year. Complications included recurrent equinus, early onset calcaneal gait, and late-onset calcaneal gait.6

All patients were GMFCS levels I to III and examined using ankle ROM, the Medical Research Council scale for Manual Muscle Testing (MMT), the MAS, and 3-D gait analysis. Barefoot gait analysis was done along a seven meter walkway. Passive ankle DF with knee extended (KE) prior to surgery, one year post-op, two to four years post-op, and six to thirteen years post-op was -3°, 8°, 6°, and 4° respectively (Table 1). Similarly, passive ankle DF with knee flexed (KF) was 6°, 15°, 13°, and 9°. The ankle DF power as shown by MMT was 3, 3, 4, and 4 for the same time periods as above. The triceps surae tonus, assessed via the MAS, was 2, 1, 0, and 1 with KE and 2, 1, 1, and 1 with KF. Lastly, the mean ankle DF in stance was -5°, 4°, 5°, and 5°.6

In their retrospective study, Klotz et al. examined 26 limbs of 19 patients with bilateral spastic cerebral palsy (BSCP). The patients had a mean age of 9.4 years, equinus deformity with toe-walking pattern, primary genu recurvatum (GR), no prior surgical treatment of the lower extremities, and the ability to ambulate independently (Table 1). GR was defined as knee hyperextension in stance phase. All patients had an aponeurotic lengthening of the calf muscles in Zone 1, as described by Baumann and Strayer et al. Adjunct procedures included Hoke
percutaneous Achilles tendon lengthening, Achilles tendon Z-lengthening, proximal or distal femur osteotomy, psoas lengthening, rectus tendon transfer, hamstring lengthening, gastrocsoleus aponeurotic lengthening, tibialis posterior tendon transfer, and hindfoot reconstruction. Post-operative management included the use of casts, orthoses, and physiotherapy according a standardized protocol. The mean follow-up was 13.7 months after surgery.\textsuperscript{11}

All patients were level II on the GMFCS. Kinematic values of the ankle during mid-stance of all 26 limbs were taken using 3-D motion analysis. Patients walked barefoot, except for two patients (three limbs) who used a four-point cane. Mean pre-operative ankle range of motion (ROM) was $-2.7^\circ$ (±13.4), while post-operative ankle ROM at follow-up was $6.8^\circ$ (±5.3). In addition, the Silverskiold test was performed on all 26 limbs. This test is used to evaluate the gastrocsoleus complex and ankle equinus, while ankle DF is tested with the knee fully extended and then flexed to 90°. Klotz et al. report a significant improvement after surgery in passive ankle DF of 11° while the knee is extended and 10° when the knee is flexed. Lastly, 5 patients (6 limbs) did not show significant improvement in ankle DF, and had a recurrence of knee hyperextension during stance.\textsuperscript{11}

Lin et al. compare a new Mesh ATL procedure to Vulpius and Z-lengthening in a prospective study. A total of 22 diplegic or monoplegic patients (36 limbs) underwent the Mesh ATL, 20 patients (33 limbs) underwent the Vulpius procedure, and 13 patients (24 limbs) underwent the Z-lengthening procedure. All patients were GMFCS level I to III. Patients with gastrocnemius equinus had the mesh ATL or Vulpius procedure, whereas patients with a fixed equinus contracture had the Z-lengthening procedure. Adjunct procedures included lengthening of the tibialis posterior, flexor hallucis longus or flexor digitorum longus, psoas lengthening at the brim of the pelvis, hamstring lengthening, and adductor longus and gracilis release. After surgery all patients received below knee casts. ATL and Vulpius recipients had casts removed after one week, while Z-lengthening patients removed casts at four weeks. After cast removal, all patients were given a splint to maintain KE and underwent physiotherapy, rehabilitation, and gait training.\textsuperscript{13}

Passive ankle DF with KE was evaluated in all patients using a goniometer pre-operatively, post-operatively, and 2 years post-op. The passive ankle DF values for the Mesh ATL were as follows: $-10.4^\circ$, $25.7^\circ$, and $15.1^\circ$ at follow-up times listed above. Similarly, the passive ankle DF for the Vulpius ATL procedure had the following values: $-11.3^\circ$, $25.5^\circ$, and $15.8^\circ$. Finally, the Z-lengthening procedure yielded passive ankle ROM values: $-13.8^\circ$, $26.4^\circ$, and $20.1^\circ$. Before surgery, 3-D Gait Analysis in the Mesh ATL group showed that the ankle was, on average, in 10-20° of plantarflexion (PF) in stance and swing phase. After the mesh ATL surgery, 3-D Gait Analysis showed that
the ankle was, on average, in 0-10° of DF, which resembles a normal gait pattern. Lin et al. also recorded the number of days post-operatively patients took to hit certain milestones: return to rehabilitation, return to walking training, stability for running, and one-legged hopping. Overall, Mesh ATL group reached all milestones earlier than those in the other groups.13

Rutz et al. report on a group of children with spastic equinus due to CP who underwent Zone 3 open Z-lengthening of the Achilles tendon (ZLAT) and tibialis anterior tendon shortening (TATS). In this retrospective study, 29 subjects, categorized as GMFCS I-III, were able to ambulate, and had no active ankle DF during gait. Participants were further subdivided into groups I and II based on whether they were hemiplegic, diplegic, or quadriplegic. Our systematic review excluded data pertaining to group II because that group included subjects who are quadriplegic. Group I consisted of 21 hemiplegic children with CP at an average age of 15.2 years who had not received a botulinum injection 6 months prior to the surgery. The 21 limbs in this group underwent a Zone 3 open ZLAT and TATS. TATS consisted of shortening and reattaching the distal tibialis anterior tendon to the medial cuneiform to keep the foot plantigrade. The ankle was dorsiflexed to 10° past neutral. Adjunct procedures include adductor lengthening, tibialis posterior shortening, hamstring lengthening, femoral derotational osteotomy and supramalleolar osteotomy.

After the operation, all patients were cast immobilized with the ankle at neutral. Subjects were weightbearing in the cast at 4 weeks and casts were removed after 6 weeks. Some subjects were switched into a hinged AFO with PF block after cast removal if active ankle DF was not immediately achieved. They report no surgical complications and no functional deterioration at follow up.15

Outcome measures of ZLAT with TATS were visually observed gait pattern, 3D gait analysis parameters the MAS, and MMT. Authors report parameter values pre-op and at a mean of 14 months post-op. Before the operation, all subjects presented with a toe walking gait pattern and no active ankle DF. After the operation, 93% of subjects exhibited active ankle DF one subject had heel-toe gait, three subjects had a plantigrade foot during gait, and seventeen subjects had toe-heel gait. The 3D gait analysis parameters included the Movement Analysis Profile (MAP) for the ankle variable and the Gait Profile Score (GPS) and Gait Deviation Index (GDI) values for overall gait evaluation. Before the operation, the average MAP was 20.64° away from the normal, GPS was 12.47° away from the normal, and GDI was 72.07 out of 100. At follow up, the MAP was 9.62°away from normal, GPS was 9.18° away from normal, and GDI was 82.61 out of 100. All three improvements were statistically significant. The MAS and MMT were evaluated for both the gastrocnemius group and the tibialis anterior. They report the pre-op MAS was
2.27 out of 4 for the gastrocnemius and 0.80 for the tibialis anterior. At follow up, the MAS was significantly improved for both muscle groups, with score at 0.79 for the gastrocnemius and 0.29 for the tibialis anterior. The MMT score was not significantly changed in either muscle groups. The pre-op MMT was 3.56 out of 5 for the gastrocnemius and 3.55 for the tibialis anterior, while post-op MMT was 3.83 for the gastrocnemius and 4.10 for the tibialis anterior. Svehlik et al. present a retrospective study on the long-term surgical outcome of children with spastic equinus due to CP. This study includes 18 diplegic patients of 11.51-year average age who were GMFCS I-III, had fixed equinus contracture with equinus gait, and had only one multilevel surgery. Fixed equinus contracture was defined as the lack of ankle DF to neutral with the KE and KF under general anesthesia. They defined equinus gait as peak ankle DF during stance phase greater than one standard deviation below the mean. Patients with history of dorsal rhizotomy or intrathecal baclofen were excluded from the study. All patients underwent the Zone 1 Baumann technique of fractional lengthening of the gastrocnemius and soleus muscles. Adjunct procedures included psoas tenotomy, adductor lengthening, hamstring lengthening, rectus femoris transfer, soft tissue and bony foot surgeries, tibial derotational osteotomy, and femoral derotational osteotomy. After the operation, subjects were placed in below knee or long legged casts, depending on concomitant procedures. Subjects underwent daily physiotherapy and gait retraining and were standing in a support frame seven to ten days post-op. Participants were discharged from in-patient care at 6 weeks and received outpatient physiotherapy as necessary. Two limbs with overcorrection and five limbs with recurrence of equinus were recorded at the ten-year follow up visit. They defined overcorrection as peak ankle DF two standard deviations above normal for age and recurrence as peak ankle DF two standard deviations below normal for age.5

Outcomes were measured using passive ankle DF angle and 3D gait analysis parameters (timing of maximum ankle DF as percentage of gait cycle, maximum ankle PF power, GDI). The study includes pre-op values and values one, two, five, and ten years post-op. Before the operation, the average passive ankle DF angle was -17.5°. After the operation, the DF angle was 8.4° at 1 year, 9.9° at 2 years, 12.8° at 5 years, and 9.1° at 10 years. A follow-up passive ankle DF values were significantly increased from pre-op values. In normal gait, maximum ankle DF occurs at an average of 42% of the gait cycle. The pre-op timing of maximum of ankle DF as percentage of gait cycle reported in this study was 18.6%. The timing post-op was 37.8% at one year, 42.9% at two years, 42% at five years, and 41.9% at ten years. The maximum ankle PF power was 0.7 watt/kg pre-op. The post-op power was 1.1 W/kg at one year, 1 W/kg at two years, 1.1 W/kg at
five years, and 1.5 W/kg at ten years. The pre-op GDI was 62.3 out of 100. Post-op GDI was 79.8 at one year, 86.8 at two years, 83.8 at five years, and 76.4 at ten years. The improvements in all 3D gait analysis parameters were significantly improved from pre-op values at every follow up.5

The Tinney et al. study evaluates outcomes of the Zone 2 Vulpius procedure on children with spastic equinus due to CP. This prospective study includes 26 subjects, 14 diplegics and 12 hemiplegics, who were GMFCS I-III and had fixed equinus. Researchers defined fixed equinus as deformity greater than 25° with KE and KF, confirmed with Silverskiold test intra-op. All but one subject had history of botulinum toxin-A injection. The Vulpius procedure was performed on a total of 30 tendons: Four of the Vulpius procedures were performed as revisions following insufficient correction after failed Strayer procedures, 22 were unilateral and 4 were bilateral. Concomitant procedures included: White slide TAL, Hoke TAL, psoas lengthening, adductor release, plantar fascial release, peroneal brevis lengthening, tibialis anterior lengthening, hamstring lengthening, semitendinosus transfer, femoral derotational, osteotomy, supramalleolar osteotomy, calcaneal lengthening osteotomy, split anterior tibialis tendon transfer, and subtalar fusion. Subjects were in below knee plaster casts with the foot plantigrade for six weeks. There was early mobilization and weight bearing as tolerated after three weeks. Casts were changed at three weeks to take an AFO custom mold. Subjects used the AFO for twelve months after cast removal. Persistence or recurrence of equinus was reported in 2 diplegic subjects and 2 hemiplegic subjects.14

Reported outcome measures are the GMFCS and 3D gait analysis parameters, including the GPS and sagittal ankle Gait Variable Score (GVS). The mean follow up time was 2.4 years post-op. The GPS pre-op was 11.8° away from the normal in hemiplegic and 14.7° away from the normal in diplegic patients. The score significantly improved to 9.0° in hemiplegics and 9.1° in diplegics at follow up. Sagittal ankle GVS pre-op was 16.4° away from the normal in hemiplegics and 21.3° away from the normal in diplegics. GVS was significantly improved at follow up with 8.1° in hemiplegics and 7.2° in diplegics. Researchers noted that maximum ankle DF during stance was improved in all subjects, but did not provide specific values. Before the operation, five subjects were GMFCS I, nineteen subjects were II, and two subjects were III. At follow up, eight subjects were GMFCS I, sixteen subjects were II, and two subjects were III.14
<table>
<thead>
<tr>
<th>Author/s</th>
<th>N. of Subjects</th>
<th>Age</th>
<th>Subject Criteria</th>
<th>Treatment</th>
<th>Pre-Op Procedure</th>
<th>Outcome Measures</th>
<th>Pre-Op Follow-Up Data</th>
<th>Post-Op Management</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dohrer et al.</td>
<td>60 (46)</td>
<td>5.8</td>
<td>Fixed conservative treatment</td>
<td>Geplastic recession only (46 limbs) or Beomown (12 limbs)</td>
<td>As needed</td>
<td>Positive ankle DF with flexion and pronation.</td>
<td>Positive with UC:</td>
<td>Wind: 70</td>
<td>Return to walking clastic cast Early mobilization, immediate WB transfer. Walking with cast after 6-8 wk on f/t, on minimal weight. For patients not fit for post-op after cast removal.</td>
</tr>
<tr>
<td>Kocsis et al.</td>
<td>26 (19)</td>
<td>9.4</td>
<td>Does not state</td>
<td>Resection: Mal-union. Stiff knee</td>
<td>As needed</td>
<td>Mean Ho scale: 67.7.</td>
<td>Mean: 13.7 month follow up 0.84</td>
<td>Gait, orthoses, and physiotherapy</td>
<td>3 limbs in Mesh group</td>
</tr>
<tr>
<td>Kutz et al.</td>
<td>21 (21)</td>
<td>15.2</td>
<td>Anterior dog-leg</td>
<td>None active ankle dorsiflexion</td>
<td>As needed</td>
<td>Observed ankle pattern.</td>
<td>Observed ankle pattern.</td>
<td>Wind: 75.7.</td>
<td>Return to walking in 6 month, walking with minimal weight. One legged hopping with no knee.</td>
</tr>
<tr>
<td>Swain et al.</td>
<td>21 (18)</td>
<td>11.5</td>
<td>Fixation: Internal fixation</td>
<td>No patient with either medical or surgical contraindication</td>
<td>As needed</td>
<td>Positive ankle DF.</td>
<td>Positive ankle DF.</td>
<td>Wind: 75.7.</td>
<td>Return to walking in 6 month, walking with minimal weight. One legged hopping with no knee.</td>
</tr>
<tr>
<td>Tinney et al.</td>
<td>30 (26)</td>
<td>9.2</td>
<td>Fixation: Internal fixation</td>
<td>No patient with either medical or surgical contraindication</td>
<td>As needed</td>
<td>Positive ankle DF.</td>
<td>Positive ankle DF.</td>
<td>Wind: 75.7.</td>
<td>Return to walking in 6 month, walking with minimal weight. One legged hopping with no knee.</td>
</tr>
</tbody>
</table>
Non-Invasive Treatments

Botulinum Toxin Injection Therapy

A common approach to non-surgical treatment of spastic equinus in children with CP is Botulinum toxin type A (BoNT-A) injections into the gastrocnemius and soleus muscles to decrease muscle tone. BoNT-A injections are a conventional form of conservative treatment for spasticity, as the mechanism of action of the toxin effectively weakens muscles through reversible neuromuscular blockade resulting in flaccidity. Pascual et al. investigated whether alternative concentrations of Botulinum toxin injections play a role in efficacy of treating spastic equinus. They examined 117 patients, average age of 7, and 189 limbs. The average dose administered was 3.3 U BoNT-A per kilogram of bodyweight, which was diluted in three different concentrations for various limbs: 100 U/ml (n=54), 50 U/ml (n=110) and 40 U/ml (n=25). Some subjects received multi-level injections. All patients received physiotherapy and completed passive and active ankle ROM exercises. Although numeric data was not reported for MAS, authors stated the average MAS score improved significantly. However, this did not differentiate between limbs with different injection concentrations... Similarly, data for sagittal plane foot stability scores assessed by gait analysis, were not reported, however, authors stated they improved significantly. On a scale of foot position, plantar foot contact showed most improvement (Table 2). Lastly, researchers reported that the concentration of BoNT-A was positively correlated with improvements in sagittal plane foot stability.\textsuperscript{12}

Klotz et al. evaluated whether Botulinum toxin injections to decrease spastic equinus in diplegic CP patients also decrease GR. The study included 13 diplegic patients averaging 5 years old and 22 total limbs. All limbs were injected with either Dysport BoNT-A (n=19) at a dose of 9.2 U per kilogram bodyweight for gastrocnemius and 5.2 U per kilogram bodyweight for soleus injections, or with Botox BoNT-A (n=3) at a dose of 1 U per kilogram bodyweight for gastrocnemius and soleus injections. In total, all 22 limbs received gastrocnemius injections, while 18 received additional soleus injections based on results of the Silverskiold test for passive ankle DF and 16 limbs received additional injections to the hamstrings or rectus femoris muscles as needed. Klotz et al. reported a significant increase in passive ankle DF with KE at 6 weeks (-5° to 2.7°) after injection (Table 2). Active ankle DF in stance improved significantly from -3° at baseline to 6.2° at 6 week follow-up, but decreased to 4.5° by 18 weeks. While knee recurvatum improved after treatment, from -12.4° at baseline to -10.2° at 6 weeks and -6.2° at 18 weeks, the change was not significant and recurvatum deformity persisted.\textsuperscript{16}

Kim et al. evaluated the efficacy of Neuronox, a newly formulated BoNT-A injection, for treatment of spastic equinus in patients with CP. The randomized control trial included 119 patients with an average age of
4.3 and 198 total limbs. The group receiving Neuronox injections consisted of 101 limbs, while the group receiving standard Botox injections included 97 limbs. All injections were administered into the gastrocnemius muscles of the affected limbs, with a dose of 4 U per kilogram body weight in hemiplegic children and a dose of 6 U per kilogram of body weight in diplegic children. Physiotherapy was continued per each patient’s normal schedule. The outcome measures in this study included the PRS for gait analysis, passive ankle ROM and the GMFCS. The PRS assessed gait in four categories including: crouch, knee recurvatum, foot contact pattern and change after an intervention. All limbs were scored in each category, with a higher score indicating a more normal gait pattern. Kim et al. defined a positive response on the PRS as an improvement of 2 points per limb, though no pre-treatment data was reported in any outcome measures. The post-treatment positive response rate on the PRS at twelve weeks was 54.9% in the Botox group and 56% in the Neuronox group. The difference between these improvement rates was within the statistical non-inferiority margin between treatment groups, indicating Neuronox was not inferior to Botox in this parameter. While no values were reported for passive ankle ROM and GMFCS, both outcome measures improve significantly in both groups with no significant difference between groups. Lastly the frequency of adverse events was not significantly different between groups. A total of 15 adverse events were reported in the Neuronox group, 13 of which were mild, and a total of 19 adverse events were reported in the Botox group, 13 of which were mild.

Hayek et al. investigated the effectiveness of botulinum toxin type A injections combined with inhibitory casting in treatment of spastic equinus in children with CP. Their study included 20 patients with hemiplegic or diplegic equinus gait with an average age of four years old and no fixed contractures of the lower extremities. In cases of diplegia, only one limb was included in analysis, for a total of 20 limbs. Subjects were randomly allocated to one of two groups. Patients in group I received BoNT-A (Dysport) injections to the gastrocnemius muscle followed by two weeks of below-knee cast with the ankle joint in neutral Patients in group II received only the injections. Dosing for the injections was the same in both groups, with 20 IU BoNT-A per kilogram of bodyweight. All patients continued with regular physiotherapy regimens and received a second injection at 4 months with a below-knee cast. Hayek et al. utilized video-based gait analysis to produce kinematic values for the Observational Gait Scale (OGS), a modified version of the popular Physician’s Rating Scale (PRS) for gait analysis. The OGS assesses gait parameters such as foot contact in midstance, knee position, base of gait, timing of heel lift, and other scaled parameters. A score of 22 per limb indicates little deviation from normal gait. Hayek et al. report significant
improvement in OGS scores in both groups 8 months after the first injection (7.9 to 12.6 in group I, 8.5 to 10.5 in group II), though the difference between the groups was not statistically significant (Table 2). Passive ankle ROM increased significantly in group I (3.5° to 9.8°), while the increase in group II was not statistically significant (9.8° to 11.9°). Active ankle ROM increased significantly in both groups (-28.1° to -13.9° in group I, -27.1° to -22° in group II). While pre-treatment and post-treatment values for the Selective Motor Control parameter were not reported, patients in group I improved significantly in this metric. Researchers did not report values for the Modified Tardieu Scale for spasticity and the Gross Motor Function Classification Scale (GMFCS), but reported significant improvements in both groups.

Frasson et al. explored the spreading effects BoNT-A injections (Dysport) in 18 children of an average age of 6.1 (Table 2). Participants included ambulatory children with hemiplegic CP with no previous treatment in the last six months and no prior invasive treatment. BoNT-A standard dosage (15-20 U/kg) was determined based on calf circumference to minimize the effect of varying muscle size on the spread of the toxin. Children with a calf circumference size of 17-21 cm received 200 units BoNT-A and those with a 22-26 cm calf circumference received 400 units BoNT-A. Subjects received injections in one limb, reported as the treated limb, while the contralateral limb was left untreated. Frasson and team, used a 27-gauge needle to inject the appropriate dose of BoNT-A in bellies of both the lateral and medial gastrocnemius muscles.

Using compound muscle action potential (CAMP) studies, MAS, passive ankle ROM, and Visual Gait Scores (VGS), Frasson et al. recorded the spread of BoNT-A to the anterior leg compartment at 10 days (T10) and 30 days after treatment (T30). Baseline CAMP score for the lateral gastrocnemius was 30.3 mVms for both treated and untreated limbs. Baseline results for the tibialis anterior muscle was 16.45 mVms (treated) and 16.2 mVms (untreated). The CAMP scores for both muscle groups after BoNT-A injections, significantly decreased at both day 10 and day 30 in treated limbs and remained unchanged in untreated limbs however no definitive values were reported. The dynamic component of spasticity is a unique measurement that is calculated by subtracting R1 angle from R2 angle. Both R1 and R2 are two ways of measuring passive ROM. R1 angle is the point in ROM where “catch” is felt during passive ankle PF. R2 angle is the total passive ROM into DF with KE. A value greater than 15° as the dynamic component of spasticity indicates a better response to toxin treatment. In this study the baseline for dynamic component of spasticity was 19.1° and after treatment decreased to 14.2° at T10 and 14.1° at T30. The authors also used the Edinburgh VGS, which evaluates 17 gait parameters in the frontal and sagittal planes to
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<th>Author</th>
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<td>Surgery: 3.5 cGy per fraction</td>
<td>Goal: To analyze weight loss and body mass index</td>
<td>Pre-Treatment (day 0)</td>
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<td>Patients with Alzheimer's disease</td>
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<td>Pre-Treatment (day 0)</td>
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evaluate patient gait before and after treatment. Although no values were given for MAS or the VGS, authors report decrease in values and favorable outcomes were implied.8

Extracorporeal Shock Wave Therapy

Extracorporeal Shock Wave Therapy (ESWT) has been shown to be an effective short-term non-invasive course of treatment for pediatric spastic equinus. Amelio et al. studied the effect of ESWT on 12 ambulatory children with average age of 8 exhibiting unilateral spastic equinus. None had previous BoNT treatment or surgical intervention. A single active shock wave was administered to the middle aspect of the gastrocsoleus muscle using an electromagnetic coil lithotripter. A total of 0.0300 mJ/mm2 of energy was applied without anesthesia. Nerve conduction studies were performed immediately after treatment and at weeks 1, 4, and 12. Treatment outcome was measured by the MAS and passive ankle ROM. MAS decreased from a baseline of 3.3 to 1.8 immediately after treatment, 1.9 after one week, and 2.25 after four weeks. By week twelve, there was no significant change compared to baseline. Similarly, passive ankle ROM increased from a baseline of 20° to 50° immediately after treatment, 50° at one week, and 40° at four weeks. Yet again, no significant difference was seen at week twelve.7

DISCUSSION

Invasive Treatments

Dreher et al. sought to investigate the long-term results of gastrocsoleus intramuscular aponeurotic recession as described by Baumann and Koch. This was the first investigation to provide long-term results on this procedure. The study ultimately found that an increase in ankle DF with KE and KF, improvement in ankle DF power (determined using the MRC scale), and an improvement in the mean DF in stance. This is important as correct interaction of the gastrocsoleus complex and the dorsiflexor muscles is important for efficient gait. During stance phase, the posterior compartment muscles of the leg are necessary for weight bearing, stability, and propulsion. In swing phase, pathologic contracture of the gastrocnemius, soleus, or both muscles with accompanying weakness of foot dorsiflexors can lead to problem with foot clearance. The study showed that the improvement in ankle DF, both passively and during stance, was maintained throughout the follow-up period. This was highlighted by the long-lasting improvement in muscle strength, which helped achieve a more efficient gait and reduced tripping and falling.6

Although they achieved 10-15 degrees ankle DF intraoperatively, Dreher et al. acknowledge that some of this improvement was lost during follow-up. This was attributed to the dynamic component of equinus, which
is absent intra-operatively but present when the patient is not under anesthesia. One thing of concern was the recurrent equinus found nine years after surgery in 24% of the limbs. The development of calcaneal gait was also a concern if overcorrection occurred. The authors do admit that the concomitant surgeries could have had an influence on the results. For example, correction of a flexed knee in this study was done via medial hamstring lengthening and could have had an impact on ankle position during gait. Similarly, changes in body mass index and subsequent changes in muscle and bone architecture could impact the kinematic data during subsequent follow-up visits.6

Klotz et al. evaluated the reduction in primary genu recurvatum (GR) after aponeurotic lengthening of the calf muscles performed as described by Baumann and Koch and by Strayer et al. Aside from 6 limbs (5 patients), all limbs showed significant improvement in ankle DF following the surgery. This correlated with reduction in knee hyperextension during stance phase. Although the study showed that the lengthening of the calf muscles improved the equinus deformity, its sample size was limited making a true assessment of the procedure difficult. Furthermore, 23% of the limbs showed no significant improvement in ankle DF.11 Additionally, Klotz et al. acknowledge that different bony and soft-tissue procedures were combined in multilevel surgeries, and that this may have influenced the results. They fail to mention the type of influence it may have had on the study. As such, the value of the procedure to correct equinus and improve ankle DF cannot be truly determined from this study.

Lin et al. evaluated the effectiveness of a new Mesh ATL procedure when compared to the Vulpius and Z-lengthening procedures. The Mesh ATL procedure involves a posteromedial longitudinal incision at the junction of the middle and lower third of the leg. A Mesh tenotomy, which included multiple transverse cuts of 5-8mm, around 5 x 5 cuts, with at least 3-5mm between cuts, was performed on the tendinous portion of the gastrocsoleus fascia. Afterwards, the ankle was dorsiflexed, and the procedure yielded in a 20-30mm lengthening of the Achilles tendon. The Vulpius and Z-lengthening procedures have been described several times in the literature and will not be described here. The study showed the Mesh ATL group had a similar correction angle to the Vulpius group and that both procedure groups had a smaller correction angle when compared to the Z-lengthening group. Since returning to normal function is a concern to most patients, a surgeon might find it useful that recovery time was significantly shorter in the Mesh ATL group than the other two groups. Furthermore, the Mesh ATL procedure does not sever the gastrocnemius completely, thus decreasing the risk of overlengthening and iatrogenic calcaneal gait. Lin et al. found no cases of recurrence in the latest 2-year follow-up in the Mesh ATL group; however, recurrence could be observed in a longer
follow-up period. The study by Lin et al. was the first to describe the Mesh ATL, suggesting further studies are required.

In the study by Rutz et al., the combination of Zone 3 open Z-lengthening of the Achilles tendon and tibialis anterior tendon shortening was found to be an effective treatment for spastic equinus in hemiplegic children with CP. Although the combination procedure did not fully correct foot position during gait, as evidenced by only one subject achieving heel-toe gait, ankle motion and overall gait was improved at last follow up, as indicated by significant improvements in ankle MAP, GPS, and GDI. The authors also evaluated the gastrocnemius and tibialis anterior muscles for changes in spasticity and strength. The spasticity was reduced in both muscles while strength was maintained. These findings indicate that the open Z-lengthening with TATS reduces spastic equinus in children with CP without causing iatrogenic weakness of the leg muscles. The authors posit that their combination treatment was successful because they recognized the importance of addressing the weakness of the stretched tibialis anterior tendon in limbs with long standing spastic equinus. During the period of equinus contracture before intervention, the agonist muscle is shortened while the antagonist muscle becomes stretched. The overly stretched tendon muscle complex is weak and less effective. Thus, it is important to address the tibialis anterior to avoid iatrogenic drop foot. The tibialis anterior became less spastic after the procedure, despite the fact that the muscle was tightened. The authors suggest that the surgical procedures restored balance between the agonist and antagonist muscles, removing the gastrocsoleus spasticity as a trigger for tibialis anterior spasm. This cohort must be followed long term to investigate the rate of recurrent equinus and other complications.

It is notable that the study by Rutz et al. included the oldest subjects out of the six invasive treatment articles in this systematic review. The average age of subjects was 15.2 years with the age ranging from 9 to 22. The older cohort speaks to the authors’ point regarding the heightened importance of addressing the tibialis anterior in children with long standing spastic equinus. Their surgical success in managing the older population may be correlated with the shortening of the tibialis anterior tendon. As such, shortening the tibialis anterior may be indicated in the surgical plan for older children with spastic equinus.

In their long term follow up study, Svehlik et al. report successful treatment of fixed spastic equinus in diplegic children with the Zone 1 Baumann procedure. The procedure improved maximum ankle DF achieved during gait and brought the GDI closer to normal. Svehlik et al. state that the normalization of maximum ankle DF timing and ankle PF power generation is an indication that triceps surae are in better mechanical position for propulsion at end of double stance phase due to the procedure. The
3D gait analysis indicates that these improvements were maintained 10 years post-op. The authors found two limbs with signs of overcorrection at 10 year follow up. This rate of calcaneal gait is less than the reported rates in other long term studies of various procedures for equinus. Calcaneus gait is more common in subjects treated with percutaneous ATL and when subjects are followed long term. Svehlik et al. suggest that they found less overcorrection because the Baumann procedure is a fractional lengthening procedure. In spastic equinus associated with CP, the gastrocnemius is usually more contracted than the soleus. Thus, the authors used 2-3 transverse incisions in the gastrocnemius and 1-2 incision in the soleus to lengthen. Although the ankle DF to neutral after the incision stretches both muscles, the soleus muscle is more proportionally more weakened because the muscle fibers are shorter than those of the gastrocnemius. The authors also propose that the Baumann procedure leads to less overcorrection than Zone 3 procedures that directly lengthen the Achilles tendon.

Children with CP have an imbalance between the Achilles tendon length and muscle belly length, where the Achilles tendon is proportionally longer than normal. Procedures that further lengthen the Achilles tendon can lead to weakness and calcaneal gait. The Baumann procedure allows independent lengthening of the gastrocnemius and soleus muscles and restores normal muscle balance. The rate of recurrence of equinus gait at 10 year follow up was comparable to other reported short term outcomes for the Strayer and Achilles tendon lengthening techniques. Authors also note that the maintained improvements long term may partially be due to the positive effect of growth and increased weight on equinus. The authors recommend the Baumann procedure for the correction of mild fixed gastrocsoleal equinus deformity with maximum ankle DF of -10 to -15° with KE.

The Zone 2 Vulpius procedure was also found to successfully treat fixed spastic equinus deformity in hemiplegic and diplegic children with CP, as reported by Tinney et al. The 3D gait analysis showed significant improvement in sagittal ankle GVS and GPS 2.4 years post-op. The GMFCS at follow up also indicated that the subjects maintained or improved in their global function and mobility. There were two diplegic children and two hemiplegic children with persistent or recurrent equinus and no reported cases of overcorrection. Authors suggest that the Vulpius procedure is successful in addressing gastrocsoleal equinus because it strikes a balance between overcorrection, leading to calcaneal or crouch gait, and under correction leading to recurrence. They caution that the equinus deformity should be assessed intra-op to fine tune the procedure selection. They also recommend erring on the side of under correction since recurrent equinus is easier to treat than calcaneal gait after overcorrection. The authors discuss that Zone 1 procedures, such as the Strayer and the Baumann, are
proven safe and effective treatments for equinus in diplegics but do not address higher degrees of equinus, especially in hemiplegic children. Although this study does not confirm which is the optimum procedure for children with moderate equinus too severe for Zone 1 correction and not severe enough for Zone 3, the authors recommend the Zone 2 Vulpius procedure for a fixed equinus of the gastrocsoleus with at least 15° of equinus with KF under general anesthesia that increases by no more than 15° with KE. Their recommendation is in line with that of Svehlik et al., who recommend the Baumann procedure for mild fixed equinus with maximum ankle DF of -10 to -15°.14

All six studies pertaining to the surgical correction of spastic equinus and equinus gait in children with CP indicate that the procedure under study was part of a multilevel surgery. The Dreher et al., Klotz et al., and Lin et al. studies all report that various soft tissue and osseous surgeries were performed. The Rutz study reports concomitant procedures in 12 out of 21 subjects, while the Svehlik study reports a mean of 6.8 procedures and range of 2-14 procedures per subject. In the Tinney et al. study, a total of 107 concomitant procedures were performed on 30 limbs on 26 subjects. The influence of other foot and ankle procedures and suprastructural procedures on ankle function cannot be ignored. As Svehlik et al. admit, improvements in ankle function and correction of equinus cannot be solely attributed to the procedure addressing the triceps surae. They also point out that presence of hamstring contracture is associated with increased recurrence of equinus, indicating that hamstring length definitively affects the development and correction of equinus. However, these outcome studies also include evaluations of general gait function. The demonstrated improvements in ankle function and general gait, such as GPS and GDI, indicate that the various procedures discussed are critical component of a comprehensive surgical plan.

**Non-Invasive Treatments**

Botulinum Toxin type A (BoNT-A) injections work by inhibiting the release of Acetylcholine at the neuromuscular junction to temporarily reduce muscle tone. These injections are frequently used in treatment of spastic gastrocsoleus equinus; however, their effectiveness has been shown to decrease with repeated injections, highlighting the need for more long-lasting treatments.9 Controversy remains as to standard dosing and formulations, potential complications, and use of adjunctive therapies in the administration of BoNT-A injection therapy for children with CP. Though the papers reviewed utilize various outcome measures and scales for assessing muscle tone, function, gait, and range of motion at various joints, the overall efficacy or limitations of the treatment under study can be appreciated.

As evidenced by Pascual et al. in their retrospective analysis of BoNT-A therapy for
equinus, concentration of the injection is positively correlated with improved foot stability during gait analysis. This was primarily seen by the reported improvements in foot position and stability in the sagittal plane. More frequent plantar heel contact was observed, although this did not relate to an overall improvement in gait. While Pascual et al. did not report values, they conclude that these changes in foot stability were correlated to the different concentrations of BoNT-A injected, with the limbs receiving higher concentrations showing greater improvement. They also report that treatment appeared most efficacious in younger patients. They conclude that the optimal dosing differs in diplegic versus hemiplegic patients, recommending 3-4 U BoNT-A per kilogram of bodyweight per leg in diplegic patients and 5-6 U BoNT-A per kilogram body weight in hemiplegic patients. Limitations include the use of foot position scale, a subjective tool, and the inclusion criteria of children with 90° passive ankle DF which omits a large proportion of patients with equinus. Therefore, these results may be difficult to apply to children with more severe equinus deformities.

In the retrospective study by Klotz et al., investigators sought to evaluate effectiveness of BoNT-A injections for equinus. They noted that the observed significant improvement in passive ankle DF with KE, but not with KF at 6 weeks may suggest the gastrocnemius was more affected by the BoNT-A injection than the soleus. As supported by various other studies, the decline in improvements in active ankle DF and KF after 18 weeks of follow-up versus the results observed at 6 weeks highlights the temporary impact of the BoNT-A injections. The study by Klotz et al. is limited by its small sample size and the fact that it did not report data separately for those who received injections to the gastrocnemius only, both the gastrocnemius and soleus, or other muscles as this variable could affect results.

Kim et al. carried out a double-blind randomized control trial to evaluate the potential use of Neuronox compared to Botox in treating spastic equinus. Ultimately, the authors conclude that Neuronox has the same efficacy and safety compared to Botox injections and can be recommended as an alternative therapeutic option. The main parameter used to support this conclusion was improvement in the PRS for gait, which improved in both treatment groups with no significant difference between the Neuronox and Botox groups. Although significant improvement in passive ankle ROM and GMFCS were also reported, a limitation to the Kim et al. paper is that it does not report many of the pre-treatment and post-treatment data values, but instead reports whether the changes between them at various follow-up times were significant. Another limitation is the absence of a placebo group against which to compare both Neuronox and Botox patients. As the safety of Neuronox was also supported by the lack of significant difference in adverse events compared to Botox, this
paper suggests Neuronox may be a suitable treatment for equinus in children with CP.

In the prospective study by Hayek et al., the inclusion of inhibitory casting to Botulinum Toxin-A injection therapy for spastic equinus was found to prolong the benefits of the treatment. The group with injection and casting exhibited consistent outcome measure improvements after the first and second injections. However, in the group without casting, the improvements were lost between the first and second injections and regained after the second injection. Considering BoNT-A injections are known to have a temporary effect, the potential ability to preserve those results for a longer period illustrates an opportunity to improve overall treatment. The casting had a significant positive effect on passive ankle joint ROM, as well as the OGS SMC outcomes, compared with results from limbs without casting. While this study is limited by a small sample size and relatively short follow-up period, Hayek et al. conclude that these results suggest recommendation of casting with BoNT-A injection therapy to prolong the interval between necessary injections.

The study by Frasson et al. has shed light on the effectiveness of a standard dose of 15-20 U/kg BoNT-A gastrocnemius injections. The toxin spreads to anterior extensor compartment, improving gait and reducing spastic equinus. Based on the study of 18 pediatric hemiplegic patients, nerve conduction increased in both leg flexors and extensors after treatment. The analysis of nerve conduction using CAMP, visual gait analysis, and passive ROM all confirm the effectiveness of this treatment. Frasson et al. however suggest the toxin has a plateau effect with repeated treatment and at a dosage of 8-24 U/kg. The dynamic component of spasticity did not increase post treatment, possibly highlighting the limitations of a short-term neurophysiologic study with a small sample. BoNT-A injections are an effective treatment for spastic equinus in the pediatric population but the safety profile for this age population is not well understood, as it may induce weakness or other possible adverse effects at higher doses.

Based on the findings of Amelio et al. shock wave therapy holds a promising future as a solution to decreasing spasticity and increasing ROM in children with unilateral spastic equinus. The ESWT has been proven effective for up to four weeks in the pediatric population. The effects of the treatment are lost by twelve weeks, classifying this treatment as a short-term solution to improve gait and spasticity. This non-invasive method had no adverse side effects and provided immediate reduction in hypertonia. While the exact mechanism of ESWT is not fully understood, it is suggested that the thixotropic effects on the blood vessels and muscles decrease flexor tone in the limb. Another possibility for its effectiveness may be that the electrical stimulation activates non-enzymatic and enzymatic nitric oxide, triggering an anti-inflammatory effect. Despite the small subject population and
unblinded selection process, ESWT holds promise as a safe non-invasive treatment.

CONCLUSION

This paper sought to synthesize and showcase the most current invasive and non-invasive treatment options for pediatric spastic equinus due to CP. The current options for conservative treatment of spastic equinus include the use of BoNT-A injections, AFO, physiotherapy, casting, and ESWT. The mainstay surgical approaches to treating ankle equinus is a gastrocsoleus recession or lengthening.

Though the articles evaluating conservative treatments, specifically BoNT-A injections, casting, and ESWT, used a wide variety of outcome measures, results indicated overall positive outcomes. Hayek et al. found a novel way to prolong the effects of Botulinum Toxin A by applying an inhibitory cast to the patients. However, that would only prolong the interval between necessary injections. Kim et al. examined an alternative to Botox by using Neuronox instead. Ultimately, Neuronox was found to have the same efficacy as the Botox. While most of these treatments were effective and had no complications, it should be noted that they are all short-term in nature, necessitating a need for long-term intervention.

In terms of surgical approaches, all papers found an improvement in outcome measures, particularly ankle DF. However, some patients developed post-operative complications such as recurrent equinus and calcaneal gait. Furthermore, lengthy post-operative management protocols including casts, orthoses, and physiotherapy were indicated for these procedures. Lin et al., explored the use of Mesh ATL as a novel surgical approach that decreases recovery time and reduces the incidence of calcaneal gait, compared to the more established procedures, such as the Vulpious or Z-lengthening. Due to the relative prevalence of CP and its negative effects on ambulation it is imperative to establish efficacious long-term management protocols.

AUTHORS’ CONTRIBUTIONS

All authors contributed equally to this literature review. All authors agreed upon the final submission of this draft.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.
REFERENCES


The Efficacy of the Ilizarov Technique in the Management of Distal Tibial Fractures: A Qualitative Systematic Review

Justin Muser, BS, Nafis Ahmed, BS, Jake Relis, BS, Pooja Srivastava, BS

Abstract

Introduction: Distal tibial fractures are difficult injuries to treat. They often present as comminuted fractures which makes restoration of normal anatomy increasingly challenging. They can be treated using open reduction and internal fixation (ORIF), intramedullary nailing, external fixation methods, or a combination of these methods. One method of external fixation involves the Ilizarov technique, which allows for gradual bone and soft tissue distraction while preventing shortening and demonstrates a low complication rate. The purpose of this study is to assess current literature for the effectiveness of the Ilizarov technique as a treatment for distal tibial fractures.

Study Design: Qualitative Systematic Review of Literature

Methods: An English language literature search was conducted on the PubMed database. Articles related to the Ilizarov technique, distal tibial fractures, and pilon fractures were found using the search terms ("Tibial Fractures"[Mesh] AND ("distal" or "pilon")) AND ("Ilizarov Technique"[Mesh] or "ilizarov"). The search was further restricted to include papers from January 1, 2013 to December 31, 2017 and humans only.

Results: The review of the literature yielded 9 informational articles consisting entirely of case series. The studies evaluated the multiple applications of the Ilizarov technique in the treatment of distal tibial fractures secondary to trauma. These applications include intra-articular fractures, extra articular fractures, severe comminuted fractures, osseous deformities, callus distraction, and tibiocalcaneal arthrodesis. In total, the review of the literature assessed the outcomes of 172 patients. The investigators of each study indicated favorable results in a majority of the patients.

Discussion and Conclusion: Based on the literature reviewed, it was shown that the utilization of Ilizarov technique as an adjunct to internal fixation may be a better suited alternative to the above-mentioned treatment methods for distal tibial fractures. This is supported by reduced rates of infection, malunion, and non-union. It may be a better-suited alternative to amputation, and this is supported by long-term reduced healthcare costs, as well as in terms of increased patient satisfaction. Pin tract infections are commonly seen, but are relatively simple to manage. More serious complications are less commonly found. However, clinicians should be mindful regarding patient selection and education, due to the longer postoperative course associated with this technique.

Key Words:
Ilizarov technique, external fixation, distal tibia, trauma, pilon fracture, ankle fracture, distraction osteogenesis

Level of Evidence: 4
INTRODUCTION

The management of distal tibial fractures is a notoriously difficult injury to treat successfully. They present with a number of treatment challenges in terms of alignment, fixation, management, and potentially osteomyelitis. Pilon fractures for example, are tibial plafond fractures extending into the articular surface which arise from high energy trauma in the form of an axial loading force which is sometimes accompanied by a rotational element. Additionally, many ankle fractures fall under 3 of the 4 Lauge-Hansen classification of ankle fractures, more specifically stages 1, 2, and 4. Fracture types will vary according to the mechanism; bone on bone impact form oblique fracture patterns, avulsions form transverse fracture patterns, and excessive compressive forces lead to comminuted fractures. Any of these fracture patterns can pierce the skin resulting in compound fractures. Acutely, distal tibial injuries can result in fragmentation, osteoporosis, infection, soft tissue atrophy, and joint contractures. Chronically, they may lead to arthritis, joint instability, deformities, and an overall decrease in the patient’s quality of life. Healing distal tibial fractures is challenging due to the limited nature of blood supply at the distal tibial epiphysis. As stated by El-Mowafi et. al., the poor vascular status of the distal tibia often makes nonunion a common outcome of open reduction and internal fixation (ORIF). A fracture can potentially lead to the obliteration of the arterial supply which worsen the clinician’s ability to completely heal the fracture site. This may lead to the chronicity of the fracture sequelae.

Treatment protocol varies with the extent of the fracture. While low–energy fractures can be gently manipulated to anatomic position followed by casting, studies have reported “Good” and “Excellent” results performing ORIF. However, this procedure requires dissection of the soft tissue structures around the fractured bone resulting in devascularization of bone, increase complications, and additional surgical procedures. Compound fractures instead mandate surgical intervention in order to prevent bacterial infection at the site of the injury. Some complications of open fractures include infection and sloughing of skin.

Traditional external fixation is an intervention developed to treat extensive distal tibial fractures. It is reserved for trauma that demonstrates significant soft tissue injury. ORIF with early mobilization has been recommended for less severe presentations -- specifically, a two staged protocol for external fixation mentioned by Joveniaux et al. including a temporary external fixation followed by ORIF. Extensive distal tibial fractures often presents with infection.

The Ilizarov frame is a specialized form of external fixation that has been developed in Siberia by Dr. Gavril Ilizarov utilizing compression followed by distraction
to create new bone from a cartilaginous matrix. The structure itself is circular and fixated to bone through stainless steel or titanium gauge wires. In addition to being a structural support for bone, the Ilizarov frame allows deformity correction by means of distraction histogenesis which is the key principle employed.

Treatment with external fixation successfully addresses all complications associated with osteomyelitis, and is associated with favorable outcomes. Additionally, the Ilizarov external fixator reduces fracture fragments via ligamentotaxis, a technique in which a longitudinal force produces distraction, allowing the soft tissue to aid in molding bony fragments and reduction of the fracture. Fracture reduction is problematic in approximating alignment due to the multitude of fragments. Holding the structure out to length, as with external fixation, aids in maintaining the relative shape of the patient's leg. The addition of olive wires may apply compressive forces and has the advantage of customizing the rigidity to suit the extent of the fracture. The indirect nature of restoration with Ilizarov’s method causes many to question the true ability to restore soft tissue and bone. This paper aims to determine the efficacy of the Ilizarov technique in the treatment of extensive distal tibial fractures.

**METHODS**

An English language literature search was conducted through the PubMed database. The results of the search are seen in Figure 1. Articles related to the Ilizarov technique, distal tibial fractures, and pilon fractures were found using the search terms ("Tibial Fractures"[Mesh] AND ("distal" or "pilon")) AND ("Ilizarov Technique"[Mesh] or "ilizarov"). This search resulted in seventy-eight papers. The search was further restricted to include English language papers from January 1, 2013 to December 31, 2017 and humans only. Other methods of external fixation were not considered for this review, including Taylor Spatial Frames, Delta frames, etc. With this search and exclusion

![Figure 1: Summary of methods depicted by a flow chart](image-url)
criteria, nine papers and one comment from a reviewer remained. The one comment was then excluded, as the search was for informational articles only. These terms represent the inclusion criteria for the literature review.

RESULTS

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient Sample Size</th>
<th>Sex (M:F)</th>
<th>Patient Age</th>
<th>Time in Ilizarov External Fixator</th>
<th>Preoperative Evaluation</th>
<th>Postoperative Evaluation</th>
<th>Outcome Metric Scoring</th>
<th>Summary of Major Complications Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramos et al. (2013)</td>
<td>39</td>
<td>12:27</td>
<td>Median 50 years</td>
<td>Median 16 weeks</td>
<td>AO fracture classification: 5 patients A1 fractures, 11 patients A2 fractures, 5 A1 patients A3 fractures, 12 patients C1 fractures, 3 patients C2 fractures, and 3 patients C3 fractures</td>
<td>Assessment taken at 4 weeks, 12 weeks, and 1 year</td>
<td>Modified Burwell and Charnley classification: 13 cases good, 21 cases fair, and 5 cases poor</td>
<td>Pin site infections observed in 27 patients</td>
</tr>
<tr>
<td>Crawford et al. (2014)</td>
<td>15</td>
<td>5:10</td>
<td>Mean 46.33 years</td>
<td>Mean 85.93 days</td>
<td>9 patients with at least one comorbidity, 1 patient with diabetes mellitus, and 7 patients that were active smokers</td>
<td>Mean total follow-up duration 27.86 months</td>
<td>Successful arthrodesis in 11 patients</td>
<td>Pin tract infections observed in 5 patients</td>
</tr>
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<td>Danoff et al. (2015)</td>
<td>10</td>
<td>---</td>
<td>---</td>
<td>Mean 20 weeks</td>
<td>AO/OTA classification: 2 patients 43-B fractures, 3 patients 43-C2 fractures, and 23 patients 43-C3 fractures</td>
<td>Assessment taken at 2, 6, 12, and 24 weeks</td>
<td>SMFA: 22.1 ± 13.3 AAOS Foot and Ankle score: 75.0 ± 15.1</td>
<td>Deep wound infection seen in 1 patient</td>
</tr>
<tr>
<td>Study</td>
<td>No.</td>
<td>Age</td>
<td>Follow-up</td>
<td>Fracture Characterization</td>
<td>Outcome Measures</td>
<td>Complications/Additional Information</td>
<td></td>
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<tr>
<td>Schoenleber et al. (2015)</td>
<td>3</td>
<td>---</td>
<td>---</td>
<td>Mean 6.33 months&lt;br&gt;OTA fracture and dislocation classification: 1 case of type C2.3 fracture, 1 case of type C3.2 fracture, and 1 case of type C3.3 fracture</td>
<td>Mean follow-up 57.3 months&lt;br&gt;Median AOFAS ankle-hindfoot score 75.7&lt;br&gt;Reoperation required in 1 case due to a broken olive wire</td>
<td>Severe posttraumatic arthritis seen in 1 case&lt;br&gt;Superficial pin site infection seen in 1 case</td>
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<td></td>
</tr>
<tr>
<td>Fadel et al. (2015)</td>
<td>20</td>
<td>14:6</td>
<td>Mean 32.8 years&lt;br&gt;Mean of 130 days&lt;br&gt;AO fracture classification: 8 patients type A1 fractures, 6 patients type A2 fractures, and 6 patients type A3 fractures</td>
<td>Mean follow-up 26 months&lt;br&gt;Modified Mazur ankle score: 10 cases excellent and 10 cases good</td>
<td>Pin site infections observed in 6 patients</td>
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<td></td>
<td></td>
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<tr>
<td>El-Mowafi et al. (2015)</td>
<td>23</td>
<td>17:6</td>
<td>Mean 37.8 years&lt;br&gt;Mean 14 weeks&lt;br&gt;Ruedi-Allgower classification: 7 patients type I fractures, 13 patients type II fractures, and 3 patients type III fractures</td>
<td>Mean follow-up 18 months&lt;br&gt;Ilizarov alone AOFAS score: 77.8 ± 5.8&lt;br&gt;Ilizarov with arthroscopy AOFAS score: 78.4 ± 6.9</td>
<td>Delayed union observed in 3 patients&lt;br&gt;Valgus deformity of tibia observed 1 patient post-operatively</td>
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<tr>
<td>Semaya et al. (2016)</td>
<td>14</td>
<td>12:2</td>
<td>Mean 34.1 years&lt;br&gt;Mean 5.9 months&lt;br&gt;Gustilo grade classification for open fractures: 7 patients grade II, 1 patient grade IIIA, and 2 patients grade IIIB&lt;br&gt;4 patients with closed fractures</td>
<td>Mean follow-up 20.4 months&lt;br&gt;Paley et al. scoring system: 5 cases excellent, 8 cases good, and 1 case fair</td>
<td>Secondary procedures performed on 3 patients&lt;br&gt;Pin tract infections observed in 4 patients&lt;br&gt;Superficial wound infections observed in 2 patients&lt;br&gt;Valgus deformity of the tibia observed in 1 patient</td>
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</table>
The results of the literature review are summarized in Table 1. Ramos et al. described a prospective case series of 39 patients with distal tibial fractures treated with the Ilizarov technique. Their study included cases of both intra-articular fractures and extra-articular fractures of the distal tibia. Five patients had Muller AO classification of fracture type A1 fractures, eleven patients had type A2 fractures, five patients had type A3 fractures, twelve patients had type C1 fractures, three patients had type C2 fractures, and three patients had type C3 fractures using the AO fracture classification. Of the eighteen patients with type C-fractures, ten patients had Ruedi-Allgower type I, five patients had Ruedi-Allgower type II, and three patients had Ruedi-Allgower type III. Thirty patients had closed fractures and nine patients had open fractures, which included

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Mean Age</th>
<th>Mean Follow-up</th>
<th>Fracture Classification</th>
<th>AOOFAS Score</th>
<th>Secondary Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eralp et al. (2016)</td>
<td>39</td>
<td>47 years</td>
<td>198 days</td>
<td>Muller classification: 8 patients type A1, 1 patient type A2-1, 2 patients type B2, and 2 patients type B3. Cierny-Mader classification for bone infection: 9 patients type IIIA and 4 patients type IVB.</td>
<td>68.8</td>
<td>5 patients</td>
</tr>
<tr>
<td>Osman et al. (2017)</td>
<td>30</td>
<td>26 years</td>
<td>48 months</td>
<td>Ruedi-Allgower classification: 11 patients type II fractures and 19 patients type III fractures.</td>
<td></td>
<td>10 patients</td>
</tr>
</tbody>
</table>

SMFA = Short Musculoskeletal Function Assessment Questionnaire, AOFAS = American Orthopaedic Foot And Ankle Society ankle-hindfoot score.

Table 1: Summary of Results from Literature Review
six cases classified as Gustilo I and three classified as Gustilo II. Their study concluded that the Ilizarov technique provided “satisfactory outcomes” independent of the fracture pattern. To evaluate their outcomes, they used a modified version of Burwell and Charnley criteria described by Marsh et al, and the results are seen in Table 1 above. One main complication seen in the study were pin tract infections. To treat the pin tract infections, the investigators used short-term antibiotics in nineteen patients and removed the offending wire in fifteen patients. Only one of their patients developed a deep S. aureus infection which was treated successfully with curettage, stabilization, and progressive correction with a new Ilizarov external fixator for 23 additional weeks, and antibiotic therapy with clindamycin for 12 weeks. Additionally, one of the patients within their study developed a residual deformity that lead to post-traumatic sympathetic dystrophy. The investigators treated this patient with an ankle joint arthrodesis 1.5 years later, but the procedure was unsuccessful in relieving the patient’s pain.

Crawford et al. described a retrospective case series of fifteen patients that underwent tibiocalcaneal fusion using the Ilizarov technique, twelve cases in which trauma was the main cause of hindfoot pathology. The purpose of this study was to determine a correlation between comorbidities and complications, and between nonunion and amputation. All the patients in this study had at least one comorbidity, including rheumatoid arthritis, diabetes types 1 and 2, smoking, past open trauma, or previous nonunion. Ten patients had multiple comorbidities. Arthrodesis was performed on these patients using a transfibular and anteromedial arthrotomy when needed, and the surgeons placed the Ilizarov fixator in compression across the fusion site. Successful arthrodesis was defined by successful union radiographically. Successful arthrodesis was eventually achieved in eleven patients as reported by the investigators of this study. Nine patients needed additional surgery post-operatively, including seven outpatient hardware removal procedures. Three patients required below-the-knee amputation due to nonunion, three patients required wound revision for either infection or wound dehiscence, and one patient required pin revision during application of the frame due to metal fatigue failure. An additional finding from the study is that the investigators determined a strong correlation (Pearson r = 0.63) between wound infections and smoking tobacco.

Danoff et al. described a retrospective case series of twenty-eight patients with Orthopaedic Trauma Association (OTA) type 43-B and 43-C open pilon fractures of the distal tibia, wherein, eighteen patients were treated with internal plate fixation and ten were treated with Ilizarov frames. Thirteen patients were male and fifteen were female. The mean age of the patients was 43 years old. To assess the post-operative
functional outcomes of each of the patients, the investigators utilized the Short Musculoskeletal Function Assessment Questionnaire (SMFA) and the AAOS Foot and Ankle Questionnaire. The SMFA is a general health instrument with six subscores rated on a scale of 0-100 with a higher score representing worse function. The AAOS Foot and Ankle Questionnaire is another instrument that includes a core score for twenty items, scored on a scale of 0-100 with higher scores representing better outcomes. The mean SMFA dysfunction score for patients in this study was 19.4 ± 14.6; the patients who received treatment with the Ilizarov frame reported a mean score of 22.1 ± 13.3, and the patients who received treatment with internal plate fixation reported a mean score of 17.6 ± 11.2. The mean AAOS Foot and Ankle score for patients in this study was 72.0 ± 17.7; the patients who received treatment with the Ilizarov frame reported a mean score of 75.0 ± 15.1, and the patients who received treatment with internal plate fixation reported a mean score of 71.0 ± 19.6. Of the ten patients who were treated with an Ilizarov frame, only one patient developed a deep infection that was treated successfully with debridement and pin removal. One patient developed severe bone loss and required revisional surgery with bone graft to treat the nonunion, and one patient required an ankle arthrodesis for post-traumatic arthrosis.

Schoenleber et al. described a retrospective case series of eight patients diagnosed with hypertrophic nonunion of the distal tibia from previous trauma and treated with callus distraction via revisional external fixation. All eight patients considered in this study had previously received surgical treatment using circular external fixation, but resulted in either hypertrophic nonunion or early malunion with an unacceptable varus/valgus deformity of 5° or more. Prior to the revisional procedures, one patient was diagnosed as type A3, two patients diagnosed as type C2, and five patients diagnosed as type C3 according to the AO fracture classification. Of the eight patients in the study, three patients received treatment with an Ilizarov frame and five patients received treatment with a Taylor Spatial Frame. The investigators report all patients achieved union in an average of 5.8 months with two patients with residual sagittal plane malalignment in the Ilizarov frame group and one patient with residual coronal plane malalignment in the Ilizarov frame group. The investigators utilized the AOFAS ankle-hindfoot scoring system (scored from 0-100, with higher numbers representing “better” outcomes) to assess the outcomes of each patient, and reported a median score of 82.5. Reported complications observed in this study include two cases of superficial pin site infections in the Taylor Spatial Frame group. Additionally, there was one case of a deep pin site infection in the Ilizarov frame group, which required an incision and drainage procedure and IV antibiotics. Lastly, there was one patient with a 2 cm limb length
discrepancy in the Taylor Spatial Frame group. For the purposes of this review, the results from the Taylor Spatial Frame group are not considered applicable for the inclusion criteria, which solely analyzes the efficacy of the Ilizarov technique. These findings are accounted for and represented in Table 1 above.

Fadel et al. described a prospective case series of forty patients with extra-articular fractures of the distal tibia, wherein, twenty patients were treated with Ilizarov external fixation and twenty were treated with internal dynamic compression plates. Within each group, eight patients had type A1 fractures, six patients had type A2 fractures, and six patients had type A3 fractures using the AO fracture classification. The investigators’ intention was to compare results between internal dynamic compression plates and Ilizarov external fixation on patients with the same classification. To assess the post-operative functional outcomes of each patient, the investigators utilized a modified Mazur ankle score, which is assessed on a 0-100 scale with higher scores indicating a better outcome. For the purposes of the study, the investigators designated “excellent” results for scores greater than 92, “good” results for scores 87-92, “fair” results for scores 65-87, and “poor” results for scores less than 65. In this study, there were ten “excellent” and ten “good” results within the Ilizarov fixation group. Likewise, there were two “excellent,” eight “good,” four “fair,” and six “poor” results within the internal compression plate group. The investigators reported pin site infections in more than four sites in six patients in the Ilizarov fixation group, which were successfully treated with either oral or parenteral first generation cephalosporins.

El-Mowafi et al. described a prospective case series of twenty-three patients with pilon fractures of the distal tibia treated with an Ilizarov external fixator. In this case series, the investigators randomly divided the twenty-three patients into two groups, where eleven patients were treated using an Ilizarov external fixator exclusively and twelve patients were treated by the Ilizarov technique assisted with ankle arthroscopy. Pre-operatively, the investigators assessed the patients using the Ruedi-Allgower classification system for both groups, as seen above in Table 1. To assess post-operative functional outcomes of each patient, the investigators evaluated each case with an AOFAS ankle-hindfoot scale and a grading system described by Bone et al. The AOFAS scores were 77.8 ± 5.8 for the Ilizarov external fixator group alone and 78.4 ± 6.9 for the Ilizarov technique assisted with arthroscopy. In the Ilizarov external fixator group alone there were three reported cases of “excellent,” four reported cases of “good,” two reported cases of “fair,” and two reported cases of “poor” according to the Bone et al. criteria. In the Ilizarov technique assisted with arthroscopy group there were four reported cases of “excellent,” six reported cases of “good,” and two reported cases of
“fair” according to the Bone et al. criteria. The investigators concluded no statistically significant improvement to the results of fracture reduction with the addition of ankle arthroscopy to the Ilizarov technique, and reported p > 0.05. There were four complications reported by the investigators in this study. Delayed union was seen in one case in the Ilizarov external fixator alone group and in two cases in the Ilizarov technique assisted with arthroscopy group. Additionally, there was one reported case of residual valgus deformity of the tibia reported in the Ilizarov external fixator alone group.2

Semaya et al. described a case series of fourteen patients who were previously treated for open tibial fractures with debridement and external fixation, but had developed post-traumatic bony defects of the tibia. Thus, the investigators treated these patients with tibial reconstruction via a vascularized fibular graft combined with Ilizarov external fixation.25 The patient sample had an average age of 34.1 years at operation. There were twelve males and two females. The size of the bony gap was 10.4 cm and the average length of the fibula used was 16.4 cm. The mean follow up period was 20.4 months. All patients had bony union at both proximal and distal ends of the fibula primarily, except one patient who required a secondary iliac bone graft at the distal end of the fibula to obtain union. The average time for bone healing was 3.9 months. The average time spent in Ilizarov frame was 5.9 months. “Unprotected full weight-bearing” was achieved within an average of 7.3 months. After the initial procedures, secondary procedures were performed in three patients due to complications. Ankle arthrodesis was done in one patient with ipsilateral common peroneal nerve injury. Stress fracture occurred in one patient 6 months after removal of the Ilizarov frame. This patient was managed with above knee plaster casting for 3 months, leading to full union. Bone and functional results of patients were given grades of “excellent, good, fair, or poor,” according to a grading system described by Paley et al.26 “Excellent” results were achieved in five patients, “good” in eight, “fair” in one. Complications reported in this study were pin tract infections in four patients, superficial wound infections in two, stiffness of the ankle in one, and premature closure of the distal tibial epiphysis due to the original trauma in one.25

Eralp et al. described a retrospective case series of thirteen patients who were treated for infected juxta-articular nonunion around the ankle joint, with a mean bone loss of 4.8 cm.3 These patients were all treated with Ilizarov external fixation, with eight patients treated with joint preserving procedures, and five treated with arthrodesis. Mean age of the patients was 50 years, and mean number of previous operations was 1.77. Mean duration of follow-up was 36 months. Mean external fixation time was 198 days, and mean external fixation index (days with frame divided by shortening in cm) was 29 days/cm. The authors utilized the Paley’s
bone healing criteria to determine objective clinical outcomes.\textsuperscript{27} According to Paley’s bone healing criteria, there were ten excellent, two good, and one poor result(s). Additionally, according to the criteria, there were five excellent, six good, and two fair results. The authors utilized the AOFAS ankle-hindfoot scoring system to determine subjective clinical outcomes.\textsuperscript{22} The mean AOFAS score was 68.8, and, according to the authors, there was no statistically significant difference in mean AOFAS scores between patients with arthrodesis (70.8) and patients with joint preservation procedures (72). However, no p values were given by the author to verify this claim. There were eleven complications that had to be resolved in an outpatient clinic setting including seven Paley grade 2 pin tract infections, three cases of ankle joint stiffness, and one case of knee joint stiffness, as well as five complications that required additional operative intervention for resolution -- two Paley grade 3 pin tract infections, three equinus deformities, and one sequela according to Paley’s classification of complications.\textsuperscript{26,27} The sequela was one persisting nonunion, which underwent a failed revision using a Taylor Spatial Frame. This was then further revised and ultimately treated with a retrograde intramedullary nail.\textsuperscript{3}

Osman et al. described a retrospective case series of thirty patients who underwent surgical repair for complex tibial pilon fractures as a result of high-energy trauma, all between 1999 and 2012.\textsuperscript{28} All thirty patients were managed using Ilizarov external fixation. Within the study, twenty-six patients were male, four were female. The mean age of the patients was 47 years. The mean time spent in the Ilizarov frame was 22 weeks. The mean follow-up interval was 48 months. Patient satisfaction outcomes were evaluated according to the subjective AOFAS ankle-hindfoot scoring system.\textsuperscript{22} According to the AOFAS system, sixteen patients recorded an “excellent” score, six recorded a “good” score, and two recorded a “poor” score. Eighteen patients reported that they were “satisfied” with the surgery, however the authors did not define a criteria for patient satisfaction. Full union was obtained in a mean of 3 months. Twenty patients were able to return to their pre-injury professions. The final alignment was neutral +/- 5 degrees on the frontal plane for twenty-seven cases. One case had a 20 degree valgus malalignment, and was eventually treated with ankle fusion. One case showed a 5 degree valgus deformity and was treated with a short leg cast for 30 days, leading to a “good” final clinical result. On the sagittal plane, twenty-six cases showed neutral +/- 5 degrees. In post operative follow-ups, radiological evidence of arthritis was noted in eleven of the patients, and in one patient, arthrodesis was required. Two patients with a Ruedi-Allgower type III fracture experienced delayed union, and were treated with corticotomy and dynamization of the Ilizarov frame.\textsuperscript{10,28} Another type III case showed secondary displacement after 2 months, and was treated by adjusting two wires. Ten cases showed pin tract infections,
and those were treated with antibiotics and local antiseptic. No cases demonstrated nerve injury due to introduction of pins. Malunion occurred in four patients.28

**DISCUSSION**

In this review of the literature, it was noted that one-hundred sixty-seven patients across nine studies were treated using the Ilizarov technique for distal tibial fractures. Eighteen of these cases were revisional procedures. These studies utilized different metrics to measure clinical and functional outcomes. As seen in Table 1, in all but one study the majority of patients were judged to have favorable structural and functional outcomes, both objectively and subjectively. When this is considered, it becomes clear that the Ilizarov technique is a viable and effective method with which to treat distal tibial fractures.

When measuring functional outcomes, there were various subjective and objective scoring systems utilized. Four studies utilized the AOFAS hindfoot-ankle scoring system, which is considered an objective measure. Other scoring systems including, AAOS, SMFA, Burwell and Charnley, Mazur, and Paley were utilized with little consensus and consistency. Thus, it became difficult to compare these other systems to the AOFAS scoring system.13,18,19,22,23,26,27

The most common complication seen using the Ilizarov technique was pin tract infections. The majority of pin tract infections were treated with basic antibiotic regimens, and management of these infections were often treated according to a standard protocol.27 Few of these progressed to tissue infection. When looking at the outcome data from all of the studies in this review, the complication rate when including these pin tract infections was 59.88%, however, this rate decreases to 23.95% once pin tract infections are managed with an appropriate antibiotic regimen. Other complications of major concern were nonunion, delayed union, and malunion. As seen in three cases of nonunion in Crawford et al., below knee amputations were performed to correct the deformity.15 According to the investigators, this was chosen because patient comorbidities prevented successful union, and they did not wish to subject the patient to additional future revisional surgeries.15 Patients experiencing delayed union as seen in Danoff et al. and El-Mowafi et al. were treated via the Ilizarov technique for an extended period of time.2,16 Proper patient education and selection should be emphasized in order to prevent issues of non-compliance; such as untimely weight-bearing, smoking, and disregard for the condition of the frame components. Another complication to note was residual deformities due to malalignment. Of the cases reviewed, there were six of such deformities. Some were addressed with secondary procedures, which included osteotomies, bone grafts, revisional Ilizarov procedures, and joint destructive procedures.3,15,16,21,25 A chronic
complication of Ilizarov patients is ankle arthritis and arthrosis, as seen in Danoff et al. and Osman et al. There is a risk of these complications occurring in any osseous surgical procedure, and more research is necessary to see if there is a true correlation between ankle arthritis and the usage of the Ilizarov technique. Another consideration of the usage of Ilizarov external fixators is the effect on patient lifestyle and patient post-operative compliance. In the literature reviewed, the mean length of time that patients are in the external fixator is 138 days. A clinician looking to utilize this technique should consider the psychosocial toll incurred on the patient. According to Patterson, in a study involving adolescent patients treated with external fixation devices revealed that children treated with them required “significant psychosocial support.” According to the data gathered in this review, patients seen required a mean length of 33.4 months of post-operative evaluation with their respective surgeon, ranging from 18 to 57.3 months. The clinician must also consider whether the patient’s occupation would allow for them to accommodate this extended treatment period.

A further consideration discussed in Crawford, et. al. is the reduced cost of limb salvage via Ilizarov technique versus amputations in patients with multiple comorbidities. A patient undergoing amputation can expect to pay $10,000 more in healthcare costs in the first two years post-operatively, and up to three times as much in healthcare costs over their lifetime. This figure includes considerations for complications, prosthetic devices, and assistive devices. Crawford et. al. concluded that smoking tobacco showed a strong correlation with wound infections (Pearson r = 0.63), and that infected wounds lead toward a definitive procedure such as an amputation.

A major limitation of the articles reviewed were the investigators’ use and interpretation of various outcome scoring systems. As seen in Table 1, the nine articles in this literature review used a total of five different scoring systems to grade patient satisfaction and functional outcomes. In addition, a “good” AOFAS score and a “bad” AOFAS score were defined differently by the respective investigators. This inconsistency in interpretation made it difficult at times to compare outcomes between articles.

Another limitation is that there is no consistent application in the usage of the Ilizarov technique. This is seen in the variety of cases including tibiocalcaneal fusion, reduction of open Pilon fractures, revision of infected nonunions in the distal tibia, reduction of extra-articular distal tibial fractures, hypertrophic distal tibial nonunion, and post-traumatic bone defects of the tibia using vascularized fibular grafts.
Lastly, another limitation of this literature review is that it does not consider other methods of external fixation outside of the Ilizarov technique. This includes Taylor Spatial Frames, which were utilized in Schoenleber, et. al.\textsuperscript{21} The data pertaining to the usage of Taylor Spatial Frames was not included in analysis of this review, as outlined in the previously stated exclusion criteria. This data also did not factor into this review’s conclusion about the efficacy of the Ilizarov technique.

**CONCLUSION**

High-energy fractures of the distal tibia resulting from high impact axial load and/or shear mechanisms can be challenging to treat in all patient populations. ORIF has been the standard of care for high impact distal tibial fractures for years, however such methods often require extensive soft tissue dissection, and greater devascularization of the bone fragments which leads to lead to higher rates of complications and need for secondary surgery.\textsuperscript{6} In addition to serving as a structural support for bone, the Ilizarov frame allows deformity correction by means of distraction osteogenesis. In comparison to ORIF, the Ilizarov technique is less invasive, with minimal soft-tissue exposure and blood loss. If needed, the fixator also allows for adjustment of the alignment and for compression/distraction both during and after surgery. An additional advantage is that the fixation is stable enough to allow early weight-bearing, which leads to earlier soft tissue rehabilitation.\textsuperscript{8}

A multitude of cases within current literature demonstrates the *combined therapy* of high impact distal tibial fractures with an intramedullary device in addition to an external fixator.\textsuperscript{3} This technique has many advantages, including maintenance of alignment during segment transport, and a reduction in complications, such as refracture and plastic deformation.

Currently, research is limited regarding the use of Ilizarov fixation as a potentially therapeutic approach for distal tibial fractures. However from the literature presented, it can be concluded that Ilizarov fixation adjunct to internal fixation may be a viable alternative as the therapy for such fractures. This conclusion was reached after noting the following: (1) the majority of complications seen consisted of manageable superficial pin tract infections; (2) there is reduced rates of serious complications such as deep tissue infections, malunion, and nonunion; and lastly (3) there is the added benefit of earlier bony and soft tissue rehabilitation versus ORIF alone.

**AUTHORS’ CONTRIBUTIONS**

All four authors contributed to producing this systematic review of the literature. All authors participated equally in the conception of the research topic, extraction of the data,
and drafting of the final manuscript. All authors agreed upon the final submission.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

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The Efficacy of Phototherapy in the Treatment of Diabetic Foot Ulcer: A Literature Review

Kwame Doh, Laurel Yee, Stephanie Solanki

Abstract

Introduction: Foot ulcers are common complications of diabetes. The incidence of developing foot ulcers for a diabetic patient is 25%. Poor management of foot ulcers is a high-risk factor for Lower Extremities Amputations (LEA). The Center for Disease Control (CDC) has reported that more than 60% of non-traumatic LEAs occur in Americans with diabetes. The primary treatments for Diabetics Foot Ulcers (DFU) is mechanical wound debridement and standard dressing. The purpose of this article is to investigate the efficacy of phototherapy in the treatment of DFU.

Study Design: Qualitative Systematic Review of Literature

Methods: A literature search was conducted in the PubMed database using the query ("Foot ulcer"[MeSH] AND "Phototherapy"[MeSH] AND "Diabetes mellitus"[MeSH]). Inclusion criteria were clinical trials, randomized controlled trials, full text, publication date between 2007/01/01 and 2017/12/31, humans, and English. Exclusion criteria were non-direct phototherapy treatment, non-ulcerous pathologies, and reviews.

Results: The search yielded a total of 12 results, 6 of which met all criteria and were selected for review.

Conclusion: The findings of the literature review suggest that phototherapy can be an effective treatment option for diabetic patients with foot ulcers when used as an adjunct therapy.

Keywords:
Diabetic foot ulcers, phototherapy, Type II diabetes

Level of Evidence: 4
INTRODUCTION

Diabetes Mellitus (DM) is a common chronic disease resulting from the defective secretion or function of insulin that impacts millions of people worldwide. According to the 2017 National Diabetes Statistic Report (NDSR) an estimated 30.3 million people, 9.4% of the U.S. population, were living with DM in 2015.

Diabetic Foot Ulcers (DFU) are a common but problematic complication of both Type I and Type II DM. Patients diagnosed with DM have up to a 25% risk of developing a DFU. Peripheral neuropathy, peripheral artery disease, infection, and trauma can contribute to the development of a DFU. Peripheral neuropathy is a condition in which nerves are damaged, and it can be caused by DM, hereditary disorders, inflammatory infections, and autoimmune disorders amongst other things. High blood sugar levels observed in diabetic patients can negatively affect their peripheral nerves, thus causing peripheral neuropathy. Symptoms of diabetic peripheral neuropathy manifest as tingling, burning, and loss of protective sensations to pain and temperature in the extremities. For a patient suffering from peripheral neuropathy, these symptoms can allow a minor traumatic injury to progress to a DFU. Patients who have peripheral vascular disease, which is also a complication of DM, can also develop ulcers because their traumatic injuries become ischemic and do not heal. Angiogenic properties and growth factors are decreased in DFUs, so they can be difficult to treat and heal.

Poor or inadequate management of DFUs is a high-risk factor for Lower Extremities Amputations (LEA), as it is reported that 50-70% of all LEAs are due to DFUs. The CDC has reported that more than 60% of non-traumatic LEAs occur in Americans with DM, and the NDSR reported that a total of 108,000 hospitalizations in 2014 were due to LEA alone. According to the NDSR, the total direct and indirect estimated cost of diagnosed DM in the United States in 2012 was $245 billion. A more efficient and effective treatment would decrease the burden put on the healthcare system each year. Aside from the increased cost put on both the healthcare system and the patient, in the majority of patients with DFUs, the ulcer will worsen as DM is exacerbated over the years. Multiple complications like cardiovascular disease, kidney problems, and osteomyelitis are likely to arise in addition to LEAs. In short, a more efficient and effective treatment for DFU will reduce the number of resources spent on extended hospitalizations, rehabilitation, home care, and will also improve the quality of life of the affected patients.

The standard podiatric treatment of DFUs is dependent upon the DFU’s location and severity. First, the DFU is cleaned and debrided. This is done using either saline or an enzymatic wound debridement treatment.
The mechanical debridement method entails using a surgical blade and handle. The wound must then be dressed and managed to prevent further complications, such as an infection. Rest and offloading is recommended to the patient, and this is achieved by bed rest, orthotics, and footwear alterations. Patients are commonly treated with Total Contact Casts (TCC). TCCs allow for healing of DFUs by distributing weight over the plantar aspect of the foot. Pressure is relieved from the area of the foot where the ulcer is located, and thus the patient can remain ambulatory using this treatment. If an infection is present then oral, topical or intravenous antibiotics are administered as needed. The standard treatment of DFUs is without the use of phototherapy; this paper investigates how adding phototherapy as an adjuvant therapy to standard care impacts DFU treatment results.

One of the most common ways to generally classify ulcers is the Meggitt-Wagner system. This system, along with the University of Texas diabetic wound classification, has been found to be the best prognostic system of grading, or scaling, a DFU’s ability to progress to an LEA. Studies in this review often included patients presenting with DFUs of one specific grade in Meggit Wagner system. Its grading scale is shown in the table below.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Pre-ulcerative lesion</td>
</tr>
<tr>
<td>1</td>
<td>Superficial wound not penetrating dermis</td>
</tr>
<tr>
<td>2</td>
<td>Full thickness wound extending to tendon or joint capsule but without bone involvement or osteomyelitis</td>
</tr>
<tr>
<td>3</td>
<td>Full thickness wound involving bone</td>
</tr>
<tr>
<td>4</td>
<td>Localized gangrene</td>
</tr>
<tr>
<td>5</td>
<td>Gangrene of entire foot</td>
</tr>
</tbody>
</table>

Table 1. Meggitt Wagner ulcer grading system.

Phototherapy as a treatment method has been reported to increase epithelialization, increase granulation, decrease inflammation, enhance muscle repair, and increase collagen production. It involves using a device that emits light, usually a red He-Ne laser of a short wavelength, which is composed of photons that are received by photoreceptors in the body. The light then affects cytokines to reduce edema, leukocyte influx, and oxidative stress, effectively reducing inflammation. It has also been shown to relieve pain in patients. Phototherapy has been described as a therapy that decreases healing time for ulcers with minimal to no side effects. This paper aims to discuss the effectiveness of phototherapy on treating and healing DFUs.

Low Light Laser Therapy (LLLT) is a low irradiation intensity type of phototherapy.
treatment used for ulcers because its efficacy and low cost. LLLT has been known to promote tissue healing by modulating the activity of Cytochrome C oxidase in mitochondria. In the presence of tissue damage such as ulcers, Nitric Oxide (NO) competes with Oxygen (O₂) binding sites on Cytochrome C Oxidase, thus inhibiting tissue repair. LLLT reverses NO inhibition of Cytochrome C Oxidase resulting in an increase in ATP production and the promotion of tissue healing at the transcription level in biological cells. Additionally, LLLT has been reported to increase skin microcirculation in patients with diabetic microangiopathy, promoting healing. However, the usage of LLLT for the treatment of DFUs has not been greatly studied as of yet.

Patients who receive phototherapy treatment often are also given the Visual Analog Scale (VAS) to assess their level of pain due to the DFU to compare the effectiveness of any given treatment before and after the treatment is conducted. One type of VAS consists of a straight line with one endpoint being “no pain at all” and the other endpoint being “pain as bad as it can be.” Patients are asked to place a mark on the line where they would rate their pain, and the researcher can quantify the patient’s pain by measuring the distance between the endpoint of “no pain at all” and the place where the patient has placed their mark. The second type also has both extremes anchoring the endpoints of the line, but patients are instead asked to rate their pain intensity by choosing a number between zero and ten, with ten being the highest pain level. A lower pain level reported after phototherapy will be considered evidence that phototherapy is an effective treatment for DFUs.

**METHODS**

A literature search was conducted in the PubMed database using the query ("Foot ulcer"[MeSH] AND "Phototherapy"[MeSH] AND "Diabetes mellitus"[MeSH]). Inclusion criteria consisted of clinical trials, randomized controlled trials, full text, publication date between 2007/01/01 and 2017/12/31, humans, and English. Query and inclusion criteria yielded a result of 12 articles. After a survey of abstracts, articles were excluded under the criteria of non-direct phototherapy treatment, non-ulcerous pathologies and reviews. After application of exclusion criteria, 6 articles were retained.

![Figure 1. PubMed acquisition of papers based on inclusion and exclusion criteria](image-url)
## RESULTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Experiment parameter</th>
<th>Laser</th>
<th>Pre-Treatment Measurements and Assessments</th>
<th>Post-Treatment Measurements and Assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feitosa et al.</td>
<td>16 Type II diabetics with ulcers randomized into 2 groups. Group 1 was given only sodium chloride washout while Group 2 was treated with both sodium chloride and LLLT</td>
<td>λ632.8 nm Application time: 80 seconds</td>
<td>Ulcer Area (cm²) Group 1: 2.55 ± 0.77 cm²</td>
<td>Ulcer Area (cm²) Group 1: 8.43 ± 1.84 cm²</td>
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<tr>
<td></td>
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<td></td>
<td>Group 2: 7.98 ± 2.06 cm²</td>
<td>Group 2: 2.39 ± 1.26 cm²</td>
</tr>
<tr>
<td>Carvalho et al.</td>
<td>32 type II DM patients randomized into four groups: control, LLLT, Fatty Acid (FA) treatment, and LLLT with fatty acid treatment</td>
<td>λ658 nm Application time: 80 seconds, 4 J/cm² LLLT: 7.98±2.06</td>
<td>Ulcer Area (cm²) Control: 2.55±0.77</td>
<td>Ulcer Area (cm²) Control: 8.43±1.84 cm²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LLLT: 7.98±2.06</td>
<td>LLLT: 2.39±1.26 cm²</td>
</tr>
<tr>
<td>Mathur et al.</td>
<td>30 type II DM patients randomized into two groups of 15. Control group: wound dressings and offloading. Experimental group: wound dressing and LLLT</td>
<td>λ660 nm Application time: 60 seconds, 3 J/cm²</td>
<td>Ulcer Area (mm²) Control: 1352</td>
<td>Ulcer Area (mm²) Control: 1146</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LLLT: 1484</td>
<td>LLLT: 930</td>
</tr>
<tr>
<td>Nteleki et al.</td>
<td>Device: three 630nm light-emitting diodes, and eight 850nm LEDs.</td>
<td>Pre-treatment ulcer sizes were not provided in this report</td>
<td>Complete healing rates:</td>
<td></td>
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<td></td>
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<tr>
<td>7 type II DM patients Group 1: standard podiatric care and placebo phototherapy Group 2: standard podiatric care with phototherapy Group 3: podiatric care with phototherapy on the ulcers as well as on regional lymph nodes.</td>
<td>Application time: 51 seconds, 3 J/cm²</td>
<td>Control: 10%</td>
<td>LLT: 67%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kaviani et al.</th>
<th>-Randomized double-blind control trial. -LLLT and Conventional therapy: 13 patients. -Placebo (Conventional therapy alone): 10 patients.</th>
<th>Both groups exposed to illumination 6 times/week for 2 weeks then every other day.</th>
<th>Reduction in ulcer size:</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Device: (BTL, 685 nm, 50 mW) -Duration: 200 sec -Fluence: 10J/cm²</td>
<td>Grade 1 &amp; 2 foot ulcers according to Wagner classification. Ulcer size per group *LLLT group: 10.7 ± 25.7 cm². *Placebo group: 7.8 ± 11 cm². (p = 0.799). No significant difference despite the greater ulcer sizes in the LLLT group.</td>
<td>LLLT: (73.7 ± 10.2%) Control: (47.3 ± 15.4%) (p = 0.03 &lt; 0.05)</td>
<td></td>
</tr>
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</table>
Carvalho et al. enrolled 32 type II diabetic patients of both genders in their randomized, controlled, prospective, interventional clinical case study conducted in Brazil by Brazilian physicians. Patients’ eligibility criteria included: 40-70 years of age, fasting blood glucose levels between 150-350 mg/dL, presenting with a lower extremity ulcer, and were being treated at the clinic where this study was conducted. The patients were randomized into four groups: control, Low Level Laser Therapy (LLLT), essential fatty acid treatment, and LLLT with essential fatty acid treatment. Essential fatty acid treatment entails using oil from the marigold plant, and has been recommended by the Brazilian government as a treatment for wounds and skin ulcers. This study tested the efficacy of this common treatment. The patient’s foot ulcers were measured, and the data was entered into Image J, a software program to calculate the total area of injury. The ulcers were measured before and after the

| Landau et al. | Placebo controlled double blind randomized study. Treatment group: 10 patients. Control group: 6 patients. | -Vireo broadband light device. -Treatment group: 180 mW/cm² broadband (400-800 nm) visible light. -Placebo group: 10 mW/cm² (non-therapeutic). | Grade 1 & 2 foot ulcers according to Wagner classification. Average Baseline ulcer area per patient: *Treatment group*: 1.08 cm². *Placebo group*: 0.45 cm². Average area of remaining open ulcers post intervention: *Treatment group*: 0.12 cm² *Placebo group*: 0.21 cm². Reduction in wound size: *Treatment group*: 89% *Placebo group*: 54% Percentage of wound closure per group: Treatment group 90% vs. Control 33% (P=0.0357) |

Table 2: summary of the experiments results
30-day treatment program, and the values were entered into Microsoft Excel. These values were analyzed for significance using a One-Way ANOVA and a Post hoc Tukey test, with the significance set at \( p < 0.05 \). Patients were also given the Brief Pain Inventory Questionnaire and the Visual Analogue Scale (VAS) to assess their intensities of pain. Patients in the LLLT group were subjected to the following protocol: 658 nm, 30 mW power, 80s application time (4 J/cm²), continuous wave, visible beam, on an area equivalent to 12.566 mm² (Laser - HTM manufacturer). The results showed the LLLT, isolated or applied with fatty acid oil, has an analgesic effect as the patients reported a significant reduction in pain via the VAS. The control group’s pain assessment measurement value was 9.00±0.32 before the treatment, and 9.40±0.40 after the treatment, and the size of their ulcers were measured to be 2.55±0.77 and 8.43±1.84 cm² before and after the treatment, respectively. The LLLT group’s pain assessment values were 9.00±0.32 and 4.80±0.20 before and after the treatment, respectively, and the sizes of their ulcers were 7.98±2.06 before treatment and 2.39±1.26 cm² after treatment. The group that received essential fatty acid oil treatment reported pain levels of 9.00±0.32 and 8.80±0.37, and their ulcers’ sizes were 4.95±1.74 and 3.30±1.31 cm² before and after the treatment, respectively. The group that received essential fatty acid oil treatment and LLLT reported pain levels of 9.20±0.20 and 5.00±0.32, and the sizes of their ulcers were 9.27±0.87 and 2.57±2.51 cm² before and after the treatment, respectively. The two LLLT groups showed significance after statistical analysis, with the LLLT treatment group showing significance of \( p = 0.0428 \), and the LLLT and essential fatty acid treatment group showing significance of \( p = 0.0032 \). This study shows that LLLT can result in a statistically significant reduction of the size of DFU.

In Mathur et al., 30 type II diabetic patients were randomized into two groups of 15. Patients who had Meggitt-Wagner grade 1 DFU for at least 6 weeks were included in the study. All patients received daily wound debridement using saline and antibiotics as needed. Patients in the treatment group received LLLT daily for 15 days. Patients in the control group were given betadine and saline solutions for their ulcers. Photographs were taken on the first day, Day 7, and Day 15, and uploaded onto a computer software to calculate the ulcer area. Significance was determined using the Student's t-test, a one-way ANOVA, and a Fischer’s LSD test, with the significance level set at \( p < 0.05 \). Before treatment, the average DFU sizes were 1352 and 1484 mm² in the control and LLLT groups, respectively. After fifteen days of treatment, the DFU sizes were 1146mm² in the control group and 930mm² in the LLLT group. Statistical analysis reported a reduction in the area of the DFU after the LLLT treatment (\( p = 0.09 \)). The patients who received LLLT had a reduced percentage wound area, 37.3 ± 9% as compared to 15 ±
Nteleki et al. conducted a study in which 7 patients were randomized into three groups. These patients had presented with DFUs for four weeks on their feet. Group 1 received standard podiatric care of ulcers involving saline debridement, or mechanical or enzymatic debridement if needed, dressing of the wound, offloading achieved by bedrest, orthotics, aircast boots, and other devices, and antibiotic therapy. Because this was a single blind study, patients received placebo phototherapy and were given safety goggles that blocked out visible light. The patients were unaware of receiving phototherapy or not. Group 2 received standard podiatric care and LLLT on their ulcer via a 1200mW cluster probe with three 630nm LED and visible light emitting diodes, and eight 850nm LED diodes. The treatment lasted 51 seconds each time, and delivered 3 J/cm$^2$ per spot on the DFU. The number of treatment spots depended on the size of the ulcer. Group 3 received standard podiatric care, LLLT on their ulcer, and LLLT on lymph nodes within the region of the ulcer to increase drainage. Patients were treated for a maximum of 90 days and received treatment twice a week. 10% of ulcers in patients who had received placebo phototherapy and standard podiatric care were healed, whereas 67% of ulcers in patients who had received phototherapy had healed. 40% of ulcers that were treated with phototherapy had resolved completely. Statistical analysis was not used for this pilot study. For patients in the control group, their DFUs had regressed by percentages of 10% and 18%. Regarding the patients who received LLLT on their DFUs, they experienced DFU regression percentages of 38%, 100%, and 26%. Patients who received LLLT on their DFUs and regional lymph nodes saw their DFUs regress by 100% and 45%. The DFU regression percentages are much higher for patients who received phototherapy as opposed to patients who did not. The article claims significance for the effectiveness of phototherapy as a treatment method for DFU.

Feitosa et al. conducted an experiment in which 16 non-controlled type II diabetic patients with ulcers in their foot were randomized into two groups. Group 1 received the standard care of sodium chloride (saline solution .9%) for daily asepsis of their ulcers for a total of 30 days (4 weeks). Group 2 received the standard care as well as low-level laser therapy (LLLT) for a total of 12 procedures; three per week, every alternating day for four weeks. The low-level laser utilized was a pulsed waveform with a wavelength of 632.8 nm and a peak potency of 30mW. The application time was 80 sec for each procedure without contact (1mm distance). Each patient was monitored for 30 days. Image J software was used to measure the total area of ulcers in square cm (cm$^2$). Each patient was photographed on the first
and last appointments. Pain was measured with a visual analogical scale from 0-10 (0 being the weakest and 10 being the strongest) both prior and after the experiment. The patients who had received LLLT had significant improvement in the size of their wound as well as increased tissue repair. The size of the ulcers was 7.98 ± 2.06 cm² prior to the LLLT, and 2.39 ± 1.26 cm² after. Pain level also decreased from 9.00 ± .32 before to 4.80 ± 0.20 after LLLT treatment. The results were statistically significant with p< 0.05. The patients in the control group had an increase in the size of the wound and one patient had to have a transfemoral amputation. The size of the ulcers prior and post to the experiment in the control group were 2.55 ± 0.77 cm² and 8.43 ± 1.84 cm² respectively. Additionally, the pain level for the control group was nearly constant with 9.0 ± 0.32 prior and 9.40 ± 0.40 post experiment. The results were statistically significant with p = 0.01. This study shows that LLLT seems to be an effective method in the treatment of diabetic foot ulcers as well as the management of their pain.

Another study conducted by Landau et al. investigated the treatment of diabetic foot ulcers and venous ulcers using the vireo device, which is a visible broadband light source. All patients had a DFU except two patients who had venous ulcers in the treatment group. Ulcers were classified as Stage 1 and Stage 2 according to Meggitt-Wagner classification. Despite the focus of the intervention on the treatment of diabetic foot ulcers, two venous ulcer patients were included in this study because the healing process of both types of wound is dependent on oxygen supply. In other words, the rationale behind the treatment applies to both types of ulcers because the wound healing changes induced by light involve Reactive Oxygen Species (ROS) . In a randomized placebo-control double-blind study design, six study subjects were assigned to a control group receiving non-healing light fluency (10 mW/cm²) projections and ten patients were assigned to a treatment group which received 180 mW/cm² broadband light twice a day (4 min/session) for 12 weeks. The broadband light was used because preliminary studies by the same group have shown that the blue component of visible light plays an important role in Nitric Oxide (NO) formation, which is normally inhibited in ulcers. The vascularity of all diabetic feet were evaluated by Doppler, followed by the application of wound dressing to ulcers in both groups, then the vireo device was provided to each patient for home use. Patients also received wound care once a week at the Kaplan medical center over the course of the study. An assessment of wound closure after a 12 week follow-up period showed a significant reduction in wound size in the treatment group compared to the control group. Wound closure was observed in 90% of the patients that received the broadband light treatment while only 33% of patients enrolled in the control group displayed closed wounds (p=0.0357). Additionally, patients were also evaluated one
month after recovery to assess a lack of recurrence. A reduction in wound size was observed in the treatment group (89%) compared to the control group (54%).

In a preliminary report of their RCT, Kaviani et al. report on the effect of LLLT on the treatment of DFU. 23 patients with stage 1 and 2 ulcers according to the Meggitt-Wagner classification were enrolled in the study and were randomly assigned to two groups as follows. 13 patients were assigned to a LLLT (685 nm, energy density 10 J/cm(2)) treatment group (LLLT and conventional therapy) and ten patients to a placebo group (conventional therapy and sham irradiation). In other words, LLLT was applied as a complementary therapy in the treatment group for a period of 20 weeks. Ulcers in both patient groups were illuminated six times per week for two consecutive weeks followed by irradiation every other day up to complete healing. Each illumination lasted 200 seconds with the laser device at a distance of 1 cm from the skin surface. As mentioned earlier, only the treatment group truly received treatment. Reduction of ulcers size was observed in the LLLT group (47.5±9%) as early as two weeks, but compared to the control group (29.4±7.6%) it was not statistically significant (p=0.125). Four weeks after the beginning of treatment, patients in the LLLT group (73.7±10.2%) exhibited a significant reduction in the size of ulcers (p = 0.03) compared to the control group (47.3±15.4%) relative to baseline measurements. Ulcer sizes were measured using AutoCAD 2000 (a digital imaging and tracing software) and reported in cm². Additionally, 8 of 13 subjects in the treatment group had complete wound healing as opposed to 3 of 10 patients in the control group at week 20. Overall, there was no statistically significant difference in wound healing in both groups at week 20 relative to baseline measurements (P=0.470), even though the mean time for complete healing time was lower in the LLLT group. Last, two patients from the placebo group were amputated due to extreme gangrene.

**DISCUSSION**

Out of the studies retained for this review, only the Landau et al. study involved the use of phototherapy as a self-administered treatment modality for DFU. Even though the experimental design was a randomized and double-blind placebo experiment, researchers had limited control over parameters such as patients’ compliance. This study showed the effectiveness of using a visible light source to treat foot ulcers at the intensity of 180 mW/cm² after 12 weeks because of the statistically significant rate of wound closure observed in the treatment group compared to the control group (p=0.0357). This small-scale experimental design is not strong enough to generalize the finding of this study. However, these results indicate the potential of broadband light therapy, especially the blue wavelength as an adverse effect-free treatment for DFU. Additionally, this study
shows the simplicity of phototherapy by having patients self-administer the radiations.

Most studies used phototherapy as a complementary modality to standard podiatric care. Carvalho et al. investigated the potential role of phototherapy in the reduction of wound size. Treatment of DFU using LLLT as compared to the control group yielded a p-value of 0.0428, which is statistically significant. In addition, a stronger p-value of 0.0032 was observed when LLLT is applied along with fatty acids treatment. These results clearly demonstrate the effectiveness of LLLT alone, and as an adjunct to essential fatty acids oil treatment in reducing the size of a DFU.

Similarly, Mathur et al. studied LLLT as an complementary therapy to standard podiatric care and antibiotics in patients with superficial foot ulcers as defined by the Meggitt-Wagner scale. This study used a slightly higher wavelength (660 nm) for a shorter period (60 sec) compared to the Carvalho et al. study which used 658 nm for 80 seconds. Interestingly, a statistically significant reduction in wound size (p<0.001) was observed in the LLLT patients after 15 days, which is half the time it took Carvalho et al. to obtain significant results compared to the baseline measurements. These results must be reproduced in a larger randomized controlled trial to confirm the observed outcomes. DFU measurements were not provided in this report, and it was difficult to assess the raw data by looking at the graphs. Additionally, statistical significance was not calculated. However, based on the raw data of the reduced wound size and the patients’ self-report that they were experiencing less pain, one can conclude that phototherapy was an effective treatment for DFU. A further investigation should be made to assess the significance of these results.

Feitosa et al. also showed the effectiveness of LLLT as a complementary modality to standard daily asepsis of ulcers. A significant reduction in wound size, as well as pain level, was observed in LLLT treated patients compared to the control group which only received standard care of sodium
chloride (P<0.05). Unlike the other studies, LLLT was administered every other day for four weeks as opposed to every day. These results indicate that a discontinuous use of LLLT as an adjunct treatment to foot ulcer can also be effective. However, additional studies involving a larger patient sample are necessary to generalize these findings. In their discussion, Feitosa et al. also mentioned several other experiments regarding the effect of LLLT on animals such as rats. Those studies correlate with their results that the utilization of light therapy will reduce the time for wound healing by promoting tissue repair, revascularization, and fibroblast proliferation.

In their preliminary RCT report, Kaviani et al. did not show a statistically significant difference in the rate of wound closure or healing between the LLLT and control groups after a long-term treatment (20 weeks). However, the size of ulcers decreased significantly in the LLLT group compared to the control group at 4 weeks (short-term). The authors mentioned that the satisfying rate of wound closure observed in the placebo group may be the result of effective wound care and metabolic control. This detail is an indication that effective wound care requires a multifactorial approach. Furthermore, no significant side effects and treatment interactions were reported, therefore making LLLT a safe adjunct therapy for DFU. However, the sample size is small (23 patients) and a long-term, large-scale RCT will be needed to validate the results of this study for the general population. While these studies are valid in their respective settings, only two were reported as peer-reviewed randomized controlled trials. These results show the effectiveness of LLLT as an adjunct therapy in addition to conventional treatment.

Feitosa et al. and Kaviani et al. have reported a transfemoral amputation and amputations of two patients due to extended gangrene respectively in their control groups. Interestingly, no amputations were reported in the treatment (phototherapy) groups in all studies. This observation may indicate a potential role of phototherapy in the prevention of lower extremities amputations. Furthermore, no major adverse effects were reported in the treatment groups. However, some minor side effects such as skin irritations or burns caused by therapeutic light devices have been reported. These observations show the potential importance of phototherapy as a key procedure in the future of limb salvage if all these results are confirmed by large scale RCTs.

CONCLUSION

Overall, the results of this literature review suggest that phototherapy, especially LLLT is therapeutically effective for the treatment of diabetic foot ulcers. LLLT has been shown to reduce ulcer sizes in DFU and most studies also report a reduction in the perception of pain. Furthermore, phototherapy may help alleviate side effects
such as pain associated with conventional pharmacological treatments of DFU. More studies are needed to investigate the potential of phototherapy as a primary treatment for DFU.

AUTHORS’ CONTRIBUTIONS

All authors contributed equally to this literature review. All authors agreed upon the final submission of this draft.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

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Mesenchymal Stem Cell Therapy for Treating Diabetic-Induced Maladies of the Foot: A Systematic Review

Rupinder Kaur Boora, MSc and Michael Fox, BA

Abstract

Introduction: Diabetes Mellitus, categorized into types I and II, is a systemic disease that affects multiple organ systems and poses multiple challenges to global health. Type I is characterized by inadequate insulin production, while type II involves insulin resistance. Both types consequently result in increased levels of glucose in the blood. Eventually, a patient can progress to diabetic neuropathy, which is associated with complete or partial lack of sensation in the lower limb and may lead to osseous deformities such as claw and hammertoes. Along with neuropathic conditions, diabetics may concurrently experience a variety of vascular and soft tissue pathologies including peripheral arterial disease and ischemia leading to painful ulceration, and increased susceptibility to infection. The objective of this paper is to conduct a systematic review of the literature to assess the efficacy of the use of mesenchymal stem cells (MSCs) derived from various body tissues in the treatment of diabetic neuropathy and peripheral arterial disease secondary to ischemia. We hypothesize that MSCs are an effective treatment modality in that they may help restore the angiogenic, neuroprotective and immunomodulatory capabilities of nerves and arteries lost in diabetic patients. We further believe that MSC treatment may ameliorate the symptoms experienced in diabetic neuropathy and angiopathy and may be used prior to or in conjunction with current therapeutic options.

Study Design: Qualitative Systematic Review of Literature

Methods: An English language search was conducted using PubMed databases. The search employed MeSH terms and Boolean Operators (AND, OR, & NOT). The search was: Diabetic Neuropathies/Therapy AND Mesenchymal Stromal Cells. This search resulted in 21 articles. The inclusion criterion comprised papers published in English and in the last five years involving Human and rat subjects. Review articles were excluded from further analysis. The application of this inclusion and exclusion criteria yielded five articles for the final analysis in this qualitative systematic review.

Results: Five articles were chosen for review. The study design, sample size, therapeutic potential and conclusion from each paper were summarized.

Conclusion: MSCs derived from different bodily tissues have proven effective in controlling inflammation, preventing apoptosis, enhancing wound healing, reducing ischemia and may serve as a viable alternative treatment for diabetic maladies when used in conjunction with current therapeutic options.

Key Words: Diabetes Mellitus (DM), Diabetic neuropathy (DN), Mesenchymal Stem cells (MSCs), Diabetic peripheral neuropathy (DPN)

Level of Evidence: 4
INTRODUCTION

Diabetes Mellitus is a systemic disease that affects multiple organ systems and can cause a variety of severe health complications. By the year 2030, it is estimated there will be more than 360 million people afflicted with diabetes worldwide. In the year 2012, the treatment of diabetes in the United States cost approximately 20% of the total healthcare expenditure. Type I diabetes, in which the beta cells of the pancreas do not produce enough insulin, and type II diabetes, in which the body cannot utilize the insulin produced, can lead to both neuropathy and angiopathy. Defective pancreatic beta cells in type I as well as unresponsive insulin receptors in type two result in an increase in glucose levels in the blood as insulin’s primary role is the uptake of glucose from the blood to cells of the body where it can be used for energy or stored. Certain individuals may inherit a predisposition to both types of diabetes, while environmental factors such as poor diet and exercise habits trigger its presentation. Diabetes Mellitus is a manageable condition with exogenous insulin, other blood sugar-lowering medications, and changes in lifestyle such as increased exercise and a low sugar diet.

Mechanisms of Diabetic Neuropathy and Subsequent Angiopathy

The excess glucose in diabetes gets converted to sorbitol and fructose which then results in decreased synthesis of myoinositol, a second messenger important for signaling pathways. This results in nerve conduction issues and defects in myelin synthesis. There is also a decrease in nitric oxide production which causes vasoconstriction and further nerve injury. The defective glucose metabolism also causes an increase in the reactive oxygen species (ROS) which leads to nerve fiber degeneration, neuronal apoptosis, decreased blood flow in the lower limbs, and a state of chronic inflammation. In addition to the pro-inflammatory environment with oxidative stress, there is a reduction in the neuroprotective agents and pro-angiogenic factors in the nerves. A combination of all of these factors leads to diabetic neuropathy (DN) and angiopathy—major complications of both types of diabetes.

DN can be divided into sensory, motor and autonomic pathologies. In sensory neuropathy, the patient either fully or partially loses protective sensation in their lower limbs. This may further complicate ulcerations as the patient no longer has system intact to indicate damage or pain in the affected area. Neglected wounds leave a patient increasingly susceptible to infection and may result in necrotic gangrenous tissue and osteomyelitis, often requiring amputation of the entire affected limb. Additionally, hyperglycemia causes glucose to act as a solute by escaping out of the blood into the tissue and pulling fluid along with it. The
edematous action of glucose may cause compress of nerves and consequently result in painful burning and numbing sensations.

Motor neuropathy is due to a lack of motor innervation to muscles of the lower extremity. This can lead to myopathy and muscle tissue breakdown as well as a variety of osseous deformities in the foot due to an imbalance in muscle power between the flexors and extensors. In many of these deformities, there is often a change in the plantar pressure points on the foot which can further lead to pain and ulceration.

Autonomic neuropathy leads to a variety of issues including decreased innervation of sweat and oil glands and dilation of small arteries due to arteriovenous shunting. This combination further contributes to skin breakdown and causes the feet to become dry, keratinized, swollen and painful.

Treatment Modalities for Diabetic Maladies.

The main therapeutic approach for diabetes involves lowering blood glucose levels in the blood with oral medications, insulin injections and hypoglycemic dieting. Additional therapeutic approaches for include oral neuropathy medications such as NSAIDs, proper skin care, compression stockings to reduce edema, surgical intervention for osseous complications and debridement of wounds and percutaneous angioplasty for ischemia. [3]. While these therapies may temporarily offer relief for diabetic neuropathy and ischemia they lack the ability to truly reverse the condition as the angiogenic, neuroprotective and immunomodulatory factors are severely depleted following neuronal and vascular damage due to hyperglycemia. In recent years, mesenchymal stem cells (MSCs) have been of interest for the treatment of DN as they help replenish these factors leading to enhanced wound healing, reduction in ischemia due to improved neurovascular health. In addition to their neuroprotective and pro-angiogenic effects, MSCs are an especially viable option because they can be isolated from different tissues, are expandable in vitro, and can differentiate into neurons.

Objective and Hypothesis

The objective of this paper is to conduct a systematic review of the literature to assess the efficacy of the use of MSCs in the treatment of neuropathy and angiopathy secondary to diabetes. We hypothesize that MSCs are an effective treatment modality in that they may help restore the angiogenic, neuroprotective and immunomodulatory capabilities of nerves and arteries lost in diabetic patients. We further believe that MSC treatment may ameliorate the symptoms experienced in diabetic neuropathy and angiopathy and may be used prior to or in conjunction with current therapeutic options.

METHODS
An English language search was conducted using PubMed databases. The search employed MeSH terms and Boolean Operators (AND, OR, & NOT). The search was: Diabetic Neuropathies/Therapy AND Mesenchymal Stromal Cells. This search resulted in 22 articles. The inclusion criterion comprised papers published in English and in the last five years involving Human and rat subjects. Review articles were excluded from further analysis. The application of this inclusion and exclusion criteria yielded five articles for the final analysis in this qualitative systematic review (Figure 1).

**RESULTS**

Ezquer et al. conducted a study on female patients undergoing liposuction to understand the mechanisms of MSCs to provide alternatives to the standard care for individuals with diabetic neuropathy. The group isolated MSCs from fresh subcutaneous adipose tissue from the abdominal region. They showed that preconditioning adipose tissue-derived MSCs with iron chelator deferoxamine (DFX), instead of using MSCs directly, increased the production of pro-angiogenic, neuroprotective and anti-inflammatory factors. DFX is a hypoxia mimetic agent that has antioxidant properties and is safe and currently used to treat iron overload diseases in humans. Additionally, it has no toxic effects on MSCs in terms of morphology and survival, making it ideal for preconditioning. The purpose of adding DFX to the MSCs was to increase their tolerance to the hypoxic environment in the lower limb of the DN patient. During preconditioning, cells were incubated with the DFX at sub-lethal concentrations. There was an observed increase in the main hypoxia marker HIF-1α when human adipose tissue-derived MSCs were preconditioned with 150µM or 400µM of DFX for 48 hours (Figure 2A). This increased expression of HIF-1α led to the upregulation of the mRNA levels of pro-angiogenic factors like vascular endothelial growth factor alpha and angiopoietin 1 (Figure 2B). There was also an increase in the expression of potent neuroprotective factors such as nerve growth factor, glial cell-derived neurotrophic factor, neurotrophin-3, and cytokines with anti-inflammatory activity like IL4 and IL5. Furthermore, dorsal root ganglion (DRG) neurons were treated with the secretome of DFX preconditioned MSCs (i.e. the previously mentioned molecules secreted by the conditioned MSCs) and then subjected to
hyperglycemic levels of glucose to mimic diabetic conditions. DRG neurons that had not been treated with the secretome experienced a significant rate of apoptosis while those that had been treated showed a significant decrease in the glucose-induced death as shown with the TUNEL stain. Using DRG neurons as an in vitro model, this group was able to demonstrate the neuroprotective benefits of using the secretomes of DFX preconditioned cells.

Chandramoorthy et al. wanted to determine if umbilical cord blood (UCB) MSCs could improve the survival of human neuronal cells and/or fibroblasts that had been exposed to diabetic peripheral neuropathy (DPN) sera that had been obtained from 50 male patients with a known history of type II diabetes. They cultured human neuronal cells or fibroblasts with DPN sera and saw an increase in inflammatory and apoptotic signals. Following this, they co-cultured UCB MSCs with human neuronal cells and/or fibroblasts that had been treated with DPN sera and saw that cell death was prevented. There was a downregulation in the fibroblast and neuronal cell expression of TNF-alpha, IL-1beta, IFN-gamma and IL-12, which are pro-inflammatory cytokines. Additionally, there was an increase in the expression of anti-inflammatory cytokines such as IL-4, IL-10, and TGF-beta (Figure 3A). There was also a decrease in the expression of pro-apoptotic factors p53 and Bax coupled with an increase in anti-apoptotic factors Bclxl and Bcl2 (Figure 3B). These data correlate with the increased cell survival and proliferation of the human neuronal cells and fibroblasts in the DPN sera treated co-culture. Additionally, DPN sera treated human cells without UCB MSCs showed an increase in intracellular calcium, indicating abnormal calcium homeostasis, and an increase in ROS levels which were both restored in the co-cultures. Based on the fact that MSCs improve cell survival, the group administered MSCs derived from rat bone marrow to diabetic rats through peripheral blood circulation and saw that there was an improvement in the nerve conduction velocities.
H. L. Qin et al. performed a clinical evaluation to determine the perfusion and healing efficacy of transplanted Human Umbilical Cord Mesenchymal Stem Cells (HUMSCs) following percutaneous angioplasty in patients with diabetic foot ulcers and peripheral arterial stenosis and/or occlusion. 53 patients with severe symptoms of type II diabetic mellitus were divided into control and experimental groups. 25 diabetic individuals in the control group received conventional percutaneous angioplasty treatment without HUMSC stem cell infusion while 28 diabetic individuals of the experimental group received HUMSC infusion following treatment with percutaneous angioplasty. Out of all 53 study participants, a total of 116 diseased peripheral arteries were reported (78 stenotic arteries, 38 occluded) and treated with percutaneous angioplasty. Ankle Brachial Index, skin temperature, claudication distance, and transcutaneous oxygen tension were measured 1 month and 3 months following treatment. In comparison to the control group,
experimental group patients saw substantially higher ankle brachial indices, transcutaneous oxygen tensions, skin temperatures, as well as increases in angiogenesis, claudication distances (Figure 4) and ulcer healing (Figure 5). After 1 month following treatment, 87% (68/78) of the stenotic arteries showed decreased stenosis while 68% (26/38) of the occluded arteries showed decreased occlusion. In both groups, perfusion to the foot angiogenesis and collateral vessel diameter were both increased as confirmed by angiographic imaging. Furthermore, angiograms taken 2 months following treatment demonstrated significantly greater arterial perfusion to the foot, collateral vessel diameter and angiogenesis, in comparison to parallel results in the control group. Out of
19 subjects with diabetic ulcers in the experimental group, 15 experienced complete healing three months following treatment while two experienced significant reduction in ulcer size. It should be noted that one subject experienced no healing due to chronic popliteal artery occlusion while another underwent foot amputation due to severe gangrene six weeks following HUMC infusion. However, the study authors stated that HUMC treatment may have reduced the extent of amputation as this subject’s heel was preserved due to increased arterial perfusion\textsuperscript{10}.

Kato et. al studied the healing and therapeutic efficacy of bone-marrow derived mesenchymal stem cells (BM-MSCs) on impaired-healing ulcers in diabetic rats, placing a specific focus on the correlation between BM-MSC’s and human epithelial keratinocyte healing activity. In efforts to determine whether BM-MSC’s could ameliorate this issue and enhance keratinocyte healing and re-epithelialization of the ulcerated wound, the researchers set out to create a novel diabetic foot model that would measure re-epithelialization of complex diabetic ulcers in rodents. After the rats were induced with diabetic hyperglycemia via streptozocin, the researchers creating wounds via punch biopsy on the plantar feet and thighs to compare healing processes of each. Keratinocyte pFAK, MMP, EGF, and IGF-1 and saline were administered to identical wounds to rats in a control group. The results showed that re-epithelialization was enhanced, and impaired healing was resolved on the plantar foot diabetic ulcers, but not on thigh ulcers in the experimental group where increased wound contraction was observed. Conversely, healing was impaired in the plantar ulcers of the control group while thigh ulcers demonstrated increased healing. (Figure 6) Further evaluation of the ulcers indicated that the keratinocytes cultured with BM-MSC effectively reversed the decreased pFAK levels usually seen in hyperglycemic conditions. Moreover, keratinocyte MMP, EGF and IGF1 levels were increased as well, allowing keratinocytes to effectively migrate and promote healing at the ulceration site. This study indicates that diminished keratinocyte activity due to hyperglycemia may be responsible for prolonged, inadequate healing of diabetic wounds and that culturing keratinocytes with BM-MSC may not only enhance keratinocyte activity, but also ameliorate wound healing issues in diabetic humans\textsuperscript{11}.

In a similar study, He, et. al. Investigated the effects of Brain-Derived Neurotrophic Factor (BDNF) on Bone Marrow derived Mesenchymal Stem Cells (BM-MSCs) in treating diabetic ulcers in rats.
As BDNF has proven angiogenic and neuroprotective specifically through its the researchers wanted to know if this would enhance the wound-healing and angiogenic capabilities of MSCs by providing an adequate environment for these stem cells. A control group of diabetic rats was injected with BM-MSCs alone, while the experimental group received a complex of BM-MSCs and BDNF. The results supported the theory that

\[\text{Figure 6- Epithelial healing was accomplished in plantar foot ulcers of the experimental group (A, C) while impaired healing remained in thigh diabetic ulcers of the control group (B,D)\textsuperscript{11}}\]

\[\text{Figure 7- Cell viability of human keratinocytes is diminished when subjected to high glucose medium (C) yet restored when cultured with BM-MSCs (CM)\textsuperscript{11}}\]
transplantation with BM-MSCs is an effective treatment for diabetic wound tissue as those in the control group saw healing and increased angiogenesis. However, researchers noted even greater angiogenesis, faster ulcer healing and smaller wound areas in the experimental group containing the BM-MSC-BDNF complex. The researchers attribute these findings to their observation that BDNF enhances proliferation and migration of MSC’s into the wound site and stimulates their secretion of pro-angiogenic cytokines that activate endothelial cells.

<table>
<thead>
<tr>
<th>Author</th>
<th>Sample size</th>
<th>Type of MSC</th>
<th>Study Aim</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezquer et al.</td>
<td>8 embryos from 2 litters of rats for in vitro study with DRG neurons</td>
<td>Adipose tissue-derived MSCs</td>
<td>To determine if the factors secreted by iron chelator deferoxamine (DFX)-treated MSCs would be sufficient in providing neuroprotective benefits to DRG neurons.</td>
<td>They showed that preconditioning adipose tissue-derived MSCs with DFX, instead of using MSCs directly, increased the production of pro-angiogenic, neuroprotective and anti-inflammatory factors. Using DRG neurons as an in vitro model, this group was able to demonstrate the neuroprotective benefits of using the secretomes of DFX preconditioned cells.</td>
</tr>
<tr>
<td>Chandramoorthy et al.</td>
<td>5 x 10⁶ UCB MSCs from donor umbilical cord blood for the induction to neuronal cells</td>
<td>Umbilical cord blood MSCs</td>
<td>To determine if umbilical cord blood (UCB) MSCs could improve the survival of human neuronal cells that had been exposed to diabetic peripheral neuropathy (DPN) sera.</td>
<td>In comparison to the UCB MSCs alone that had been treat with DPN sera, the co-cultured UCB MSCs with human neuronal cells showed a significant decrease in cell death.</td>
</tr>
<tr>
<td>Qin et. al.</td>
<td>53 (Human) 28 control 25 experimental</td>
<td>Human Umbilical Cord Mesenchymal Stem Cells</td>
<td>The efficacy of transplanted Human Umbilical Cord Mesenchymal Stem Cells (HUMSCs) following percutaneous angioplasty in treating human diabetic peripheral arterial disease and foot ulcers.</td>
<td>In comparison to the control group, experimental group patients saw substantially higher ankle brachial indices, transcutaneous oxygen tensions, skin temperatures, as well as increases in angiogenesis, claudication distances and ulcer healing.</td>
</tr>
<tr>
<td>Kato et. al.</td>
<td>24 (Rodent) 12 control 12 experimental</td>
<td>Rodent Bone Marrow derived Mesenchymal Stem Cells</td>
<td>Effect of bone-marrow derived mesenchymal stem cells (BM-MSCs) on human keratinocyte activity in treating diabetic ulcers in rats.</td>
<td>Keratinocyte MMP, EGFr and IGF1 levels and activity were increased following incubation with BM-MSCs. Wound re-epithelialization was enhanced and impaired healing was resolved on plantar foot diabetic ulcers, but not on thigh ulcers in the experimental group.</td>
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</table>
DISCUSSION

Recently, MSCs have been gaining momentum as a potential therapeutic model for DN. They secrete a number of different beneficial cytokines, chemokines and growth factors that are important for cell survival. Their use is advantageous because they can be isolated from multiple tissues (bone marrow, adipose, umbilical cord, blood, etc.), they have higher biosafety, can be made immediately available since the factors secreted by the MSCs can be stored without the need for cellular expansion everytime, are easier to handle in the lab and have lower production costs. Additionally, the use of a patient’s own cells could avoid tissue rejection as well as ethical issues.

In this study, we analyzed papers that showed the effectiveness of MSCs from different sources in controlling inflammation and preventing apoptosis. Ezquer et al. showed that the pre-conditioning of adipose tissue-derived MSCs with DFX improved the production of pro-angiogenic, neuroprotective and anti-inflammatory factors needed for DRG neuronal survival in DN. DFX has previously been used to treat iron overload diseases and can safely be used at high doses. Most importantly, DFX can be removed from the final product before use for studies, which would translate well for biological therapy. Specifically, the MSCs increased the stabilization of HIF-1α when they were preconditioned with DFX and consequently there was upregulation of pro-angiogenic factors like vascular endothelial growth factor alpha and angiopoietin 1 and an increase in the expression of potent neuroprotective factors such as nerve growth factor, glial cell-derived neurotrophic factor, neurotrophin-3, and cytokines with anti-inflammatory activity like IL4 and IL5. These results show that the MSC preconditioning with DFX increases their antioxidant and protective capacity. This is important because high levels of oxidative stress have been associated with DN as neurons and schwann cells are especially sensitive to ROS. Normally, neuronal cells release survival factors, which are necessary for axonal regeneration. The loss of these
neuroprotective factors in DN patients prevents nerve fiber regeneration leading to further damage. Further studies were done using DRG neurons that were subjected to hyperglycemic levels of glucose to mimic diabetic conditions but were not been treated with the MSC secretome experienced a significant rate of apoptosis while those that had been treated showed a significant decrease in the glucose-induced death. Using DRG neurons as an in vitro model, this group was able to demonstrate the neuroprotective benefits of using the secretomes of DFX preconditioned cells.

Additionally, Chandramoorthy et al. showed the positive effect of UCB MSCs in the modulation of neuronal and fibroblast cell metabolic activity. Overall, this in vitro study was able to show the role of UCB MSCs in the reversal of cell death mechanisms that were induced in neuronal cells and fibroblasts exposed to sera obtained from male subjects with a history of type II diabetes. The increased levels of \([\text{Ca}^{2+}]\) in DPN sera treated cells caused increased mitochondrial uptake of calcium, which induced ROS and led to apoptosis. The co-culture of MSCs with the DPN sera resulted in the restoration of this pathway which improved cell survival. This group showed that UCB MSCs are sufficient in protecting neuronal cells and fibroblasts from inflammation and apoptosis associated with DN. The improved nerve conduction studies in diabetic rats treated with MSCs is also evidence of their rescue potential.

The results of Qin’s study demonstrate the angiogenic capabilities of HUMCs and the significant role they play in improving ischemic vascular disease secondary to diabetes. Based on these results, the team suggested that the additional neo-vessel formations, collateral circulation routes, and perfusion avenues may be a direct consequence of the angiogenic factors provided by the transplanted HUMSCs [10]. The study further indicates that percutaneous angioplasty in conjunction with HUMC infusion is a more efficacious treatment for the diabetic foot than angioplasty alone as it promotes ulcer healing. HUMCs ability to improve advanced diabetic ulcer healing may have important clinical ramifications as this could lead to reduced rates of foot amputations and improvements in quality of life for type II diabetic individuals [10].

Kato et. al created a novel diabetic foot model in rats and demonstrated that transplantation of MSC’s on diabetic wounds enhanced human keratinocyte activity and tissue re-epithelialization which may help improve impaired diabetic wound healing. The primary mechanisms of wound healing differ between humans and rats. In humans, healing begins by re-epithelialization and granulation of the ulcerated wounds, specifically by keratinocyte phosphorylated focal adhesion kinase (pFAK) and matrix metalloprotease (MMP) Epidermal growth factor (EGF) and IGF (insulin-like growth factor) activity. Conversely, in rodents, wound healing begins with contraction of the
skin surrounding the wound. Previous studies have suggested that impaired healing and re-epithelialization of human diabetic foot ulcers may be due to diminished re-epithelialization capability of keratinocytes, specifically decreased levels of (pFAK) and (MMP) when subjected to high glucose conditions. This study indicates that diminished keratinocyte activity due to hyperglycemia may be responsible for prolonged, inadequate healing of diabetic wounds and that culturing keratinocytes with BM-MSC may not only enhance keratinocyte activity, but also ameliorate wound healing issues in diabetic humans.

He et. al demonstrated that healing capabilities of BM-MSCs are greatly enhanced when given in conjunction with BDNF. These results strongly suggest that a combination therapy of BM-MSC and BNFP acts as a more effective therapy for treatment of diabetic foot ulcers in rats than transplantation of BM-MSC’s alone.

While the researchers of these studies were able to demonstrate the therapeutic capabilities of various stem cells in treating multiple symptoms seen in diabetic limbs there remain limitations that should be addressed.

While the results in the studies done by Ezquer and Chandramoorthy seem promising, they did not look at the therapeutic potential of MSCs directly in human subjects with DPN. Ezquer and his colleagues isolated and treated DRG neurons from rats with the secretome of DFX treated MSCs while Chandramoorthy used human cells in order to obtain data that would be the closest to that obtained in future human trials. Though their data had positive outcomes, Ezquer et al. also need to translate their work to human DRG neurons in future trials. Furthermore, they only used adipose MSCs obtained from four women undergoing liposuction. The group could have increased their sample size and demographic by including males and patients with DN. This way they could have determined if autologous MSCs obtained from patients with DN would be a viable option for treatment, as opposed to MSCs obtained from healthy patients. While Kato and his team were able to duplicate human re-epithelialization mechanisms on rats and demonstrate the therapeutic benefits of BM-MSCs on diabetic foot ulcers they acknowledged a considerable limitation to their study. A main causative factor for foot ulcerations is peripheral arterial ischemia, commonly seen in chronic diabetics and not in recent onset diabetics. In this experiment, the rats were quickly induced with diabetes and then immediately ulcerated which is inconsistent with the common progression of human diabetic ulceration. The researchers have suggested the need to incorporate limb ischemia within their rat diabetic foot model in order to create a more accurate parallel for human wound healing. Similarly, while he demonstrated the wound-healing and angiogenic capabilities of BM-MSCs combined with BDNF, studies must be performed in order to determine whether this
therapy would have similar efficacy in human wound healing.

Though this paper focused on the mechanisms by which MSCs are beneficial for the treatment of diabetic maladies, there have also been clinical trials, not discussed in this paper due to the inclusion and exclusion criteria, that have been taking place with positive outcomes. Li et al. injected human UCB MSCs in the quadriceps thigh muscles of 15 type II diabetes patients with foot disease and saw a reduction in blood glucose levels post-transplantation with a decrease in the requirement for insulin\textsuperscript{16}. Lu et al. did a comparison of bone marrow mononuclear cells (BM-MNCs) with bone marrow MSCs in 41 diabetic patients with critical limb ischemia and foot ulcers. They saw that BM-MSCs were better than BM-MNCs in healing foot ulcers as well as promoting lower limb perfusion\textsuperscript{17}. Dash et al. focused on chronic lower extremity wounds in 24 patients and injected BM-MSCs directly in and around their nonhealing ulcers\textsuperscript{18}. They saw a reduction in the size of the ulcers at 12 weeks and an improvement in the quality of life in the patient since they were able to walk pain-free. These studies further support our thesis which states that using MSCs alone or in conjunction with current therapies in may serve as an extremely effective method for reducing the detrimental symptoms experienced in diabetes.

**CONCLUSION**

This systematic review strengthens the hypothesis that MSCs offer significant therapeutic benefit and may serve as a viable alternative treatment for diabetic maladies when used in conjunction with current therapeutic options. While still novel in concept, we encourage physicians to consider these therapies when assessing treatment options for diabetes and its associated symptoms. The data in this review supports the use of MSCs in cells derived from humans and animal models. Though there have been some clinical trials as briefly described in this study, more focused research is needed to make a stronger conclusion in support of the use of MSCs for diabetic neuropathies and associated symptoms, especially if we are to draw parallels from experiments using non-human subjects. This research would prove to be valuable since current treatments and follow-up for diabetes are not only limited but may be an economic burden for some.

**AUTHORS’ CONTRIBUTIONS**

All authors contributed equally to this literature review. All authors agreed upon the final submission of this draft.
STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

REFERENCES


Efficacy of Honey-Based Therapy Methods in the Treatment of Diabetic Foot Ulcers: A Literature Review

Johnny Dong, BS, MBS, Norman Li, BA, MBS, Saad Islam, BS, Mujtaba Qureshi, BS

Abstract

Introduction: Diabetic foot ulcers (DFUs) are a complication experienced by approximately 15% of patients diagnosed with diabetes mellitus as a result of their susceptibility to pedal neuropathy. It not only causes a great number of hospitalizations but also contributes to the majority of all lower limb amputations. This study explores the efficacy of using honey-impregnated wound dressings as a way of enhancing the healing process of DFUs.

Study Design: Qualitative systematic review of literature.

Method: A systematic search was conducted on PubMed using the search phrase "Honey"[Mesh] AND "Diabetic Foot"[Mesh] AND "Foot Ulcer"[Mesh] AND "Therapeutics"[Mesh]. The initial search yielded 11 articles. After including full-text articles that were published in English between 1/1/2005 to 12/31/2017, focused on human subjects, and excluding those that did not mention foot ulcers or honey used as a therapeutic treatment option, a total of six articles were used.

Results: There were six studies selected which included a total of 848 patients with diabetic foot ulcers. Length of healing time, prevention of bacterial infection, and toe and lower limb salvage were evaluated. Overall, over 75% of patients with foot ulcers healed using honey impregnated dressings, as compared to 57% of patients that healed using saline based dressings. Only 14 of the 848 patients received amputations, three of which were below-the-knee. Based on these criteria, honey was shown to significantly reduce healing time, decrease bacterial load, and minimize the need for amputation.

Conclusion: Honey based dressings is a novel and effective way to treat all grades of diabetic foot ulcers as defined by the Wagner Classification System. However, the quality of the currently published studies may be questioned. In the future, more randomized controlled trials should be performed to compare controls with experimental variables to provide more data on the usage of honey-based dressings as the standard to treat diabetic foot ulcer.

Key Words
Diabetic foot ulcer (DFU), honey, wound dressings, therapeutics.

Level of Evidence: 4
INTRODUCTION

Epidemiology

Diabetes mellitus (DM) is a disease caused by the inability of the body to produce or respond to insulin, resulting in hyperglycemia and its associated symptoms. Epidemiological data show that DM affected 30 million people in 1985, and in 2010, this number has risen to 285 million. At this rate, the number of people with DM is estimated to be 360 million by 2030.

Individuals with DM are prone to a vast amount of complications and issues, one of which is the diabetic foot ulcer (DFU). Around 15 percent of diabetic patients develop this wound, with high probability of appearing on the sole of the foot. 20 percent of diabetics seek treatment of their DFU and six percent are hospitalized for infection or more serious complications. 20 to 24 percent of diabetics that develop DFUs undergo amputation, which contributes to 50 to 70 percent of all lower limb amputations. Even with medical advancements, the three-year mortality rate after an initial amputation is between 20 to 50 percent, a statistic that has not changed in the past 30 years. Financially, healing one ulcer costs around $8000, whereas the cost of treating an infected ulcer is $17,000. Meanwhile, performing an amputation costs between $30,000 and $45,000. Overall, DFUs have a tremendous impact on the well-being of the patient physically, emotionally, and economically, leading to a decreased quality of life.

Etiology

Research has identified many risk factors that contribute towards the development of DFUs, classified as either systemic or local. Systemic factors include hyperglycemia, peripheral vascular disease, renal disease, and age. Local risk factors include peripheral neuropathy, foot deformities, trauma, calluses, high pressure, and limited mobility. The majority of DFUs are caused by ischemic or neuropathic conditions that arise from nerve damage as a result of hyperglycemia, thus systemic decline is the inciting agent prior to local effects. Although the mechanism of peripheral sensory neuropathy is unclear, it is hypothesized that its onset is caused by the glycosylation of certain compounds, free radicals, protein kinase Cβ, as well as hyperglycemia. Ultimately, neuropathy leads to high plantar pressure, foot deformities, and gait instability, all increasing the risk of developing a DFU.

One of the most common and severe complications associated with DFUs is the high risk of bacterial infection, specifically bacteria that can produce biofilm as a shield against stresses such as immune responses and antimicrobial agents. The most common organisms cultured from DFUs include Staphylococcus aureus, Enterococcus,
*Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella*, and *Proteus*, among others. Not only do these organisms have multi-drug resistance but they can also establish colonies on the surface of the ulcer, which provides an ideal environment for further invasion. In addition, these bacteria can exist independently or coexist to form microcommunities within the biofilm. These virulence factors pose a huge obstacle for treating diabetic foot ulcers due to the conducive environment it generates for chronic infection as well as its developed resistance against many antibiotics.¹³

**Ulcer Evaluation**

Standard DFU evaluation includes neuropathy, vascular, and ulcer assessments. Neurological status is assessed with the Semmes-Weinstein monofilament, which determines whether or not the patient has “protective sensation”, or the 128 C tuning fork, a tool used to test the patient’s vibratory sensation.⁴ To ensure the delivery of adequate blood flow and nutrient supply necessary for ulcer healing, vascular assessment is performed, which includes checking pedal pulses and capillary filling time in the toes.⁴ Lastly, ulcer evaluation requires documentation of its physical characteristics such as location, size, shape, and signs of infection. Once the assessment is finished, a differential diagnosis can be established.

The large variability in ulcer presentation led to the development of numerous classification schemes that consider parameters such as infection, neuropathy, ischemia, and location.⁵ These classification schemes are a systematic way of approaching ulcers not only in terms of treatment but also for prediction of outcome.⁵ The Wagner Classification System, as seen in the table below, is the most widely accepted.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No open lesions; may have deformity or cellulitis</td>
</tr>
<tr>
<td>1</td>
<td>Superficial diabetic ulcer (partial or full thickness)</td>
</tr>
<tr>
<td>2</td>
<td>Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis</td>
</tr>
<tr>
<td>3</td>
<td>Deep ulcer with abscess, osteomyelitis, or joint sepsis</td>
</tr>
<tr>
<td>4</td>
<td>Gangrene localized to portion of forefoot or heel</td>
</tr>
<tr>
<td>5</td>
<td>Extensive gangrenous involvement of the entire foot</td>
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</tbody>
</table>

**Table 1. Wagner Ulcer Classification System.⁵**
**Wound Dressings**

Part of the treatment and management of DFUs is the application of wound dressings, which are used to ease symptoms, protect from further damage, and promote healing. There are several types of dressings commercially available, however, due to lack of research in this area, there is not a single type of dressing that fulfills each one of these treatment goals. The types of dressings available correspond to different aspects of treatment, guiding dressing choice. The most important factor that typically guides dressing choice is the promotion of wound healing. Research shows that a moist wound environment is most desirable for effective healing. Current wound dressings

<table>
<thead>
<tr>
<th>Dressing</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>Low-adherence</td>
<td>Simple</td>
<td>Minimal absorbency</td>
</tr>
<tr>
<td></td>
<td>Hypoallergenic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inexpensive</td>
<td></td>
</tr>
<tr>
<td>Hydrocolloids</td>
<td>Absorbent</td>
<td>Concerns about use for infected wounds</td>
</tr>
<tr>
<td></td>
<td>Can be left for several days</td>
<td>May cause maceration</td>
</tr>
<tr>
<td></td>
<td>Aid autolysis</td>
<td>Unpleasant odor</td>
</tr>
<tr>
<td>Hydrogels</td>
<td>Absorbent</td>
<td>Concerns about use for infected wounds</td>
</tr>
<tr>
<td></td>
<td>Aid autolysis</td>
<td>May cause maceration</td>
</tr>
<tr>
<td></td>
<td>Donate Liquid</td>
<td></td>
</tr>
<tr>
<td>Foams</td>
<td>Thermal insulation</td>
<td>Can adhere to wound</td>
</tr>
<tr>
<td></td>
<td>Good absorbency</td>
<td>Occasional dermatitis with adhesive</td>
</tr>
<tr>
<td></td>
<td>Confirm to contours</td>
<td></td>
</tr>
<tr>
<td>Alginate</td>
<td>Highly absorbent</td>
<td>May need wetting before removal</td>
</tr>
<tr>
<td></td>
<td>Bacteriostatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemostatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Useful in cavities</td>
<td></td>
</tr>
<tr>
<td>Iodine preparations</td>
<td>Antiseptic</td>
<td>Iodine allergy</td>
</tr>
<tr>
<td></td>
<td>Moderately absorbent</td>
<td>Discolors wound</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avoid in case of thyroid disease or pregnancy</td>
</tr>
<tr>
<td>Silver-impregnated</td>
<td>Antiseptic</td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td>Absorbent</td>
<td>No proven advantage</td>
</tr>
</tbody>
</table>

**Table 2.** Commercially available wound dressings with advantages and disadvantages listed by Hilton et al.
are designed to allow and maintain moisture while simultaneously inhibiting growth of bacteria and providing ventilation along with insulation. Moreover, dressings should ideally provide an accessible view of the ulcer, offer protection and comfort, and be affordable.\textsuperscript{6} The table below, provided by Hilton et al., presents the types of dressings available along with their advantages and disadvantages.

A lack of research and evidence discourages the use of one dressing over another. Many of the randomized controlled trials that involve wound dressings exclude the diabetic patient and patients with active wound infections.\textsuperscript{6} The few published studies on dressings had small sample sizes, which do not provide enough evidence and generalizability to affect clinical practice.\textsuperscript{6} Yet, even with this lack of research on wound dressings, there is no substitute for the use of antibiotics, proper debridement, and dressing changes as part of the proper care and treatment protocol for DFUs.

\textit{Honey Wound Dressings}

DFUs are sustained in an inflammatory state during the healing, essentially maintaining an environment conducive to inflammation and infection. Several studies have shown that honey, an antiquated topical remedy used for burns and wounds, can be used as an effective treatment for DFUs due to its antimicrobial and anti-inflammatory properties.\textsuperscript{7,8,9,10} Honey has a low pH, ranging from 3.2 to 4.5, which inhibits the growth of bacteria. It also produces hydrogen peroxide after combining with wound secretions, a by-product that is also supplied by the oxidative burst of immune cells.\textsuperscript{8,9} Other bioactive components of honey aid in reducing inflammation and debridement, which further encourages subsequent stages of healing.\textsuperscript{10} Additionally, research indicates that honey mimics the effects of insulin, promotes cellular regeneration by triggering angiogenesis, the growth of fibroblasts, and epithelial cells.\textsuperscript{10}

This is indicative of the clinical potential that honey has in speeding up the healing process of DFUs especially used in the context of dressings which aid in keeping the honey in direct contact with the ulcer as well as providing a clean environment.

Furthermore, different types of honeys have varying levels of healing efficacy. “Supermarket honey” yields slower healing time due to the processing it undergoes, which eliminates its antibacterial activity and other properties.\textsuperscript{10} Nevertheless, studies that focus on honey therapeutics use honeys that have been shown to have a higher antibacterial potency. These include honeys such as: Manuka, jellybush, and Beri. The antibacterial activity of most honey comes from an enzyme that bees secrete into nectar which generates hydrogen peroxide.\textsuperscript{10} In comparison, the potency of Manuka and jellybush is due to an antibacterial component that comes from the nectar of \textit{Leptospermum}, a genus of shrubs and small trees from which Manuka and jellybush honeys are cultivated.\textsuperscript{10} Moreover, the catalase found in ulcers breaks down hydrogen peroxide, relegating
most honeys as having weaker antibacterial properties than honey extracted from *Leptospermum*. Therefore, those with higher antibacterial potency such as Manuka and jellybush are preferred for use in honey wound dressings.

**Objective**

The purpose of this paper is to conduct a review of literature that focused on the efficacy and novelty of honey-impregnated dressings as a treatment method for DFUs.

**METHODS**

A comprehensive PubMed literature search with the query "Honey"[Mesh] AND "Diabetic Foot"[Mesh] AND "Foot Ulcer"[Mesh] AND "Therapeutics"[Mesh] yielded 11 articles. The inclusion criteria included human subjects and English language full-text articles published between 1/1/2005 to 12/31/2017. Articles with no mention of foot ulcers, no adequate information regarding honey as a treatment option along with the clinical implications, and those that mentioned treatment methods other than honey were exclude. Systematic review articles were also excluded. Five articles are excluded based on these criteria. Ultimately, a total of six articles are include.

**RESULTS**

Six studies out of 11 met the inclusion and exclusion criteria. The average length of time the studies took place was one and a half years. The ulcers based on four studies were categorized based on Wagner Ulcer Scale 1 through 5, listed in Table 3, with 237 unidentified Wagner levels of ulcers. The results of the studies are listed in Table 4.

The patients’ in all of the studies first underwent standard DFU treatment, which consists of an initial debridement of dead tissue followed by irrigation with a saline wash. The ulcers were then covered with a sterile honey-coated dressing three times a day. Efficacy of the honey-coated
dressing was assessed via the length of healing time, prevention of bacterial infection, and toe and lower limb salvage.

**Healing Time**

Imran et al. compared the use of honey-impregnated dressing to saline dressing in treating DFUs of Wagner grade 1 or 2. Patients were divided into two groups: A (n = 179) treated with beri honey dressing and B (n = 169) treated with normal saline dressing. Of the 179 patients treated with honey in group A, 136 wounds were completely healed (75.97%). As indicated in table 5, of the 169 patients treated with saline, 97 wounds were completely healed (57.39%).

The mean wound healing time in group B was

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</thead>
<tbody>
<tr>
<td>Wagner 1 &amp; 2</td>
<td>348</td>
<td>172</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>524</td>
</tr>
<tr>
<td>Wagner 3</td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Wagner 4 &amp; 5</td>
<td></td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Unidentified</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>60</td>
<td>255</td>
<td>315</td>
</tr>
<tr>
<td>Total</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>850</td>
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</tbody>
</table>

Table 3. Number of Patients Per Wagner Level. 7,8,9,10,11,12

<table>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg. Healing time (honey)</td>
<td>18 days</td>
<td>21 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of deteriorated ulcers (saline)</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of deteriorated ulcers (honey)</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of patients healed (saline)</td>
<td>97/169 (57.39%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of patients healed (honey)</td>
<td>136/179 (75.97%)</td>
<td>147/172 (85.46%)</td>
<td>9/14 (57%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amputations (Wagner 1-3)</td>
<td>5/172 (2.9%)</td>
<td>9/14 (57%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td># of infected ulcers</td>
<td>105/172 (61%)</td>
<td>14/14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Healing Time, Ulcer deterioration, and Infection for Honey vs Saline Treatments. 7,8,9,10,11,12

or 2. Patients were divided into two groups: A (n = 179) treated with beri honey dressing and B (n = 169) treated with normal saline dressing. Of the 179 patients treated with honey in group A, 136 wounds were completely healed (75.97%). As indicated in table 5, of the 169 patients treated with saline, 97 wounds were completely healed (57.39%). The mean wound healing time in group B was
29 days, ranging from seven to 120 days. 19 wounds deteriorated and contained eschar in group B (11.2%). The mean wound healing time for group A was 18 days, ranging from six to 120 days. 11 wounds deteriorated in group A (6.15%). Overall, 18.58% more patients completely healed in group A honey treatment versus group B saline treatment.\(^7\)

<table>
<thead>
<tr>
<th></th>
<th>Number of patients in saline treated dressing</th>
<th>Number of patients in honey treated dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wounds healed within 120 days</td>
<td>97</td>
<td>136</td>
</tr>
<tr>
<td>Non-healed wounds</td>
<td>53</td>
<td>32</td>
</tr>
<tr>
<td>Deteriorated</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>TOTAL HEALED</td>
<td>97/169 (57.39%)</td>
<td>136/179 (75.97%)</td>
</tr>
</tbody>
</table>

**Table 5. Number of Wounds Healed Using Saline vs. Honey.**\(^7\)

The study conducted by Surahio et al. looked at the role of honey in non-healing chronic diabetic foot ulcers. Surahio et al. studied 172 patients with complicated, chronic non-healing DFUs. All patients underwent early surgical debridement and dressing with a thick layer of honey locally available. Dressings were applied three times in 24 hours, washing the wound with saline between each 8-hour interval.\(^9\) 50 patients (29.1%) healed in seven to 15 days, 95 patients (55.2%) healed within 15 to 30 days, and 27 patients (15.7%) healed within 30 to 35 days. With honey based treatment, all of the 172 patients in Surahio’s study were healed within 35 days.\(^9\)

The case study conducted by Eddy et al. described the course of treatment with honey on a patient who recently had two toes amputated. He had severe diabetic ulcers and was on the verge of losing his foot until he began honey treatment. A thick coating of processed honey using smearing gauzes was placed on the wounds and then wrapped. Oral antibiotics, as well as saline dressings, were discontinued. Debridement of dead tissue was continued. Granulation, which is new vascular tissue replacing ulcerated tissue, appeared within 2 weeks of treatment. In six to 12 months, the ulcers resolved. Within two years, the ulcers have not recurred.\(^11\)

Abdelatif et al. studied the effectiveness and safety of Pedyphar ointment (an ointment prepared from natural royal jelly and honey and panthenol in an ointment base) in the treatment of patients with limb-threatening diabetic foot infections. 60 patients were placed into three groups based on the severity of their lesions. Group 1 included patients suffering from full thickness ulcers (Wagner grades 1 & 2). Patients with deep tissue infection and osteomyelitis (Wagner grade 3) were placed into Group 2. Group 3 was categorized by gangrenous lesions (Wagner grades 4 and 5).\(^12\) After cleansing with a saline solution, wounds were
treated with Pedyphar ointment, and surgically debrided when necessary. Patients were followed up for six months or until full healing occurred. No other specific treatment was given apart from insulin treatment to control the diabetes. The primary endpoint was the clinical response at weeks three, nine, and 24 from the start of treatment. 96% of the patients in groups 1 and 2 responded well with clinically complete cures. A complete cure is defined as “complete closure of the ulcer without signs of underlying bone infection,” by the end of week nine and for the duration of the six-month follow-up period. 12 100% of the ulcers in group 1 completely cured, and 92% of the ulcers completely cured in group 2. 100% of patients in group 3 completely cured following surgical excision, debridement of necrotic tissue and conservative treatment with Pedyphar ointment. 12

Infection

The efficacy of honey treatment in lowering bacterial infections in patients with DFUs was assessed. The study conducted by Surahio et al. observed 67 of 172 patients (38.95%) with no growth of infectious bacteria. 35 of 172 patients (20.35%) were infected with methicillin-resistant Staphylococcus aureus. 20 patients (11.63%) were observed infected with non-methicillin resistant Staphylococcus aureus. 30 patients (17.44%) were infected with Pseudomonas aeroginosa. 20 patients (11.63%) were infected with Streptococcus group-A.9 In total, the number of patients with DFU infections were limited to only 105 of the 172 patients in this study. As indicated in Surahio’s study, all 172 patients healed from their ulcers, even those patients infected with bacteria.9 The honey was able to heal the ulcer while simultaneously lowering and

<table>
<thead>
<tr>
<th>Grade</th>
<th>Number of Feet</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wagner 2</td>
<td>4</td>
<td>28.57%</td>
</tr>
<tr>
<td>Wagner 3</td>
<td>6</td>
<td>42.85%</td>
</tr>
<tr>
<td>Wagner 4</td>
<td>4</td>
<td>28.57%</td>
</tr>
</tbody>
</table>

Table 6. Percentage of Feet Displaying Wagner Levels 2-4 in Makhdoom Study. 8

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Number of Feet</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcus aureus</td>
<td>8</td>
<td>57.14</td>
</tr>
<tr>
<td>E.coli</td>
<td>4</td>
<td>28.57</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>1</td>
<td>7.14</td>
</tr>
<tr>
<td>Proteus</td>
<td>1</td>
<td>7.14</td>
</tr>
</tbody>
</table>

Table 7. Percentage of Feet Displaying Specific Bacterial Infections in Makhdoom Study. 8
preventing more bacteria from growing in the wound.

In the study conducted by Makhdoom et al., the ulcers of 12 patients were cultured. Of these 12 patients, two cases presented with bilateral diabetic foot ulcers. As indicated by Table 6, four feet presented with ulcers at Wagner grade 2, six feet presented with Wagner grade 3, and four feet presented with Wagner grade 4. Table 7 indicates that all 12 feet were infected with bacteria, 8 of which infected with staphylococcus aureus. The use of honey impeded the spread of bacteria to other areas of the patients’ feet, and all except one patient was able to lower infection and salvage majority of their foot with minor amputations, as indicated in table 8.

Under the Eddy et al. study, the patient had previously received oral antibiotics and standard saline treatment to prevent further infection. However, the antibiotics did not work and infections were maintained along with a deteriorating ulcer. Once the treatment method was changed from only antibiotics, to antibiotic plus honey based dressings, the infection subsided and the ulcer finally healed.

Molan et al. demonstrated that the minimum inhibitory concentration (MIC) of Manuka honey is two to three percent for Staphylococcus aureus, 3.3 to four percent for coagulase-negative staphylococci, 5.5 to nine percent for Pseudomonads, 2.7 to three percent for MRSA, and 3.8 to five percent for VRE.

**Amputations**

In addition to healing time and infection rate, studies were conducted to measure surgical outcome and the level of limb salvage. In the Surahio et al. study, the patients included in the study were Wagner grades 1 & 2. Only five out of 172 patients featured an amputation. Only three patients (1.75%) underwent big toe amputations and two patients (1.16%) underwent below the knee whole foot amputations. Honey was effective in salvaging 97% of the limbs.

In the study by Makhdoom et al., the patients included Wagner grades 2 to 4, further detailed in Table 6. The study observed 12 patients with a total of 14 diabetic foot ulcers. Two of the 12 patients

<table>
<thead>
<tr>
<th>Amputation</th>
<th>No. of Feet (total 14)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big Toe</td>
<td>3</td>
<td>25%</td>
</tr>
<tr>
<td>2nd &amp; 3rd toe with ray</td>
<td>2</td>
<td>16.67%</td>
</tr>
<tr>
<td>4th &amp; 5th at MTPJ level</td>
<td>3</td>
<td>25.0%</td>
</tr>
<tr>
<td>Below Knee</td>
<td>1</td>
<td>8.33%</td>
</tr>
</tbody>
</table>

**Table 8. Percentage and Location of Each Amputation in Makhdoom Study.**
presented with bilateral diabetic foot ulcers. Honey was slightly less effective in this study compared to Surahio’s, because of the severity of these diabetic foot ulcers. There was a much higher rate of amputation within the small sample size. There were amputations of the big toe in three patients (25%), second and third toe rays in two patients (16.67%), and fourth and fifth toes at the level of the metatarsophalangeal joints were done in three patients (25%). Only one patient had a below knee amputation (8.33%).

The case study by Eddy et al. described a patient who had two toes amputated. His diabetic foot ulcer was severe with recurring episodes of heel osteomyelitis and deep tissue infections. He was a 79-year-old patient with type 2 diabetes mellitus. He received care for 14 months, which included five hospitalizations and four surgeries. During this treatment, the patient lost two toes, and was faced with the choice of either losing his limb or his life. The patient then began honey based treatment with thick applications once daily. No further amputations occurred after honey based treatments and the patient healed.

In terms of limb salvage, the study with Surahio et al. displayed that 167/172 (97%) of the patient's limbs were salvaged. The study by Makhdoom et al. showed nine out of 14 patients (64%) had either a toe or the whole foot amputated. There were no amputations in the Abdellatif study, which included a patient sample size of 60 patients with life threatening diabetic foot infection. The sample included patients from Wagner grades 1 to 5, 5 being the worst diabetic foot ulcer condition.

**DISCUSSION**

DFUs, a complication of having diabetes mellitus, is a pathology that requires clinical intervention. DFUs become more complicated when infected with
microorganisms and effectively lead to an increase in the rate non-traumatic amputations. There are many methods to treat DFUs, with the standard treatment using normal saline solution. The articles chosen for this literature review evaluated the efficacy of using honey as a topical treatment of DFUs. Honey has antibacterial activity which helps control the growth of microorganisms. The broad-spectrum characteristics of honey in turn allows for faster healing time, less deterioration, and reduces the necessity of amputations.

Honey treatment

The type of honey and dressing applied to the DFUs affects the outcome. The articles highlighted that when it comes to treating wounds, the use of processed honey is not as effective as the natural and raw honeys Beri and Manuka. Processed honey does not have the beneficial wound-healing and anti-bacterial phytonutrients that raw honey contains. Natural and raw honey has a high osmolality that removes excess water in the wound, lowers the surface pH and contains the enzyme glucose oxidase. Glucose oxidase reacts with wound fluid to make the mild antiseptic hydrogen peroxide which facilitates wound healing.

Although honey removes excess water in the wound, honey based dressings still maintain a moist healing environment by balancing the water lost with new fluid from blood circulation. In their comprehensive review of different types of honey, Molan et al., highlighted that *Leptospermum scoparium* honey, which is also known as Manuka honey, was the most effective because of its phytochemical antibacterial component. The MIC of Manuka honey is the concentration of maximum dilution of the honey by wound exudate that prevents bacterial growth. Based on these results, Manuka honey was shown to be an effective as an anti-bacterial agent. High antibacterial activity is important because wound tissue secretes catalase containing fluids that rapidly break down hydrogen peroxide. It is important that the honey maintains constant contact with the wound so the anti-bacterial mechanisms of the honey applies onto the wound. The study by Molan et al. showed that the best dressings were honey impregnated alginate dressings pads where the honey-to-wound contact is maximized. The data from the studies supported that honey based treatment was more effective than conventional DFU wound care practices.

Honey and infections

Honey has anti-inflammatory and anti-bacterial properties that contributes to better clinical outcomes by limiting microorganism wound infections. Table 4 shows that Makhdoom et al. and Surahio et al. studied ulcers with infections and how the use of honey-based dressings got rid of the infections. Table 7 highlights that the most common DFU bacterial infection is caused by *Staphylococcus aureus*, with 57.14% of the patients in the trail infected. The anti-bacterial
properties of honey effectively contributed to the clearing of the infections in the wounds. Eliminating the complications of wound infection reduce healing time.

**Honey and healing time**

The use of honey-based dressing as treatments significantly reduced the DFU healing time when compared to saline-based standard treatments. In a randomized controlled clinical trial of honey-impregnated dressings for treating DFU, Imran et al. focused on the average healing time using saline solutions versus honey dressings. The results from Table 4 and Table 5 shows that using honey dressings resulted in faster healing time and decreased the rate of wound deterioration. Imran et al.’s study was clinically significant because the usage of honey dressings drastically improved the condition of large number of patients over a duration of 4 years. Table 4 also shows the results of Abdelatif et al. in their prospective pilot study of Pedyphar, a new honey ointment, on DFUs. The greater than 96% DFU healing rate on patients that had Pedyphar applied supports that honey based dressings are effective as DFU treatment. Aside from the anti-inflammatory and antibacterial properties of honey, honey demonstrated that their growth factors, debriding effects, and increase in lymph flow helps heal DFUs.

**Honey and amputations**

The effect of honey based treatments on the rate of non-traumatic foot amputations that resulted from DFUs was analyzed. Makhdoom et al. observed excellent results from their study in treating DFUs with honey. Table 8 shows the specific types of amputation that were performed. The rate of amputation caused by DFUs decreased with the application of honey based treatment. However, table 4 shows that despite treatment with honey, nine out of 14 patients (64%) had either a toe or the whole foot amputated. This could be in part due to Makhdoom’s small sample size consisting mainly of severe, infected Wagner grades 3-5 patients, as indicated in table 3. Nevertheless, treatment with honey was capable of salvaging most of the foot in all but one of the patients. Furthermore, there was no control in this study to compare the use of honey versus other forms of treatment, therefore no solid conclusion could be made from Makhdoom et al. about the efficacy of honey in DFU treatment. Next, Table 4 shows that no amputations were performed in Abdellatif’s study. Eddy et al. conducted a case study of using topical honey for treating a patient with toe amputation with DFU. Figure 3 displayed the result from using honey as a topical treatment. Since no further amputations were observed after the foot healed from honey based treatments, it shows that honey is an effective treatment for treating DFU. In terms of limb salvage, the study by Surahio et al. displayed that treatment with honey significantly reduced
the rate of amputation. The results from all articles showed that honey yielded reduced rate of amputation and improved wound healing when used for wound dressing in chronic diabetic foot ulcers.

Despite all the studies that show the effective and promising results of honey, the use of honey clinically is still limited. Clinicians may not trust honey based dressings as a form of treatment because of there is no standardized preparation of honey based dressings available globally and in the United States. Honey based treatments may still be perceived as a pseudo-medicine that has not been scientifically proven. Thus, more studies need to be conducted nationwide before honey based treatments can be used as a method for treating DFU.

**LIMITATIONS**

There were limitations to each of the articles, some of them being more profound limitations than others. Imran et al. included study subjects that mostly belonged to lower socioeconomic class, so despite being treated for DFU, their primary preventative treatments were not discussed and probably lack proper medical care. Also, despite treating the DFU’s this study did not acknowledge the microorganisms that may have infected the wounds. The study was also not blinded and patients could tell if they were receiving saline or honey, as honey has a specific odor and color. The study by Surahio et al. did not include control subjects, and despite showing convincing numbers displaying the decrease in bacterial infections, there was not a normal infection rate in an untreated DFU to compare it to. The study with the most limitations was Makhdoom et al., mainly because of the extremely small sample size and no control group that resulted with ambiguity in the data. Another study with significant restrictions in the data included Abdelatif et al. because there was no control group and the study was not blinded. In the case study by Eddy et al., the only limitation was that processed honey was used instead of natural raw honey. Every other study used sterile natural raw honey such as Beri and Manuka. The shortcoming in the study by Molan et al. mainly stems from the fact that the study does not use empirical data as evidence to support the study’s conclusions. Most of the information stated by Molan et al. was summarized based on other case studies. Despite minor deficiencies, no study concluded drastic enough results to claim honey as an ineffective form of treatment. All studies agree that honey is an effective treatment for DFU.

**CONCLUSION**

As the number of individuals suffering from diabetes rapidly increases, there will be an even greater likelihood of DFUs. While there are many traditional methods of treating DFU, such as using saline dressing as a
topical treatment, advancements must be made in the type of treatment available. Honey based treatments is an effective, newer, and safe alternative treatment that can benefit diabetic patients. Honey has been shown to be more effective than standard treatment methods when comparing the number of ulcers healed, their healing time, and the level of limb salvage. Natural honey is determined to have more antibacterial and anti-inflammatory properties compared to processed honey. These properties contribute to improved wound healing and lead to the reduction of foot amputations. After honey based treatment, the degree of wound deterioration also declined. Wounds that were otherwise chronic, recurred much less or not at all with honey, as opposed to other treatment methods. However, there were limitations based on the quality of some of the published studies, so a definitive conclusion is not imminent. In the future, more randomized controlled trials should be performed to compare controls with experimental variable. Overall, honey-based dressings should be considered as a standard to treat diabetic foot ulcer.

**AUTHORS’ CONTRIBUTIONS**

All authors contributed equally to this literature review. All authors agreed upon the final submission of this draft.

**STATEMENT OF COMPETING INTERESTS**

All authors declare they have no competing interests.

**REFERENCES**


A Literature Review of Invasive Treatment Outcomes for Morton’s Neuroma

Mohammed Gheith, Mike Hsieh, Mohammed Anwar, Monique Dyquiangco

Abstract

Introduction: Morton’s neuroma is a pathology of the lower extremity that can manifest as pain and discomfort but is identifiable through imaging studies. Although it is a neuroma, it is the thickening of the epineural and perineural tissue of the nerve on the plantar aspect of the forefoot. The etiology of Morton’s neuroma is most commonly an entrapment of the nerve in the 2nd or 3rd intermetatarsal spaces beneath the Deep Transverse Metatarsal Ligament (DTML). The purpose of this paper is to research the efficacy of treatment outcomes for using invasive treatments for Morton’s neuroma.

Study Design: Qualitative Systematic Review of Literature

Methods: The authors conducted a search using PubMed with the term "Morton Neuroma/surgery"[Mesh] AND "Treatment Outcome"[Mesh] that yielded 4 articles. The inclusion criteria included an English-only search and articles published between 01/01/2016 and 11/01/2017. Exclusion criteria were non-invasive treatments. After applying the inclusion and exclusion criteria, four papers were included in our review.

Results: A total of four papers were assessed for screening. All four articles fit the inclusion criteria and were further analyzed.

Discussion: Invasive surgical methods are used for the treatment of Morton’s neuroma if a conservative approach is not effective in the beginning stages of treatment. There are multiple surgical choices to treat the neuroma that include dorsal excisional approach, longitudinal plantar approach, and nerve grafting. Each surgical option presents as a viable option in reducing pain and discomfort caused by Morton’s neuroma.

Key Words:

Morton’s neuroma, neurectomy, surgery

Level of Evidence: 4
INTRODUCTION

Morton's neuroma is a pathology seen in the lower extremity.¹ It usually presents as pain in the forefoot, but can also exist without the patient exhibiting clinical symptoms. In the latter case, Morton's neuroma is still identifiable through radio imaging studies. Although the medical term for this pathology includes the word "neuroma", there is no tumor of the nerve that is part of the disease process.¹ What is present in the nerve is a thickening of the epineural and perineural tissues.¹ This thickening of the nerve is mostly found in the plantar region of the forefoot.¹

There is no agreed upon etiology for Morton's neuroma and most evidence points to it being caused by the entrapment of plantar nerve branches beneath the Deep Transverse Metatarsal Ligament (DTML).² This entrapment causes there to be an inflammatory process of the nerve that causes pain in the forefoot.³ The diseased nerve mostly presents in the 2nd or 3rd intermetatarsal space of the metatarsal heads of the foot.¹-³

The treatment options for Morton's neuroma begin with a conservative approach that includes orthotics and steroids. If these measures are exhausted without satisfactory relief of pathological symptoms, then a surgical approach is usually attempted. The purpose of this literature review is to research the treatment outcomes of invasive treatments for Morton’s neuroma. The treatments include excision with interpositional nerve grafting, excision using a longitudinal plantar approach, and dorsal and plantar neurectomy.

METHODS

The authors conducted a search using PubMed with the term ("Morton Neuroma/surgery"[Mesh]) AND "Treatment Outcome"[Mesh] that yielded 4 articles. The inclusion criteria included an English-only search and articles published between 01/01/2016 and 11/01/2017. Exclusion criteria were non-invasive treatments. After applying the inclusion and exclusion criteria, 4 papers were included in our review.

Flow chart:
RESULTS

In Reichert et al, the average American Orthopedic Foot and Ankle Society (AOFAS) score prior to surgery was reported to be $39.4 \pm 7.84$; this number changed to $83.4 \pm 12.1$ after surgery. On the other hand, average Visual Analog Scale (VAS) score before surgery was observed to be $7.04 \pm 1.4$, with the numbers falling to $1.4 \pm 0.8$ after surgery. The research group found that among 41 patients, 76% (31) achieved “very good” results, 15% (6) had “good” results, 7% (3) had “poor” results, and 2% (1) had satisfactory results. Researchers observed significant differences in patient outcomes in relation to number and size of neuromas as well as duration of symptoms prior to excision. Results were found to be better among patients with single neuromas than in patients with multiple neuromas. However, when comparing preoperative versus postoperative AOFAS and VAS scores, no significant differences were observed. While improvement was similar among patients in both groups, patients with single neuromas exhibited better final results since they had fewer symptoms initially. Patients with neuromas measuring 3 mm and larger had significantly better AOFAS and VAS score results compared to those with neuromas smaller than 3 mm. No statistically significant differences were observed among AOFAS and VAS scores in relation to corticosteroid use, nor among patients who received less than 6 months of conservative treatment prior to surgery. Those patients who underwent surgery within the first 12 months at the onset of symptoms saw the best results. Among the patients in the study, histological results of their neuromas revealed that 27% exhibited macroscopically visible inter-metatarsal neuromas, 14.5% had no pathological changes, and 58.5% had changed nerves that exhibited classical patterns of fibrosis and inflammatory infiltrates. The histological results had no significant correlation with treatment outcome.

In Kundert et al, researchers treated 56 neuromas in 44 patients. In 6 patients, the second and third inter-metatarsal spaces had neuromas that were in the same foot, and 5 of these patients had both surgically excised simultaneously. Whereas the mean VAS score was 8 prior to surgery, this number dropped to 0.4 at final follow-up. At the final follow-up, patients used tactile self-assessment to determine sensory reduction of the toes formally affected by the neuromas pre-surgery, and they reported either no sensory reduction or slight sensory reduction. At final follow up to surgery patients reported either “excellent” or “good” results and described having either “no pain” or “subjective discomfort in daily activities” according to this study. However, 2 patients stated they had slight discomfort in walking. Researchers found no significant difference in relation to pre-surgical symptoms and subjective satisfaction with relation to location of the
neuromas. Furthermore, researchers observed complications in 4 neuromas among all patients with interventions and scarring issues among 3 of those neuromas. There were no reports of plantar fat pad atrophy, skin necrosis, or functional issues with toes. Among the patients with simultaneous excision of the neuromas, no complications or wound sloughs were observed.

Studies conducted by Ratanshi et al included 8 patients with 9 neuromas and presurgical pain reported among all patients. The mean pre-operation VAS score was 7 ± 1.7, and the post-operative score was 0.4 ± 1.0. Macroscopic thickening of the nerve at or near the common digital nerve bifurcation was reported among all patients. Neuromas were excised using inter-positional nerve grafting after non-surgical procedures were exhausted. Researchers observed that pain scores had improved at final follow-up compared to initial presentation. There were no recurrences of neuromas at final follow-up, and all patients were capable of weight-bearing. Researchers reported only one major complication: wound dehiscence secondary to hematoma. Pain scores improved at one year.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Number of Neuromas Excised</th>
<th>Average Follow-Up</th>
<th>Visual Analog Scale Averages</th>
<th>AOFAS Averages</th>
<th>MOXFQ Averages</th>
<th>Subjective Patient Satisfaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichert et al</td>
<td>41</td>
<td>41 neuromas 2nd MSN: 7</td>
<td>7.4 years follow up period: post-op 6 and 12 months, and 5 years</td>
<td>Pre-op: 7.04 ± 1.4 Post-op: 1.4 ± 0.8</td>
<td>Pre-op: 39.4 ± 7.84 Post-op: 83.4 ± 12.1</td>
<td>N/A</td>
<td>Very Good: 76% Good: 15% Satisfactory: 2% Poor: 7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd MSN: 20 4th MSN: 6</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Multiple MSN: 8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Kundert et al</td>
<td>44</td>
<td>56 neuromas 2nd MSN: 25</td>
<td>At 12 months post-op</td>
<td>Pre-op: 8 Post-op: 0.4</td>
<td>N/A</td>
<td>N/A</td>
<td>Excellent or Good: 95.5% Slightly Limited: 4.5%</td>
</tr>
<tr>
<td></td>
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<td>3rd MSN: 31</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ratanshi et al</td>
<td>8</td>
<td>9 neuromas 2nd MSN: 1</td>
<td>At 12 months post-op</td>
<td>Pre-op: 7 ± 1.7 Post-op: 0.4 ± 1.0</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd MSN: 8</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Bucknall et al</td>
<td>99</td>
<td>137 neuromas 2nd MSN: 65</td>
<td>At 6 months post-op</td>
<td>N/A</td>
<td>N/A</td>
<td>Pre-op: 59.71 Post-op: 39.53</td>
<td>Excellent: 49.5% Good: 29.3% Indifferent: 11.1% Poor: 8.1% Very poor: 2.0%</td>
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<tr>
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<td></td>
<td>3rd MSN: 72</td>
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MSN: Metatarsal Space Neuroma
post-surgery evaluation in all cases, and symptom improvement was reported among all patients.

Bucknall et al excised neuromas in 99 patients, who were later asked to fill out a Manchester-Oxford Foot Questionnaire (MOXFQ), a Short Form-12 (SF-12), and a patient satisfaction survey 3 months prior to and 6 months after surgery. They observed statistically significant differences between pre-surgical and post-surgical MOXFQ and SF-12. Approximately 50% of patients reported excellent satisfaction, while about 29% reported “good.” However, poor satisfaction was reported from 8.1% of patients, and very poor from 2%. In addition, 63% of patients reported no pain at follow up. Nonetheless, MOXFQ scores worsened among 8.1% of the population. While no significant differences were observed between patients with one or multiple surgical sites, MOXFQ scores decreased significantly following revision surgery ($p = 0.004$).

**DISCUSSION**

The treatment of Morton’s neuroma generally follows a basic path that features a conservative approach at the beginning stages of treatment which progresses to surgical treatment if the former does not work. When conservative treatment options have failed to remedy the condition, that is when surgical intervention is introduced. There are multiple surgical choices to treat the neuroma that include a plantar excisional approach, dorsal excisional approach, longitudinal plantar approach, and excision with nerve grafting. Each surgical option has supporting evidence for its benefits and efficacy in treating Morton's neuroma.

Ratanshi et al. conducted a study to determine the benefits of combining neuroma excision and nerve grafting to treat Morton’s neuroma. The authors used a dorsal excisional approach to remove the neuroma, and the Deep Transverse Metatarsal Ligament (DTML) was incised if better access to the neuroma was needed. If a graft was needed the favored nerve to use was the proper digital nerve of the 3rd toe because of its relatively large diameter. At follow-up, all patients in the study reported pain relief, improvement of symptoms, and there were no reported recurrences of neuroma. The use of nerve grafting alongside an excision of the neuroma shows merit as an approach to surgically treat Morton’s neuroma.

Kundert et al. conducted a study using a longitudinal plantar approach to treat Morton’s neuroma. The authors used radio imaging preoperatively to exclude pathologies that were not Morton’s neuroma in their 44 patient pool. The VAS showed that the average preoperative pain was 8.0 and the average post-operative pain 0.4, with only 2 of the original 44 patients reporting pain after surgery. Of the 44 patients, 42 rated surgical results as excellent or good with no post-surgery complications in daily
activities. There were complications in 7.1% and scarring issues in 5.3% of the surgeries, and these patients were prescribed orthotics. The use of a longitudinal plantar approach to treating Morton’s neuroma shows benefit but there is some risk for post-surgery complications.

Reichert et al and Bucknall et al agree on the dorsal approach for a neurectomy as a viable option for providing pain relief for patients with Morton’s neuroma. What comes as a difference is the way each outcome is scored. Bucknall et al’s inclusion criteria was for patients receiving surgery for a suspected neuroma. There was no requirement for patients to receive conservative treatment prior to surgery. However, most patients did receive some form of conservative treatment in the form of steroid injections, orthotics, or both. Surgeons also performed one of 6 concurrent surgeries to the neuroma excision: the cheilectomy, first ray osteotomy, Weil’s osteotomy, proximal interphalangeal joint fusion, Lapidus fusion, or a BioPro hemiarthroplasty. Bucknall et al used the MOXFQ, the SF-12, and the Likert Scale.

Reichert et al had stricter inclusion criteria that required all patients to have a minimum three-month period of similar conservative treatment prior to surgery. All patients underwent the same neurectomy where surgery was performed through a dorsal approach to remove the neuroma while protecting sensory branches coming from the superficial fibular nerve. Reichert et al studied outcomes based on the patients’ subjective assessment, the VAS, and the AOFAS questionnaire.

One main difference between the two is that the Bucknall et al study only followed the patients up to their 6-month post-operative visit whereas the Reichert et al study provided post-operative visits of 6 months, 12 months, and up to 5+ years of follow-up. One advantage of a longer follow-up is seeing the long-term benefits and whether revision surgery is required for neuroma recurrences. In Reichert et al, they saw only 2 out of the 41 surgeries that required a revision. In Bucknall et al, some patients did not see a reduction of pain at the follow-up visit. The problem with not having a longer follow-up is not being able to see if this is a condition that would clear up on its own or is a sign that further revision surgery is required. In the Bucknall et al study, 7 out of 99 patients did require revision but it was not reported which surgical method was employed or if there were any other comorbidities or foot pathologies in those patients.

Both studies acknowledge that Morton’s neuroma often coincides with other foot pathologies that may cause the neuroma. Therefore, an excision may not always provide the pain relief a patient seeks. Reichert et al acknowledges that their inclusion criteria were based on a clinical examination while excluding those who develop foot pain due to other pathologies.
Moreover, the studies also show that excising multiple neuromas from the same foot or location of the intermetatarsal spaces does not create a statistically significant difference in the surgical outcome.\textsuperscript{3-4}

Lizano-Diaz et al did a double-blinded randomized, placebo-controlled trial to determine the efficacy of using steroid injections as a conservative treatment option for Morton’s neuroma. The study exhibited a final sample of 35 participants with Morton’s neuroma, 16 in the experimental group that received steroid and anesthetic injection and 19 in the control group that received only anesthetic injection.\textsuperscript{5} Using VAS to measure pain scores and AOFAS, the study concluded that there was not a statistical difference in satisfaction at 6 months following their treatment between the experimental and control group.\textsuperscript{5} At the conclusion of the study, 17 patients of the initial 35 participants requested surgical intervention for the Morton’s neuroma, with 7 coming from the experiment group and 10 from the control group.\textsuperscript{5}

In the Reichert et al study there was a comparison between a group of patients who received steroid injections prior to surgery and another group that did not receive any steroid injection prior to surgery. There was no statistical difference between the groups in the post-surgery VAS and AOFAS scores.\textsuperscript{4} Also, patients who received different lengths of conservative treatment for their neuroma symptoms prior to surgery did not differ either. A comparison of a group that had less than 6 months of conservative treatment with another group that had more than 6 months of conservative treatment did not show any significant statistical difference in their VAS and AOFAS scores.\textsuperscript{4}

Mahadevan et al reported that 29 out of 57 feet that received a corticosteroid treatment required further intervention within 2 years. Over half of the feet needing more aggressive intervention such as surgical excision compared to repeat injections.\textsuperscript{6} Further analysis shows that younger patients and those with larger neuromas were more likely to require more aggressive treatment.\textsuperscript{6} In addition to these findings, the Reichert et al study found that surgical excision of larger neuromas received greater reduction in pain than those with smaller neuromas. Further research could show whether more aggressive treatment such as excisional in those with larger neuromas would be more beneficial than first attempting the conservative route because of increased complications and pain discrepancy associated with larger neuromas.

Habashy et al did a study that compared the outcomes for using a dorsal approach versus a plantar approach to excise a Morton’s neuroma. Their study had a total of 37 patients, 20 patients who underwent a neurectomy from the dorsal approach, and 17 patients who underwent a neurectomy through the plantar approach.\textsuperscript{7} The authors used the Short Form Health Survey (SF-36) and Foot Function Index (FFI), and
determined statistical significance to be \( P < 0.05 \). The SF-36 showed no statistical significance between the dorsal group and plantar group (\( P = 0.18 \)), and the FFI showed no statistical significance between the dorsal and plantar groups too (\( P = 0.12 \)). The Habashy et al study supports the use of a neurectomy either through the dorsal or plantar approach as a treatment for Morton’s neuroma which reinforces the data in our results section of this paper concerning those two invasive approaches.

**CONCLUSION**

The studies reviewed in this paper provides evidence for the use of surgical treatments for Morton's neuroma and the satisfactory long-term results they provide for patients.\(^1\)\(^-\)\(^4\) Both a dorsal and plantar approach for the neurectomy show comparable positive outcomes for patients, so the general rule of strict adherence to a dorsal surgical approach for the foot can also include a plantar approach when treating Morton’s neuroma.\(^7\) There is also evidence suggesting that patients who opt for the traditional conservative approach for treating their Morton's neuroma with steroids find it unsatisfactory and opt for surgical treatment to cure their pathology.\(^5\) In conclusion, there is evidence that the surgical approach to treating Morton's neuroma gives positive outcomes for patients through a dorsal approach, plantar approach, longitudinal plantar approach, excisional nerve grafting approach, and for patients who have had unsatisfactory results with conservative treatment.\(^1\)\(^-\)\(^7\)

**AUTHORS’ CONTRIBUTIONS**

All authors contributed equally to this literature review. All authors agreed upon the final submission of this draft.

**STATEMENT OF COMPETING INTERESTS**

All authors declare they have no competing interests.

**REFERENCES**


Efficacy of Ultrasound for the Diagnosis of Gout: A Systematic Review

Basem Hakim, Amira Bekhit, Zab’di Sanchez Prada, Emma Otieno

Abstract

Introduction: Gout is a form of inflammatory arthritis caused by the presence of monosodium urate (MSU) crystals in the joints’ synovial fluid as well as different body tissues. The primarily affected joint is 1st MTPJ. Ultrasound is an imaging modality increasingly used to detect structural abnormalities and the inflammatory signs of the soft tissue in the affected joints. This study aims to identify the efficacy of ultrasound to diagnose gout in the 1st MTPJ at various stages.

Study Design: Qualitative Systematic Review of Literature

Methods: A systematic search was performed using PubMed database with the following query: ("Gout/diagnosis"[Mesh] OR ("Gout” AND “Diagnosis")) AND ("Ultrasonography"[Mesh] OR "Ultrasound" OR "Ultrasonographic") AND "First Metatarsophalangeal Joint". Inclusion criterion included English articles with a publication date between 1/1/2012 and 11/10/2017. After application of the inclusion criterion, the query returned 9 results. The authors excluded articles involving joints other than the first metatarsophalangeal joint, leaving the final count of 6 articles for review.

Results: Of the 9 articles screened, 6 were chosen for further analysis in this systematic literature review.

Conclusion: Ultrasound is an imaging modality with high specificity and sensitivity in detecting Gout in the 1st MTPJ. Ultrasonography has the ability to detect gout in 1st MTPJ in the absence of flares, in asymptomatic patients, and in acute and chronic stages.

Key Words:
Gout/diagnosis, Ultrasonography, First Metatarsophalangeal Joint.

Level of Evidence: 4
Gout is a form of inflammatory arthritis capable of affecting various joints in adults. Although the reason remains unclear, gout commonly affects the 1st metatarsophalangeal joint (MTPJ). It is suspected that the 1st MTPJ is at constant risk of being affected because of the physical stress placed on it during the normal gait cycle. There is a higher incidence of gout in men than in women and in individuals exhibiting structural and functional deformities such as Hallux limitus and Hallux rigidus. Other risk factors for developing gout include diet, obesity, family history of gout, and certain medications.

The acute phase of the disease is marked by active synovitis. Individuals with acute gout usually present with a sudden onset of severe pain, swelling, warmth, and redness at the affected joint or joints. If left untreated, acute gout can transform into chronic gout, which is characterized by the formation of tophi and repetitive gout attacks. Tophi can become swollen and tender during gout attacks and can lead to structural or functional deformities within the affected joint or joints.

For patients with the above clinical signs and symptoms, a definitive diagnosis for gout according to The European League Against Rheumatism (EULAR) states that the affected area must demonstrate “monosodium urate (MSU) crystal in synovial fluid or tophus.” Current diagnostic tools for the detection of gout include a joint fluid test at the affected joint, a blood test to measure uric acid levels and creatinine in blood, X-ray imaging, and CT-scan. Although all these diagnostic tools have been sufficient in diagnosing gout, use of Ultrasonography is increasingly becoming popular in comparison to other modalities.

In recent years, Ultrasonography has been proposed as an alternative diagnostic technique for gout. Ultrasonography provides a less invasive procedure that allows for the evaluation of the severity of urate deposition at the affected joint and the response to urate-lowering treatments. According to the 2015 Gout Classification Criteria determined by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR), “the most well-recognized ultrasound feature present in [individuals] during [acute] and [chronic] stages of gout” is known as the double contour sign.” The double contour sign is the presence of MSU crystals along the surface of articular cartilage. Ultrasonography also has the ability to visualize soft tissue and joint damage, therefore making it an ideal diagnostic technique for the diagnosis of both acute and chronic gout. The aim of this systematic review is to determine the efficacy of ultrasound as a diagnostic tool for the presence of gout in the 1st MTPJ.
METHODS

A systematic search was performed using PubMed database with the following query: ("Gout/diagnosis"[MeSH] OR ("Gout" AND "Diagnosis")) AND ("Ultrasonography"[MeSH] OR "Ultrasound" OR "Ultrasonographic") AND "First Metatarsophalangeal Joint". Inclusion criteria included English articles with a publication date between 1/1/2012 and 11/10/2017 applied only on human subjects. After application of the inclusion criterion, the query returned 9 results. The authors excluded articles involving joints other than the first metatarsophalangeal joint, leaving the final count of 6 articles for review. Figure 1 depicts a flow chart of the methods.

RESULTS

In a prospective case-control single center study performed by Norkuviene E et al., assessment of the concordance between US findings and microscopic evaluation of MSU crystals was analyzed. Aspiration of 45 intra-articular tophi was found by US examination (39 randomly selected with gout and 6 from healthy controls). MSU crystals were microscopically identified in 80% (36/45) of participants, all of which originated from the 1st MTPJ. Thirty-six tophi detected in the 1st MTPJ by US examination were confirmed as MSU (monosodium urate) crystal identification in 75% of participants. In the 5 joints with the DC (double contour) sign only present on US examination, crystals were found in 80% (36/45) of cases. The presence of both tophus and the DC sign on US examination showed 100% concordance with MSU crystal identification.

Stewart et al. had a comparative study identifying the ultrasound features of the 1st MTPJ in gout and asymptomatic hyperuricemia, in comparison to normouricemic controls. Results found that, out of 86 participants (83 % with history of 1st MTPJ acute arthritis and 26% had 1st MTPJ with clinical evidence), the presence of the double contour sign in US examination and the presence of tophus in the diagnostic group are significantly associated with higher MFPDI (Manchester Foot pain and Disability index) scores (P <0.001), increased 1st MTPJ
temperature (P = 0.005) and reduced walking velocity (P = 0.001).\textsuperscript{2} The double contour sign was the most common ultrasonographic feature of urate deposition found in both gout and asymptomatic hyperuricemia groups. However, only the gout cohort exhibited tophi at the 1st MTPJ. Synovitis was more commonly found in the gout group compared to the other two groups as well. Joint effusion was exhibited more commonly in the asymptomatic hyperuricemia group compared to the gout group. Synovial hypertrophy was less commonly observed, displayed only 2–11% of joints. Bone erosion was present in 15 (33%) patients in the 1st MTPJ of the gout group, 2 (3%) of patients in the control group, and 1 (2%) of patients in the asymptomatic hyperuricemia groups.\textsuperscript{1}

In another cross-sectional study by Stewart et al, they analyzed the association between ultrasound findings and foot pain and function in gout, asymptomatic hyperuricemia and normouricemic groups. They found that the interaction effect between the sonographic feature and diagnostic group was significant in most of analyses (data not reported), indicating the association between the ultrasound and the clinical variables were different across the groups.

A cohort study conducted by Reuss-Borst et al. to investigate the gout-specific US findings in 74 patients with musculoskeletal problems. 58 had hyperuricemia and 27 had a history of out. 888 joints were included from 74 patients. US imaging demonstrated that the DC sign was the commonly described pathological finding, specifically in joints of gout patients compared to HU (hyperuricemic) patients. The sonographic findings detected in the 1st MTPJ in 16/22 (73%) of asymptomatic patients, but normal sonographic findings in 3/26 (12%) previously affected 1st MTPJ. The DC sign was found in 17/62 (27%) 1st MTPJ. However, in 17/31 (55%) patients, the investigator described as echogenic structures and/or double contour signs in 1st MTPJ. First MTPJ synovitis and erosions were found in 5/31 hyperuricemic, but 11/192 (6%) normouricemic controls joints showed pathological ultrasound findings.\textsuperscript{6}

A pilot study by Peiteado et al. used ultrasound scanning on 29 patients, 60% of them had swollen joints and 59% had joint pain during the examination time. Twenty-seven patients (93%) had at least one characteristic sign detected via ultrasound on the 1st MPJ. The characteristic signs detected by the US were hyperechoic spots in the synovial fluid, hyperechoic cloudy areas, bright stippled aggregates and double contour sign. These signs were considered gout-related elementary lesions.\textsuperscript{3}

Yin et al. conducted a comparative study between static images acquired via gray scale US and MicroPure US techniques of 36 patients, (MicroPure is a new US image processing function that is designed to improve the visualization of microcalcifications). Those patients were
diagnosed with gout, had history of acute gouty arthritis in the 1st MTPJ with last acute attack from 1 to 15 years, and abnormal serum uric acid level (male: >416 µmol/L, female: >357 µmol/L). Some microcalcifications were observed in the 1st MTPJ by gray scale US and MicroPure. The investigators had different opinions regarding the MicroPure image quality. However, MicroPure US reported statistically significant fewer artifact than gray-scale US (p<0.009). Also, MicrPure identified more microcalcifications compared to the grey-scale US.5

DISCUSSION

Although the current gold standard for the diagnosis of gout is the identification of MSU crystals in synovial fluid microscopically, it is not always performed in medical practices and can be difficult to use in the early stages of the disease.2,4,5,6 Ultrasonography is not currently part of the standard diagnostic tools for gout, but studies have shown that this imaging modality accurately diagnoses gout by detecting the strong US wave reflection produced by MSU crystals.2 Several authors in this review demonstrated that the most sensitive sonographic indication of gout was the presence of tophi in the 1st MTPJ, which is also the joint most often involved in early stages of gout.4,5,6

Stewart et al. states that “urate deposition, soft tissue inflammation, and bone erosion” at the 1st MTPJ are ultrasound characteristics seen in patients with gout who present with clinical symptoms of inflammation and painful arthritic episodes.1 Patients with asymptomatic hyperuricemia do not demonstrate signs of inflammation or bone erosions upon US examination, however, they show a similar frequency of urate deposition (DC sign) as those with gout (36% versus 37%).1 Stewart et al. also indicates that sonographic features of urate deposition in asymptomatic patients may help explain why these patients still experience foot pain, gait impairment and functional disability in contrast to people with normal urate levels.2

Norkuviene et al. examined the presence of tophi in various joints in the upper and lower extremity in patients who were at distinct stages of gout disease. Individuals with early stage gout showed overall less tophi and DC signs compared to those in late stages of gout.4 This study found that the 1st MTP and ankle joints may be most commonly involved in the initial stages of gout development.4 Norkuviene et al. concludes that tophus deposition in the 1st MTPJ was the most sensitive US sign for gout in all stages.4

Peiteado et al. refers to US as a “useful and feasible short” test that is not only reliable based on the elemental lesions studied (1st MTPJ, midtarsal, ankle and knee)
but also on the anatomical locations of the lesions. US test is feasible because it can be performed and interpreted quickly. Ultrasonography can be used as a complementary test to diagnose gout, to study disease course and evaluate patient response to treatment.

Yin et al. concluded that MicroPure, a new US technique, has higher value identifying the microcalcifications within the joint cavity compared to grey-scale US. The use of MicroPure is predicted to be most effective in diagnosing early gouty arthritis in early stages.

Diagnosing gout in the early stages of the disease is difficult using the gold standard, predisposing patients to develop asymptomatic joint damage which may present as musculo-skeletal problems. Reuss-Borst et al. states that employing US as an imaging tool to confirm the structural changes in the early phases of gout disease may allow physicians to start urate-lowering therapy sooner, prevent the clinical manifestations and delay disease progression.

LIMITATIONS

One major limitation of this review was the exclusion of US studies on other foot and ankle joints. Additionally, Peiteado et al. suggests that US reliability as a diagnostic tool relies on the level of expertise of US readers. As new US techniques are developed, further studies with larger sample sizes, inclusion of both genders, and a more rigorous selection process will be needed to validate their use.

CONCLUSION

This systematic review emphasizes the efficacy of ultrasonography and its diagnostic value in patients with acute and chronic gouty arthritis. This review also enlightens on the high sensitivity of ultrasound in early detection of MSU deposition on the first MTP joint. It also supports the use of US in patients with asymptomatic hyperuricemia associated with foot pain or functional impairment to identify the musculoskeletal structural changes mainly at the first MTP joint before the development of the typical inflammatory clinical picture of gout. This early identification of subclinical crystal deposition, synovitis, bony erosion, and other structural changes can prevent further impairment and disability by early appropriate intervention, including urate-lowering therapy. This systematic review highlights the use of musculoskeletal ultrasonography as a screening tool for the diagnosis of subclinical gouty arthritis based on its reliability, safety, and sensitivity.

AUTHORS’ CONTRIBUTIONS

All authors participated equally in the conception of the research topic, literature
review, and extraction of data. All authors agreed upon the final submission.

**STATEMENT OF COMPETING INTERESTS**

All authors declare they have no competing interests.

**REFERENCES**


The Involvement of miRNA’s in Diabetic Foot Ulcer Healing

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Abstract

Introduction: Diabetes Mellitus (DM) is a chronic disease and its incidence and prevalence is rapidly increasing over time. DM is known to be associated with numerous complications and the disruption of the normal wound repair process is one of the major concerns. Diabetics are at a high risk of developing diabetic foot ulcers (DFU); this often leads to lower limb amputations, long term disability, and a shortened lifespan. Despite the severity of the complications DM causes, the pathophysiology of DM on human foot skin biology remains widely unknown. Recently, a number of biomarkers like microRNAs (miRNA) have been profiled to gain a better understanding of its involvement in DFU healing. Current studies have indicated the importance of miRNAs in the regulation of gene expression in various cells of the skin, including stem cells, immune cells and keratinocytes. This review aims to evaluate the involvement of miRNA in DFU wound repair and healing based on the current literature.

Study Design: Qualitative Systematic Review of Literature

Methods: Research for the systematic review was performed using the PubMed database. The database search included Medical Subject Headings (MeSH) terms and Boolean Operators (AND, OR, & NOT). A search in PubMed with the query “microRNAs” [Mesh] AND “Diabetic Foot” [MeSH]. This resulted in 9 articles. Inclusion criteria for this topic will include studies that are written in English and that uses both humans and mice as subjects. Furthermore, the inclusion criteria included articles with publishing dates restricted by the parameters (2012/08/09 [PDAT]: 2017/04/11 [PDAT]). Exclusion criteria excluded papers written about areas other than the foot and articles that did not mention diabetic wound/ ulcer healing. After applying the inclusion and exclusion criteria, a total of 6 articles were used in this qualitative systematic review.

Results: Five case studies and one case series were selected based on the inclusion and exclusion criteria. Three of the case studies profiled the effects of only one miRNA, while the others profiled three or more miRNAs. A total of thirteen miRNAs are profiled in this review. Out of the thirteen miRNAs, four were shown to be downregulated in DFU, leading to impaired wound healing and nine miRNAs were upregulated. Out of the six literatures, only one reported no statistical significance between the miRNA expressed in DFU and non-diabetic foot ulcers.

Discussion: A number of miRNAs were shown to be differentially expressed in DFU and their expression levels varied during the course of wound healing. In contrast, Ramirez et al.’s findings suggest otherwise; their study concluded that diabetes causes only subtle changes to the foot skin morphology and that mRNA and miRNA levels are not affected in a major way. Moreover, they believe concomitant health concerns, such as neuropathy, vascular complications, or duration of DM, plays an important role in further disabling the tissue’s healing process, leading to the development of DFUs.

Key Words: Diabetic foot ulcer, microRNA, wound healing

Level of Evidence: 4
INTRODUCTION

Diabetes Mellitus (DM) is a metabolic disease that impacts people globally. According to the World Health Organization, it is estimated that 422 million adults were living with diabetes in 2014, with its global prevalence being almost doubled since the 1980’s, rising from 4.7% to 8.5% in the adult population.

For years there have been an enormous amount of research being carried out for new drug discovery for DM. Unfortunately, it still remains to be an ‘untreated’ disorder and the drugs can only control sugar levels and cannot provide complete cure for the disease. DM if uncontrolled, may lead to chronic complications.

Lower limb ulcers are a major complication associated DM and have been shown to “precede amputation in up to 90% of the cases.” Some of the underlying causes of these ulcers include peripheral neuropathy, trauma, high plantar pressures and ischemia from peripheral vascular disease (PAD). Diabetic patients have up to a 25% lifetime risk of developing a foot ulcer. DFU in patients occur as a consequence of multiple risks factors interacting with one another. Some of the risk factors include forms of nerve damage and altered vascular circulation, duration of diabetes, age, blood pressure, blood glucose levels and smoking. Genetic factors and ethnicity can also play a significant role in the development of diabetic neuropathy leading to DFU. DFU has been proven notoriously difficult to treat and is associated with high amputation rates and mortality. It is known that limb amputation occurs because of limb amputation is a consequence of series of events and conditions, one of them being medical treatment failure. It further disables the patient, and decreases quality of life, all of which contributes to high morbidity, mortality and health care costs. Regrettably, the role of molecular and genetic expression involved in the causation and treatment of wounds have yet to be compellingly proven. To date, various markers have been reported and published, however “none have gained widespread acceptance, because of the lack of specificity and accuracy.”

Wound healing is a common physiological response to injury and involves the integration of complex biological and molecular events which causes cell migration, proliferation and extracellular matrix deposition. The involvement of various cell types like platelets, macrophages, endothelial cells, fibroblasts and keratinocytes are also required.

DFU is a chronic wound that has impaired healing due to “poor blood supply, impaired leukocyte function, infection, and excessive callus formation.” Normally in healthy individuals, acute wounds progress through phases of wound healing linearly, whereas chronic wounds in diabetic patients become stalled in different phases, and
progression does not occur in synchrony due to a variety of different ailments like diabetes associated neuropathy, microangiopathy, and impaired immune function. At a cellular level, diabetic wounds are described to have an increased number of acute inflammatory cells and reduced levels of growth factors. The constant presence of the inflammatory cells, mainly neutrophils and macrophages, generate proinflammatory cytokines, proteolytic enzymes, and reactive oxygen species at the wound site. As a result, it compromises the environment for wound healing. Furthermore, re-epithelialization is impaired because of the inability of the keratinocytes to migrate and differentiate. In addition, oxidative stress is enhanced due to the high-glucose environment in diabetic skin and this increases the inflammatory response of keratinocytes, furthering the damage to an already impaired healing process. It has been suggested that the impaired healing process of DFU’s may be due to molecular mechanisms underlying these abnormal cellular functions just described.

MicroRNAs (miRNAs) are a group of small non-coding single stranded RNA molecules that negatively regulate gene expressions mainly through the 3’-untranslated region (3’-UTR) binding of target mRNAs. miRNA’s are transcribed by RNA polymerase II enzymes and it forms long primary transcripts (Pri-miRNA). These pri-miRNAs are processed in the nucleus by a RNAse III enzyme called Drosha, to form precursor miRNA (Pre-miRNA). The Pre-miRNAs are then transported to the cytoplasm for further processing by a RNAse III enzyme named Dicer. Dicer causes a production of a 22-nucleotide long mature miRNA. The mature miRNA then gets incorporated into a RNA- induced silencing complex (RISC) and mediates the silencing of target genes. With the discovery of miRNAs, it has led scientists to map out its role in various cellular processes involved with issues like stress response, angiogenesis, cells death, carcinogenesis, neurological disorders, metabolic diseases and more recently wound healing. Recent studies have demonstrated the importance of miRNAs in the regulation of gene expression in various cells of the skin. Interestingly, a number of miRNAs have been shown to be differentially expressed in diabetic skins and its expression levels varied during the course of the wound healing process.

The purpose of this systematic review is to document the miRNAs researchers have discovered over time, which are directly involved with the wound healing and repair process of diabetic foot ulcers.

**METHODS**

The author performed a systematic search utilizing the PubMed database. The database search included Medical Subject Headings (MeSH) terms and Boolean Operators (AND, OR, & NOT). A search in
PubMed with the query “microRNAs” [Mesh] AND “Diabetic Foot” [MeSH]. This resulted in 9 articles. Inclusion criteria for this topic are studies that are written in English and studies involving both humans and mice as subjects. Other inclusion criteria include articles with publishing dates restricted by the parameters (2012/08/09 [PDAT]: 2017/04/11 [PDAT]). Exclusion criteria are papers written about areas other than the foot and articles that did not mention diabetic wound/ulcer healing. After applying the inclusion and exclusion criteria outlined in Figure 1, a total of 6 articles were used in this qualitative systematic review. A summary of the methods used is illustrated in Figure 1.

RESULTS

Six articles were selected based on the inclusion and exclusion criteria. Three of the case studies only profiled the effects of only one miRNA, while the others profiled three or more miRNAs. A total of thirteen miRNAs are profiled in this review. A complete miRNA profile showing which miRNAs are downregulated and upregulated and their role in wound healing is outlined in

![Figure 1. Acquisition of articles from the PubMed Database based on inclusion and exclusion criteria (6 articles were selected)](image-url)
Figure 2. Out of thirteen of the miRNAs, four miRNAs were shown to be downregulated and nine miRNAs were upregulated in DFU leading to impaired wound healing. Out of the six articles, only one reported no statistical significance between the miRNA expressed in DFU and non-diabetic foot ulcers, thus leading to the result that this particular miRNA has no impact on wound healing on its own.\textsuperscript{1} miRNA-503 was the only miRNA that was reported in two different studies, but both reported similar results; miR-503 causes diabetic vascular complications. Jhamb et al.\textsuperscript{3} showed the role of miR-503 to be preferentially increased in diabetes and results in impaired wound healing, due to persistent ischemia (decreased angiogenesis) and Pichu et al.\textsuperscript{6} noted that a deregulation in miR-503 leads to inhibition of endothelial cell proliferation and migration. It also leads to impaired reparative angiogenesis after limb ischemia.

Liu et al. reported miRNA-203 to be differentially expressed in the varying degrees of wound progression in a diabetic foot.\textsuperscript{7} The case series looked at 46 patients who had undergone wound repairing surgery and a sample of the skin around the ulcers were collected at that time. Assessment of the miRNAs in each skin tissue sample was profiled using TaqMan probe-based quantitative real time PCR (qRT-PCR) assay. The study’s results indicated that miR-203 is the most abundant keratinocyte-specific miRNA in the epidermis and plays a great role in keratinocyte function in healthy skin. miR-203 plays an important role in the impairment of diabetic wound healing.

Li et al.’s paper on “miRNA-132 with therapeutic potential in chronic wounds,”\textsuperscript{4} evaluated the therapeutic potential of miR-132 in chronic wounds using mouse in vivo and human ex vivo wound models. Biopsy samples were collected from 29 patients with Type 2 diabetes mellitus. The control group had 8 healthy volunteers who had surgical wounds placed and biopsies were collected 7 days after deliberate injury. qRT-PCR and hybridization of miR-132 specific probes were utilized. Their study showed miR-132’s role is to inhibit inflammation and promotes growth of epidermal keratinocytes. miR-132 is required for normal skin wound healing. Inhibition or knockout of miR-132 in mouse skin in this study led to delayed wound closure and increased inflammation.

The case study by Madhyastha et al. titled “NFkappaB activation and it’s essential requirement for miR-21 induction by TGF\beta1 in high glucose conditions,”\textsuperscript{5} focused their study around miR-21. They performed RT-PCR, cell culture, transfection, immunoblot assay, and staining to gain the results discussed in this study. NIH-3T3 cells, which are embryonic mouse fibroblast cells were used to quantify the results, which indicated that miR-21 is necessary for fibroblast migration and this study shows that it is impaired in diabetic wounds.

The clinical review performed by Jhamb et al., looked at the “Genetic and molecular basis of DFU.”\textsuperscript{3} The review looked
at three different miRNAs: mir126, miR503, and miR210. miR126 depletion caused defective endothelial cell proliferation, migration and angiogenesis, which ultimately leads to impaired wound healing. miR503 is preferentially increased in diabetes and results in impaired wound healing, due to persistent ischemia (decreased angiogenesis). miR210 is transcriptionally regulated by a hypoxia inducible factor 1α. miR210’s target is the gene encoding for transcription actor E2F3. E2F3 is an important component of wound healing and an upregulation of miR210 would mean increased silencing of the expression of E2F3. Thus, miR210 leads to reduced proliferation and therefore impaired reepithelialization of DFU wounds.

Pichu et al.’s study was focused on profiling 21 different miRNAs in order to document potential miRNA biomarkers in diabetic complications. Only 4 of the 21 miRNAs played a role in diabetic vascular complications: miR-125b, miR-200, miR-320 and miR-503. The study involving miR-125 and miR-200 used vascular smooth muscle cells of diabetic mice. The study involving miR-320 used myocardial microvascular endothelial cells from Type 2 diabetic rats. Finally in the study involving miR-503, muscular specimens from the amputated ischemic legs of diabetic patients were used. As controls, calf biopsies of nondiabetic and nonischemic patients undergoing saphenous vein stripping were used. The results showed that enhanced levels of miR-125 leads to increased inflammatory gene expression by targeting histone methyltransferase. Upregulation of miR-200 has a pro-inflammatory role, where it blocks the transcriptional repressor: Zeb1. Furthermore, miR-320 regulates angiogenesis and deregulation of miR-503 leads to inhibition of endothelial cell proliferation and migration. Deregulation of miR-503 can also lead to impaired reparative angiogenesis after limb ischemia.

The only contradictory case report that was documented in this review was performed by Ramirez et al. Foot skin samples were collected from 20 patients receiving corrective foot surgery and a combination of multiple molecular and cellular approaches. A comparative analyses of non-ulcerated non-neuropathic diabetic foot skin and healthy non-diabetic foot skin was utilized. QPCR and gene expression profiling were performed. Their results indicated that both miR31-5p and miR31-3p were induced in the epidermis and there was an upregulation of miR29c-3p in primary dermal fibroblasts. However, they believed that the results did not indicate any significant value of the role these miRNAs play in DFU wound healing, which is the opposite of what various other sources have stated.
<table>
<thead>
<tr>
<th>miRNA</th>
<th>Downregulated or Upregulated in DFU</th>
<th>Role in DFU wound healing</th>
<th>Source</th>
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<tr>
<td>miR-203</td>
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<td>Role in keratinocyte function. Upregulation of it causes impaired wound healing in diabetics.</td>
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<td>miR-21</td>
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<td>Madhyastha et al.</td>
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<td>miR-31-3p</td>
<td>Upregulated</td>
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<td>MiR-320 regulates angiogenesis.</td>
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**Figure 2.** Complete miRNA profile from the six case studies
DISCUSSION

Chronic diabetic wounds pose a clinical challenge and are often a major burden to the health care system. At the cellular level, diabetic wounds are characterized by pro-inflammatory state, coupled with the absence of proliferation and migration of cells, in addition to narrowing or occlusion of blood vessels within the wound edge.\(^5\)

In patients with diabetes, wound healing is severely impaired and is deemed chronic when healing is delayed beyond 8 weeks. At the cellular level, patients with diabetes experienced prolonged inflammation, impaired neovascularization and decreased synthesis of collagen.\(^2\) There are multiple factors that contribute to the impairment of diabetic wound healing.

Foot ulcers are one of the most serious complications and is associated with high morbidity and poor prognosis; they not only have a significant impact on the quality of life, but also bring a great burden on the family and to the society.\(^7\) Therefore it is imperative to come up with different therapeutic approaches to aid in the wound repair process.

A molecular genetic approach has the potential to be a therapeutic strategy to treat diabetic wounds. One such molecular approach could be the application of miRNAs. MiRNA’s are known to have a regulatory role in cellular functions via its ability to modify post-transcriptional mechanisms and suppress target gene expressions.\(^6\) There is a vast amount of evidence that suggest the diverse role miRNA has in various biological processes. Recent evidence suggests that dysregulation of specific miRNA is critical in derailing the healing sequence in chronic wounds.\(^7\)

Based on the literature review it can be suggested that miRNAs play an important role in in the regulation of various cells of the skin, including stem cells, immune cells and keratinocytes. Moreover, accumulating evidence have shown that miRNAs play a key role in contributing to the general pathology of diabetes. For example, in Liu et al.’s study, skin-enriched miR-203 were easily detected in skin tissue samples, however in comparison to the normal skin tissue, patients with DFU displayed a significantly higher expression of miR-203.\(^7\) This study’s results indicate miR-203 to have a positive correlation with the severity of diabetic foot ulcers, which can now serve as a new, accurate and validated bio-marker for evaluating the severity of DFU’s in the clinic. Dysregulation of this specific miRNA is critical in derailing the healing sequence in problematic chronic wounds.

On the other hand, miR-132 had significantly reduced expression in human diabetic foot ulcers compared to normal skin wounds. In comparison to miR-203, whose upregulation caused dysfunction in the healing process, local replenishment of miR-132 in the wounds of db/db mice
showed to accelerate the wound closure effectively and caused increase proliferation of wound edge keratinocytes and reduced inflammation.  

Throughout the review of each case report, the study by Madhyastha et al. showed that other factors also play a role in miRNA expression as well. According to their study performed on NIH3T3 cells, TGFβ1 plays a key role in miRNA stimulation in diabetic patients; TGFβ1 stimulates miR-21 in fibroblasts that are subjected to high glucose environment. However, TGFβ1 is remarkably reduced in DFU and chronic venous ulcers. This study’s results show that “manipulation of TGFβ1-NFKB-miR21 pathway could serve as an innovative approach towards therapeutics to heal diabetic foot ulcers.” This study indicates that TGFβ1 treatment can enhance healing in diabetic wounds by its effects on miR-21 that is necessary for fibroblast migration. TGFβ1 is important because it is known to activate the NFKB signal pathway and interact with Smad proteins, both of which are key players in the transcription of miR-21. The promoter region of miR-21 gene has two potential NFKB binding sites and regulation of miR-21 by TGFβ1 requires it to activate the NFKB signaling pathway. In addition, TGFβ1 can directly regulate miR-21 transcription through Smad proteins, however “the exact role of Smad proteins in the regulation of miR-21 in high glucose conditions still needs to further clarified.” Furthermore, topical injection of TGFβ1 has been reported to restore tensile strength of collagen, induce accumulation of granulation tissue and accelerate wound closure.

In addition, miR-126, miR-503, and miR-210 all showed significant involvement in causing impaired diabetic wound healing. Only one of the studies focused in this review stated that there is no statistical significance of miRNA involvement in DFU wound healing. The Ramirez et al. study concluded that “human diabetic non- neuropathic foot skin shows minor differences at the transcriptional, miR levels, or tissue morphology, compared to non- diabetic foot skin.” They believe that additional DM-associated complications like neuropathy, duration of DM, or vascular problems may have a more important role in the development of DFU. The study found 22 miRs that regulated (some upregulated and some downregulated) greater than 2-fold between diabetic and healthy non-diabetic foot fibroblasts, however none of the miRs achieved statistical significance.

Presently, there are current therapeutic advances being made in utilizing these biomarkers. As mentioned earlier, miR-132 has been identified to be down-regulated in diabetic wounds. miR-132 is the top up-regulated miRNA in the inflammatory phase of human normal skin wound healing and is known to inhibit inflammation and promotes growth of epidermal keratinocytes. Several other miRNA-based therapies have entered the clinical trial phase, showing promising results and few adverse effects; for example,
Li et al. evaluated the therapeutic potential of miR-132 in chronic wounds using mouse in vivo and human ex vivo wound models.

Local replenishment of miR-132 in skin wounds was performed to evaluate the therapeutic potential of miR-132 in wound healing. “Synthetic double-stranded miR-132 mimics encapsulated within a neutral lipid emulsion” were used to enhance delivery and to assure in vivo toleration. Based on the results, miR-132 has been confirmed to promote skin wound healing in a mouse model with type 2 diabetes. Intradermal injection of miR-132 mimics into the wound edges of db/db mice significantly accelerated wound closure and showed an increased number of proliferating keratinocytes seen via Ki-67 staining, compared to the samples receiving control mimics. Thus, by locally applying miR-132 mimics onto skin wounds, an efficient elevation of the miR-132 expression in the wounds were noted and accelerated wound closure occurred. These findings suggest that miR-132 replacement treatment should be further evaluated in controlled trials as potential therapy for DFUs.

Pichu et al. and Jhamb et al. conducted clinical reviews about the role of biomarkers in DFU. Although Pichu et al. listed various biomarkers in diabetes, its primary focus was on compiling a summary of the miRNAs relevant to diabetes and its complications, based on findings previously reported by other studies. It highlighted miRNAs involved with diabetic nephropathy, retinopathy, cardiomyopathy and vascular complications. Pichu et al. wanted to compile different molecular and genetic components involved in DFU wound healing. They believe that a multifocal approach is essential for the effective management of DFU. Similarly, Jhamb et al.’s clinical review’s aim was to evaluate if current literature indicates a molecular and genetic basis for DFU. They wanted to speculate current methods of investigation and possible clinical applications. They mainly focused on three miRNA's: miR-126, miR-503, and miR-210. Jhamb et al. believes that research on biomarkers will provide opportunities to develop tools for early diagnosis of the disease and its complications and may also serve as targets for new drug development. Both reviews examined miRNA’s association with DFUs and how it can help to identify some of the complications behind DFUs. The idea is to utilize these potential biomarkers as diagnostic and therapeutic tools for the future.

**CONCLUSION**

DFUs consist of a variety of molecular and cellular components that have the potential to promote or inhibit wound healing. Understanding these components will help develop targeted therapies specific to each individual patient. Currently, miRNAs relevant to diabetic complications can be considered a potential biomarker, however...
validation of these specific miRNA’s as biomarkers need to be established.6

The aim of this review was to evaluate if current literature indicates any relationship between diabetic foot ulcers and miRNA. The goal of profiling every miRNA reported in the six articles, was to gain a better understanding of the role miRNA plays in DFU wound healing.

Based on the review of all six articles, it is concluded that there is a strong correlation between the expression of miRNA and the level of wound healing in DFU. Furthermore, miRNA-based therapy strategies show great potential, which can possibly provide promising results and fewer side-effects, compared to the pharmaceutical drugs we often rely on. Moreover, this can be aided by the development of both in vivo and in vitro delivery strategies; for example, with the increasing rise of nanotechnology, miRNA-based therapy strategies has shown great potential in gene manipulation to aid in wound repair and healing.

**STATEMENT OF COMPETING INTERESTS**

I declare that I have no competing interests.

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Characteristics Among Adult Patients with Diabetes Who Received a Foot Exam by a Health Care Provider in the Past Year: an Analysis of NHANES 2011-2016

John Twarog, Maham Subhani, Janet Jeong, Elizabet Peraj

Abstract

INTRODUCTION: According to the American Diabetes Association (ADA), annual foot exams should be performed in diabetic patients to identify and reduce risk factors for ulcers and other complications. Little is known regarding factors that may increase or decrease the likelihood of having an annual foot examination by a health care provider (HCP) as well as the long-term effects this may have. The data includes diabetics 20 years and older who were included in the National Health and Nutrition Examination Survey conducted from 2011-2016. We performed a regression analysis with adjustment for variables including age, ethnicity, and other variables that may impact the frequency of a diabetic foot exam.

METHODS: Cross-sectional analysis of 10,905 patients age 20 years and older with a previous diagnosis of diabetes. Patients selected for inclusion in NHANES receive an in-home interview and then undergo a comprehensive physical at a CDC mobile examination center. The adjusted odds ratios for a patient having received a foot exam in the past year were conducted using appropriate weighting variables assessed with logistic regression analysis.

RESULTS: The factor that showed the greatest likelihood of receiving a foot exam by a HCP in the last year was having insurance [adjusted odds ratio (aOR): 2.33 (1.67, 3.25)]. Diabetics with hypertension were also more likely to have had a foot exam by a HCP in the last year [aOR 1.54 (1.09, 2.17)]. Both Hispanic Americans with diabetes [aOR 0.62 (0.47, 0.82)] and Asian Americans with diabetes [aOR 0.65 (0.44, 0.97)] were significantly less likely to have had a foot exam by a HCP in the last year, when compared to non-Hispanic White Americans.

CONCLUSIONS: Having health insurance and hypertension were both shown to result in a greater likelihood of having a foot exam by a HCP in the last year. This is not surprising since those with health insurance are more likely to see a HCP and those with other health problems may see a HCP more frequently. Hispanic Americans and Asian Americans with diabetes were significantly less likely to have had a foot exam by a HCP in the last year. This is significant since Hispanic Americans and Asian Americans are more prone to diabetes and foot complications compared to whites.
INTRODUCTION

Both the American Diabetes Association (ADA) and the International Working Group on the Diabetic Foot (IWGDF) recommend annual foot exams for diabetic patients to identify and reduce risk factors for ulcers and peripheral artery disease (PAD).\(^1,2\) It is estimated that between 19% and 34% of people with diabetes will develop foot ulcers in their lifetime.\(^3\) The factors that determine whether a diabetic patient will return to their health care provider (HCP) annually for a foot exam remain unexplored. Educating patients about diabetes-related foot issues is believed to encourage patients to seek regular preventative care, but without frequent interventional efforts, high-risk patients become negligent within 6-12 months.\(^4\) Cultural differences can prevent effective diabetes education, which could also contribute to a decreased likelihood of patients returning for annual foot exams.\(^5\) Factors that could also impede patients from returning for annual foot exams include age, ethnicity, culture, and income have not been adequately investigated.

Considering the risks associated with an unmanaged foot ulcer, the importance of an annual diabetic foot exam cannot be overstated. Compared to ulcer-free diabetic patients, diabetic patients that do develop foot ulcers are 2.5 times more likely to die within 5 years of their first foot ulcer visit to a HCP.\(^6\) It is estimated that up to 20% of diabetic foot infections result in amputation, and diabetic patients with PAD have an increased risk of infection and amputation.\(^7\) If an ulcer does lead to some level of amputation, the risk of death within 5 years increases to 70%.\(^8\) Once a diabetic patient has had an foot ulcer, they are 40% more likely to have a recurrence within the first year, increases to 65% within 5 years.\(^3\) Recurrence is so likely that patients with closed ulcers are considered to be in remission, as opposed to being healed.\(^3\)

This investigation seeks to assess the various factors which may increase or decrease the likelihood that patients with diabetes have an annual foot exam by an HCP. We used data from the National Health and Nutrition Examination Survey (NHANES) from 2011-2016 to perform a regression analysis on subjects with diabetes aged 20 years and older, including variables such as age, ethnicity, culture, and access to insurance and healthcare.

METHODS

Study Population

The NHANES is an ongoing, stratified, multi-stage probability sample of the U.S. non-institutionalized population designed to represent the health and nutritional status of the general population.\(^9\) Data collected for NHANES has been de-identified by the CDC, thereby exempting our study from the NYCPM IRB. We obtained
data on 2,270 U.S adults aged 20 years and older whom had received a previous diagnosis of either Type-1 diabetes or Type-2 diabetes. After excluding those with invalid or missing data on BMI (n=43 (2227), foot exams by a HCP in the past year (n=28) (2099), health insurance (n=1) (2098), household income level (n=204) (1894), and blood pressure (n=64) (1830) the final study population was 1,830 adults aged 20 years and older with a previous diagnosis of diabetes (81% of the initial population selected for inclusion).

**Diagnosis of Diabetes**

Individuals were asked “Other than during pregnancy, {have you/has SP} {Have you/Has SP} ever been told by a doctor or health professional that {you have/{he/she/SP} has} diabetes or sugar diabetes?” Those whom responded “yes” were classified as having a previous diagnosis of diabetes and selected for inclusion in the study.

**Diabetic Foot Exam in the Past Year**

Individuals were asked “During the past 12 months, about how many times has a doctor or other health professional checked {your/SP’s} feet for any sores or irritations?” Those who reported at least a single foot exam by a HCP were classified as having had a foot exam in the past year, while those who did not report a foot exam in the past year were classified as “no.”

**BMI**

Anthropometric data on body weight and height were collected from the adults in the Centers for Disease Control and Prevention (CDC) Mobile Examination Center and used to calculate BMI values based on current CDC guidelines. Individuals with a BMI value below 25 were classified as “Healthy Weight,” while individuals with BMI values between 25 and 29.99 were classified as “Overweight,” while those with a BMI value of 30 or above were classified as “Obese.”

**Blood Pressure**

The combined average of up to three brachial systolic and diastolic blood pressure readings were used to determine systolic and diastolic blood pressure values. Individuals with a mean systolic blood pressure reading of 140 mmHg, and/or a mean diastolic blood pressure reading of 90 mmHg were classified as having hypertension. Additionally, individuals who were currently taking a prescription medication for high blood pressure were also classified as having hypertension, based on CDC guidelines. The appropriate size blood pressure cuff was determined for participants based on the size of mid-arm circumference.

**Health Insurance**
Information on health insurance was obtained during the Health Insurance Questionnaire portion of the in-home interview. The participants were asked “Are you covered by health insurance or some other kind of health care plan? [Include health insurance obtained through employment or purchased directly as well as government programs like Medicare and Medicaid that provide medical care or help pay medical bills.]” Those whom responded “yes” were classified as having a health insurance, while those who responded no were classified as not having health insurance.

**Race/Ethnicity**

Individuals self-reported their race/ethnicity as either “Non-Hispanic White”, “Non-Hispanic Black”, “Hispanic or Mexican American”, “Non-Hispanic Asian”, or “Other Race- Including Multi-Racial”.

**Family Income**

Participants were asked to report their annual family income and any other sources of income, which was then used to calculated a family monthly poverty level index according to Guidelines from the Department of Health and Human Services. Participants with a monthly poverty level index of ≤1.30, the federal requirement to receive aid from the Supplemental Nutrition Assistance Program (SNAP) were classified as “poor”. Individuals with a monthly poverty level index > 1.30 but ≤1.85 were classified as “near poor”, and those individuals with a monthly poverty level index > 1.85 were classified as “stable”.

**Statistical Analysis**

We calculated weighted frequencies, adjusted odds ratios, and associated 95% confidence intervals. Using logistic regression, we estimated the adjusted odds ratios of individuals with diabetes having received a foot exam in the past year while controlling for several variables, including; gender, age, race, BMI, blood pressure, health insurance, family income and among SNAP recipients compared to eligible non-recipients. Individuals with diabetes who did not report having received a foot exam by a HCP in the past year served as the reference. We report these associations for all adults in the study sample using the appropriate weighting and nesting methods according to NHANES standards. Data were analyzed with SAS (Version 9.3. Cary, NC SAS Institute Inc. 1990).

**RESULTS**

Individuals with diabetes who reported having health insurance were significantly more likely to report having had a foot exam in the past year when compared to those individuals with diabetes whom were
uninsured (aOR): 2.33 (1.67, 3.25)]. Patients with diabetes who also had a previous diagnosis of hypertension were also more likely to have had a foot exam by a HCP in the last year when compared to individuals with healthy blood pressure [aOR 1.54 (1.09, 2.17)].

In terms of race/ethnicity, several subpopulations were significantly less likely to have received a foot exam in the past year when compared to non-Hispanic white Americans (Caucasians). Both Hispanic Americans with diabetes [aOR 0.62 (0.47, 0.82)] and Asian Americans with diabetes [aOR 0.65 (0.44, 0.97)] were significantly less likely to have had a foot exam by a HCP in the last year, when compared to non-Hispanic white Americans (Caucasians).

**DISCUSSION**

Healthcare professionals have a responsibility to address ethnic disparities in the quality of care provided. This article highlights the variance in likelihood of receiving annual foot examinations, as well as the disparities within the Hispanic and Asian American populations in obtaining yearly diabetic foot exams when compared to non-Hispanic white Americans (Caucasians). This is significant given that the prevalence of diabetes is higher among Hispanics (22.6%) and Asian Americans (20.6%) compared to the lower prevalence in Caucasians (11.3%). Because of the increased likelihood of diabetic patients to develop foot ulcers and other complications of diabetes, it is detrimental and worrisome that populations with higher rates of diabetes are not receiving regular examinations that are an essential component in disease prevention and management.

ADA recommends several guidelines to adequately perform foot care. One of the recommendations include providing self-care education to patients. It is crucial for not only health care providers to check feet conditions and screen for high risk feet, but also for the providers to properly educate patients. In works by Chen et al, researchers examined different subtypes of diabetic care, including foot exams and eye exams across ethnicities. Chen et al. also identified an additional subtype of care as ‘diabetes self-management education’ (DSME). This shows the importance of patient education and its impact on patient outcome. Furthermore, researchers concluded access to diabetic care varies by race. Results showed that white non-Hispanics were significantly more likely to utilize healthcare services when compared to Hispanics (p<.01). Additionally, Chen et al. also identified several factors that may affect clinical care, including a positive association between possessing health insurance and receiving clinical care for diabetes (p<.05). Similarly, our cross-sectional analysis shows that both Hispanics and Asians are less likely to have foot exams in the past year. Work by Chen et al further supports that proper diabetic foot education is weak in ethnicities like Hispanics and Asians.
Conducting annual foot exams prevent not only formation of ulcers and gangrenes but also diabetic polyneuropathy. Research conducted by Jaiswal et al. studied young adults with diabetes and the prevalence of diabetic neuropathy. They concluded that youth with diabetes have a prevalence of diabetic peripheral neuropathy of 25.7% for type 2 diabetes and 8.2% for type 1. Peripheral neuropathy is a dangerous condition that indicates high risk of developing other diseases including high blood pressure and microalbuminuria.

Podiatrists should encourage patients to receive annual foot exams because failure to do so will significantly affect the patient’s quality of life.

This analysis is not without limitations. The NHANES Diabetes Questionnaire includes the use of self-reported data, therefore, the reliability of recall regarding frequency of foot exams cannot be assessed. Furthermore, the NHANES data only allows for a cross-sectional design, which prevents any direct conclusions or causal inferences made about the relation between insurance, other health conditions, or ethnicity to the odds of receiving a foot exam. However, the oversampling of data provides a good representation of individuals living in the United States and the data analyzed can be used to infer trends among these factors and to suggest the need for interventions to be put in place for positive impacts.

The data emphasizes several positive correlations. Those with insurance and other chronic health conditions are more likely to see healthcare professionals and therefore, receive a foot exam. This is anticipated, as those with health insurance not only have access to a physician but the access they have is more affordable as well. It has also been shown that individuals with hypertension are statistically more likely to have had a foot exam by a healthcare professional (HCP). This is unsurprising considering individuals with other health conditions may not only be more likely to see a HCP but may also be monitored more closely by receiving more tests and examinations. Additionally, our findings indicate that certain ethnicities (Hispanics and Asian Americans) are less likely to receive foot exams compared to, when compared to non-Hispanic Whites. This is concerning, because these groups are more at risk to developing diabetes and complications and therefore, annual examinations are essential to identify predisposing factors for ulceration and amputation.

CONCLUSION

This cross-sectional analysis confirms that individuals with health insurance are more likely to see a physician and therefore obtain regular foot examinations. In addition, those with other health conditions, such as hypertension, are also more likely to visit a
HCP and receive annual foot exams. Additionally, our analysis demonstrates significant racial disparities between those receiving regular foot checks and those who do not. Hispanics and Asian Americans were less likely to receive annual exams compared to Caucasians. Given the increased rate of diabetes in Hispanics and Asian Americans, the data suggests that this disparity in care should be addressed in order to improve the quality of care and the quality of health.

**AUTHORS’ CONTRIBUTIONS**

All authors participated equally in the conception of the research topic, literature review, and extraction of data. All authors agreed upon the final submission.

**STATEMENT OF COMPETING INTERESTS**

All authors declare they have no competing interests.

**REFERENCES**


on survival after amputation in individuals with diabetes. *Diabetes Care*, 33(11), 2365-2369.


Clinical Manifestations of HIV in the Lower Extremity: A Comparison of the Pre-vs. Post-ART Era

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Abstract

Introduction: Currently, 36.7 million people are living with human immunodeficiency virus (HIV), as reported by the Joint United Nations Program on HIV/AIDS. Since the implementation of ART (anti-retroviral therapy) in 1996, HIV mortality has decreased as much as 85%. Now allowing for HIV-positive patients to live an average of 25 years or longer after their diagnosis, this increased life expectancy caused increased potential of HIV-related illnesses. The goal of this review is to aid the clinician in identifying the signs of HIV infection in the lower extremity. This review also aims to evaluate the current literature pertaining to HIV and the lower extremity and compare them to those seen in the pre-ART era.

Study Design: Qualitative Systematic Review

Methods: Four English language literature searches were conducted using Pubmed database. All searches included Boolean Operators and MeSH terms. The first search term was established by: ("onychomycosis"[MeSH Terms] OR "sarcoma, kaposi"[Mesh Terms] OR "warts"[MeSH Terms]) AND ("HIV"[All Fields] OR "AIDS"[All Fields]) AND "foot"[All Fields]. This yielded 96 articles. The second search was created by: ("peripheral neuropathy"[MeSH Terms] OR "peripheral nervous system"[MeSH Terms] OR "neurology"[MeSH Terms]) AND ("HIV"[All Fields] OR "AIDS"[All Fields]) AND “lower extremity”[All Fields]. This yielded 25 articles. The third search included: "peripheral arterial disease"[MeSH Terms] AND ("HIV infections/complications"[MeSH Terms] OR "Anti-retroviral agents"[MeSH Terms] OR "HIV infections/physiopathology"[MeSH Terms]). This search yielded 11 articles. The final search included: "Bone Diseases, metabolic/complications"[MeSH Terms] AND ("HIV infections/complications"[All Fields] OR "AIDS"[All Fields]) AND ("femur"[All Fields] OR "tibia"[All Fields] OR "Bones of Foot"[All Fields]). This produced a total of 7 articles. Inclusion criteria included articles published in 2004 or afterward, lower extremity symptoms pertaining to HIV, and treatment of lower extremity diseases in HIV-positive patients. Exclusion criteria included literature reviews, case studies, opinion articles, articles not written in English, and articles not pertaining to the lower extremity.

Results: A total of 140 articles were assessed for screening. Once the inclusion and exclusion criteria was applied, 23 total articles were selected for final review. Based on the literature search, review of clinical manifestations was based on 4 categories: dermatology, neurology, vascular, and musculoskeletal.

Conclusion: Dermatologic, neurologic, vascular, and musculoskeletal manifestations of HIV in the lower extremity are considerably common and can be devastating to the immunocompromised if not recognized in a timely manner. It is also important to reflect on the changes in diseases as well as their presentation in the post-ART era. These manifestations may potentially be alleviated via an early and strategically planned treatment and rehabilitation plan.

Key words: Human immunodeficiency virus (HIV), plantar verrucae, onychomycosis, Kaposi sarcoma (KS), peripheral neuropathy (PN), peripheral arterial disease (PAD), osteoporosis

Level of Evidence: 4
INTRODUCTION

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that 36.7 million people are living with the human immunodeficiency virus (HIV).\(^1\) Yearly incidence approaches 2.1 million, while improved treatments expand its prevalence.\(^1\) Since its discovery in 1984, HIV and the subsequent development of acquired immunodeficiency syndrome (AIDS) has developed into a pandemic.\(^1\) The virus’ mechanism of action debilitates the immune system, attacking its crucial components, leaving patients susceptible and vulnerable to opportunistic infection and disease, affecting a multitude of body systems. The Center for Disease Control and Prevention (CDC) estimates that almost 15%, or 1 in 7, of those with HIV are unaware of their infection.\(^2\)

In the three decades since the discovery of HIV, there has been tremendous progress made in its treatment and prevention. With the implementation of ART (Antiretroviral Therapy) in 1996, HIV mortality has decreased by as much as 85%.\(^1\) ART is defined as a regimen consisting of multiple antiretroviral drugs in combination, usually consisting of three antiretroviral medications. It is estimated that ART has allowed for HIV-positive patients to live an average of 25 years or longer after their diagnosis.\(^2\) However, with increased life expectancy comes increased potential of HIV-related illnesses. Given the changing epidemiology of the HIV population, it is important to examine the consequence of prolonged survival.

The mortality rates among HIV-infected patients has decreased primarily by reduction of AIDS-related events. However, with increasing CD4+ counts associated with initiation of ART, there is a concomitant increase in non-AIDS related diseases (Figure 1).\(^3\) Other studies, such as the Flexible Initial Retrovirus Suppressive Therapies (FIRST) trial has established increasing incidence non-AIDs related diseases, including liver, cardiovascular, renal diseases, and certain cancers in HIV-positive patients.\(^3\) However, to our knowledge, there are no current studies on the clinical impact in the lower extremity.

The podiatrist has a unique opportunity in the identification and fight against HIV/AIDS, as the profession must treat all body systems when they pertain to the lower extremity. Likewise, lower extremity manifestations of the disease can present in a host of fashions. This review will stratify them into five different categories: dermatology, neurology, vascular, and musculoskeletal systems. The goal of this review is to aid the clinician in identifying the signs of HIV infection in the lower extremity, thus affording the clinician another clue in the detection of the virus as well as the ability to provide patients with an appropriate clinical plan of action. In addition, this review aims to evaluate current literature pertaining to HIV and its lower extremity clinical manifestations and contrast them to those seen in the pre-
highly antiretroviral therapy (ART) era, before it’s discovery in 1996, as reported by Clinics in Podiatric Medicine and Surgery: HIV and the Lower Extremity. This book will be of reference for “pre-ART data” used as a comparison in our findings.

**METHODS**

Four English language literature searches were conducted using Pubmed database. All searches included Boolean Operators and MeSH terms. The first search term was established by: ("onychomycosis"[MeSH Terms] OR "sarcoma, kaposi"[Mesh Terms] OR "warts"[MeSH Terms]) AND ("HIV"[All Fields] OR "AIDS"[All Fields]) AND "foot"[All Fields]. This yielded 96 articles. The second search was created by: ("peripheral neuropathy"[MeSH Terms] OR “peripheral nervous system”[MeSH Terms] OR “neurology”[MeSH Terms]) AND (“HIV”[All Fields] OR “AIDS”[All Fields]) AND “lower extremity”[All Fields]. This
yielded 25 articles. The third search included: "peripheral arterial disease"[MeSH Terms] AND ("HIV infections/complications"[MeSH Terms] OR "Antiretroviral agents"[MeSH Terms] OR "HIV infections/physiopathology"[MeSH Terms]). This search yielded 11 articles. The final search included: "Bone Diseases, metabolic/complications"[MeSH Terms] AND ("HIV infections/complications"[All Fields] OR "AIDS"[All Fields]) AND ("femur"[All Fields] OR "tibia"[All Fields] OR "Bones of Foot"[All Fields]). This produced a total of 7 articles. Inclusion criteria included articles published in 2004 or afterward, lower extremity symptoms pertaining to HIV, and treatment of lower extremity diseases in HIV-positive patients. Exclusion criteria included literature reviews, case studies, opinion articles, articles not written in English, and articles not pertaining to the lower extremity. Once inclusion and exclusion criteria was applied, 23 total articles were selected for final review. Figure 2 depicts a flow chart of the methods summarized above.

RESULTS

Dermatology

Onychomycosis

Onychomycosis is a fungal infection of the nail caused predominantly by dermatophytes, but also non-dermatophytes such as Candida albicans. There are 5 classes: distal lateral subungual, white superficial, endonyx, proximal subungual, and total dystrophic onychomycosis.

A prospective study of 60 HIV-positive patients were analyzed for clinical and mycological manifestations of onychomycosis. Surjushe et al. reported toenail involvement in 63.33% of patients and both toenail and fingernail involvement in 16.66%. Ten-percent of the patients had a positive history for diabetes mellitus and 1.66% reported peripheral vascular disease. Concomitant tinea pedis was reported in 31.66% of patients. Total dystrophic onychomycosis constituted the majority of cases (55%), followed by distal lateral subungual (35%), proximal subungual (8.33%), and distal lateral subungual (1.66%). Fungal elements were demonstrated via KOH mounts in 81.66% and cultures were isolated in 46.66%. Of those samples with isolated cultures, 21.66% were positive for

![Figure 3. Prevalence of isolated species in onychomycosis according to data from Surjushe et al.](image-url)
dermatophytes and 31.66% were positive for non-dermatophytes. Figure 3 demonstrates the causative organisms and prevalence in this patient population.\(^5\)

A single site prospective pilot study conducted by Snell et al. compared the effects of Vicks VapoRub as an alternative to traditional antifungal therapies for the treatment of onychomycosis in HIV-positive patients. Twenty subjects were recruited and cultures were collected of the affected nail(s). All patients were instructed to apply Vicks VapoRub topically to the affected area twice a day. Using OnyCOE-t questionnaire, impact on quality of life associated with the onychomycosis infection was reported each visit, with an 8.5-point increase reported as statistically significant. Of the 18 patients evaluated at 24 weeks, 83% experienced improvement of affected nails (median clearance 25%). Two of these subjects have total resolution of the infection. Two out of the 3 patients with no clearing of the affected nail(s) were non-adherent with the treatment regimen. At the baseline visit, 75% of patients reported embarrassment with appearance of their nails and 53% reported pain or discomfort. These parameters decreased by 61% and 39%, respectively, by week 24. No side effects were reported in this study.\(^6\)

In a 6-patient case series conducted by Moreno-Coutino et al., onychomycosis progression was analyzed after induction of antiretroviral therapy. All selected cases in this study demonstrated improvement with initiation of ART. Complete resolution of onychomycosis was observed without the use

<table>
<thead>
<tr>
<th>Patient #</th>
<th>% Resolution w/ cART</th>
<th>Timeframe (months)</th>
<th>Addt’l treatment post cART</th>
<th>Final resolution</th>
<th>Type of onychomycosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>8</td>
<td>Terbinafine</td>
<td>100%</td>
<td>DLSO</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>n/a</td>
<td>none</td>
<td>100%</td>
<td>DLSO</td>
</tr>
<tr>
<td>3</td>
<td>n/a</td>
<td>4</td>
<td>n/a</td>
<td>TDO (\rightarrow) DLSO</td>
<td>TDO, DLSO</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>7</td>
<td>Itraconazole</td>
<td>100%</td>
<td>DLSO</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>7</td>
<td>none</td>
<td>*</td>
<td>TDO, DLSO</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>7</td>
<td>Urea 40%</td>
<td>100%</td>
<td>PWSO</td>
</tr>
</tbody>
</table>

DLSO: distal lateral subungual onychomycosis  
PWSO: proximal white subungual onychomycosis  
TDO: total dystrophic onychomycosis  
*represents 67% of nails w/ complete resolution, and 33% w/ regression from TDO to DLSO  
\(\rightarrow\) represents regression

Table 1. Description of each case reported by Moreno-Coutino et al. Table created from data reported in study.\(^7\)
of antifungal therapy in patient 2. Table 1 represents a detailed analysis of each case.\(^7\)

**Plantar Verrucae**

Plantar verrucae are benign epidermal neoplasms caused by human papillomavirus (HPV). There are three main clinical morphologies based on causative type of HPV, verruca plantaris (HPV-1), mosaic warts (HPV-2), and punctate or seed-corn verrucae (HPV-4).\(^8\)

A retrospective cohort study by Johnston et al. sought out to examine the prevalence of plantar verrucae in HIV-positive versus HIV-negative patients. Following a survey of 504 subjects, a multivariate analysis was performed with the primary outcome as the presence of plantar verrucae and the main predictor as HIV status. Covariates included age, sex, race/ethnicity. The prevalence of plantar verrucae in HIV-positive patients was 20.6%, compared with 4.7% for HIV-negative patients. After adjusting the covariates, HIV status still revealed a positive association, such that a patient with HIV was approximately 4.4 times more likely to present with plantar verrucae.\(^9\)

In another retrospective cohort study, 39 plantar verruca lesions in 17 individuals were examined. Lesions were diagnosed by a podiatric physician, classified by clinical morphology, and biopsied for strain detection via polymerase chain reaction. In HIV-positive patients, HPV-2 was most commonly isolated (52.6%), followed by HPV-27 (27.3%) and HPV-57 (22.7%). In HIV-negative patients, HPV-27 was most commonly isolated (87.5%), followed by HPV-2 (6.25%) and HPV-57 (6.25%). When assessing clinical morphology, HPV-2 and HPV-27 composed 96.0% of verrucae plantaris. Mosaic verrucae lesions were typed either HPV-27 (50.0%) or HPV-57 (50.0%). Punctate verrucae lesions typed majority HPV-57 (80.0%).\(^10\)

**Kaposi Sarcoma**

Kaposi Sarcoma (KS), caused by human herpesvirus 8 (HHV-8), typically presents as multiple bilateral plaques or patches on the lower extremity. The disease was originally sequestered to Mediterranean or Middle-Eastern elderly men, traditionally classified as Classic Kaposi Sarcoma. However, in the 1980s, AIDS-related Kaposi Sarcoma emerged in the United States. There are now 4 known classifications: Classic KS, endemic KS, iatrogenic KS, and AIDS-associated KS.\(^11\)

In a retrospective study performed by Wu et al., data was collected on 77 patients with Classic Kaposi Sarcoma (CKS) and 28 with AIDS-related Kaposi Sarcoma (AIDS-KS) between January 1997 and April 2013. Age distribution patterns revealed CKS presenting more commonly in patients 61-70 years old (36.3%), while AIDS-KS was more commonly noted in patients 31-40 years old (42.9%). The most common tumor location
for CKS was the foot (n = 57), in comparison to AIDS-KS which equally presented in the face, neck, and lower extremity (n = 12). Of the 98 samples that were large enough for analysis via PCR, 98.98% were positive for HHV-8. All 28 cases of AIDS-KS were infected with HHV-8. The most common area of lesions was between 1% and 5% in both CKS and AIDS-KS. Lymphedema was present in 29.9% of CKS and 7.1% of AIDS-KS. In addition to skin lesions, 50.0% of AIDS-KS patients were found to have additional lesions in other sites, such as the lymph nodes (n = 5), mouth (n = 3), interstitial lung tissue (n = 2), penis (n = 2), and pleura (n = 2).

Neurology

Peripheral Neuropathy

There are numerous nervous system disabilities associated with HIV that include Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, progressive polyradiculopathy, and autonomic dysregulation. The most common of these and most relevant to podiatrists is distal symmetric polyneuropathy (DSP). This disability can have a large negative impact on patients’ lives including their quality of life, emotional health, and daily function. Symptoms traveling in a “stocking” distribution include pain, sensory loss, paresthesia, and numbness.

A randomized-controlled trial enrolled 50 participants to evaluate the effectiveness of acupuncture and moxibustion (burning of mugwort leaf) in reducing symptoms associated with HIV-PN. Half of the participants were randomly assigned to a sham/placebo group and the other 25 were assigned to the true acupuncture/moxibustion group. All participants received either the sham/placebo or acupuncture/moxibustion protocol twice a week for 6 weeks. Three follow-up sessions were conducted at 9, 12, and 15 weeks to determine long-term effects of acupuncture with moxibustion. The acu/moxi group showed significant improvement (p<0.5) from baseline, using the GPS (Gracely Pain Scale), immediately after 6 weeks of treatment and at all subsequent follow up sessions (3, 6, and 9 weeks after treatment cessation). However, when comparing to the sham/placebo group, GPS significantly improved (p<0.05) only at the first follow up session three weeks after treatment cessation and showed a trend towards superiority (p<0.1) at the second and third follow up sessions.

Another randomized control trial investigated whether lower extremity splinting and parallel splint liner application alleviates pain and sleep troubles in HIV inflicted patients diagnosed with HIV-DSP. 23 subjects were assigned to the splint group and 22 were assigned to the liner group totaling 45 subjects recruited from one outpatient clinic. Degree of pain severity and sleep quality were scored using the Neuropathic
Pain Scale (NPS) and The Pittsburgh Sleep Quality Index (PSQI), respectively. The majority of the subjects (89%) were on an ART regiment at the start of the study and were taking various analgesic agents, most notably antidepressants and calcium channel α2-δ ligands. Average CD4 count was 518 cells/mm³. Splinting reduced pain by an average of 34% whereas parallel splint liner reduced pain by an average of 8%. Night calf cramps were completely eliminated in the 14 patients (all 14 in the splint group) who appeared in the final follow-up session, whereas 88% of the liner group patients continued to experience night calf cramps. Sleep scores improved by week 6, however, no significant difference was found between the two groups. This study shows that immobilization of the foot and ankle may present a viable strategy in reducing pain and improving sleep quality in HIV inflicted patients with peripheral neuropathy.

Tumusiime et al. randomly enrolled 507 HIV-infected persons from eight different HIV clinics to determine if there are any demographic and health status variables predictive of HIV-peripheral neuropathy. 59% of the enrolled individuals were diagnosed with HIV-PN using the BPNS (Brief Peripheral Neuropathy Screen). Using a multivariate model for statistical analysis, they found that age, level of education, 1 to 3 years duration on ART, and urban vs rural residence were statistically significant predictors (p<0.05) of HIV-PN. CD4 cell counts, duration of HIV infection, duration of ART treatment greater than 4 years, marital status, and gender did not correlate with HIV-PN.

Osio et al. conducted a cross-sectional study to determine if CSP (cutaneous silent period), a modality utilized in assessing Aδ fiber functionality, is altered in HIV positive subjects with DSP. They enrolled 26 HIV-positive subjects that were divided into two groups: seven without upper extremity neuropathy; and 19 with both lower and upper limb neuropathy. They also enrolled 12 healthy individuals that served as the control group. Results revealed latency in CSP was significantly increased in both HIV-positive groups compared to the healthy control group. No significant differences were found between the two HIV-positive groups.
population. Three different assessors then administered the modified LEFS to 12 randomly selected HIV-positive individuals one week apart. Out of the 20 activities in the modified LEFS, 19 were found to be strongly correlated (\(\rho \geq 0.7\)) whereas none of the activities in the original LEFS were found to be strongly correlated in the pilot study.

Venkataramana et al. collected data from the John Hopkins University HIV neurology database to evaluate the validity of the SPNS (subjective peripheral neuropathy scale) in diagnosing HIV-PN. They retrospectively analyzed 75 individuals with any history of a neurological complaint. Persons with HIV-PN were designated to one group whereas the second group was composed of HIV-infected persons without peripheral neuropathy. HIV-PN was defined as a positive SPNS, absent or diminished ankle reflex, diminished vibration perception, and sensory symptoms in a stocking distribution. Thirty-two of the participants were found positive for peripheral neuropathy based on the SPNS. After constructing a receiver operating characteristic curve, it was determined that the SPNS had a sensitivity of 47% and a specificity of 83%.

A retrospective study that analyzed data collected between February 1999 and April 2011 found a correlation between HIV-DSP and psychomotor performance. A total of 278 HIV-positive individuals were included in the study. Verbal fluency, working memory, executive functioning, learning memory, information processing speed, and motor ability were all assessed via various neuropsychological tests. HIV-positive patients diagnosed with DSP were significantly impaired (p<0.05) compared to those unaffected by DSP in motor, information processing speed, and executive functioning domains. No significant differences were found in verbal fluency, working memory, and learning memory in HIV-positive subjects with and without DSP.

**Vascular**

**Peripheral Arterial Disease**

Peripheral artery disease (PAD) is a narrowing of the arteries in arms, hands, legs, and feet due to atherosclerosis. The most common symptoms in the lower extremities resulting from the reduced blood flow are cramping, pain or fatigue in leg or hip muscles that disappear with rest (intermittent claudication). The ankle-brachial index (ABI) is a well-established screening tool for PAD and future cardiovascular events in the general population. PAD is recognized in individuals with an ABI value lower than or equal to 0.9.

A prospective study of 173 HIV-positive subjects analyzed the association of atherosclerosis and cardiovascular disease. Twenty-four patients (13.9%) were found to have PAD (defined as ABI < 0.9) in 33 legs with a median ABI of 0.82 for the PAD-involved extremities. Twenty-three patients (13.3%) had high ABI (>1.3) with a median...
value of 1.38. One hundred and twenty-six (72.8%) had normal ABI (between 0.9 and 1.3) with a median of 1.13. Eight (4.6%) patients had PAD in both legs, 5 (2.9%) in only the right leg, and 12 (6.9%) in only the left leg.\textsuperscript{20}

Qaqa et al. conducted a prospective study of 113 patients that assessed the prevalence of PAD in HIV-positive patients who had a normal rABI by measuring post-exercise ankle systolic pressure (eASP) and post-exercise ABI (eABI). PAD was defined by either an absolute decrease in eABI of more than 0.15 (2 standard deviations) or a drop in eASP by at least 20 mmHg. Thirty (26.5%) of the participates were diagnosed with PAD in at least 1 leg. Of these, 8 (27%) reported a clinical history consistent with intermittent claudication but had normal resting ABI (rABI) values. The remaining members of the group were asymptomatic. 15 patients (50%) had PAD in both legs. 28 patients had a > 0.15 drop in eABI whereas patients without PDA had an increase in the eABI. 13 patients had a drop in eASP ≥ 20mmHg. Patients without PDA had an increase in eASP. There was no association found between HIV infection parameters and PAD. These results are summarized in Figure 4 below.\textsuperscript{21}

Another prospective study with 102 patients and no controls investigated peripheral endothelial function and early atherosclerosis in HIV-positive patients by measuring carotid intima-media thickness (cIMT) and ankle brachial index (ABI). The authors found that 15% of patients had a high mean cIMT (> 900 um). One patient had an ABI ≤ 0.9 both pre- and post-exercise and one patient had an ABI ≤ 0.9 pre-exercise, but had normal ABI post-exercise. An additional three patients had ABI ≤ 0.9 only after exercise. A decrease in ABI from pre- to post-exercise ≥ 15% was found in 14% of patients. Three patients had pre-exercise ABI ≥ 1.3 and three had post-exercise ABI (eABI) > 1.3. Six of the patients had a positive Edinburgh claudication questionnaire, but only one of these had eABI ≤ 0.9.\textsuperscript{22}

A cross-sectional study of 43 patients infected with HIV were compared to 25 healthy controls. Of the clinical and biological parameters measured, there were

\begin{table}
\centering
\begin{tabular}{|l|l|l|l|}
\hline
\textbf{Clinical Characteristics} & \textbf{No-PAD Group (n = 83)} & \textbf{PAD Group (n = 30)} & \textbf{P} \\
\hline
Age (mean ± SD) years & 47.2 ± 8.2 & 46.7 ± 10.1 & 0.98 \\
Male & 43 (52%) & 25 (83%) & 0.0008 \\
Race & & & \\
White & 8 (10%) & 2 (7%) & 0.50 \\
Non-white & 75 (90%) & 28 (93%) & \\
BMI > 30 kg/m\(^2\) & 20 (24%) & 5 (17%) & 0.60 \\
GFR (mean ± SD) mL/min & 93 (24 ± 24) & 87 ± 22 & 0.11 \\
Hypertension & 26 (31%) & 12 (40%) & 0.39 \\
Diabetes mellitus & 11 (13%) & 2 (7%) & 1.00 \\
Hypertension & 13 (16%) & 7 (23%) & 0.35 \\
Hepatitis B or C & 35 (42%) & 10 (33%) & 0.40 \\
Protease inhibitor & 50 (60%) & 18 (60%) & 1.00 \\
No-protease inhibitor & 33 (40%) & 12 (40%) & \\
Smoking history & 54 (65%) & 19 (63%) & 0.90 \\
IVDU & 47 (57%) & 18 (60%) & 0.75 \\
Gender & 3 (4%) & 0 (0%) & 0.30 \\
Symptom of intermittent claudication & 21 (25%) & 8 (27%) & 1.00 \\
History of stroke & 5 (6%) & 4 (13%) & 0.20 \\
Coronary artery disease & 5 (6%) & 2 (7%) & 0.90 \\
Use of aspirin & 6 (7%) & 3 (10%) & 0.60 \\
Nadir CD4+ cell count & 34 (44%) & 10 (33%) & 0.50 \\
<200 cells/μL & 15 (19%) & 9 (32%) & 0.17 \\
Recent CD4+ cell count & 33 (40%) & 13 (48%) & 0.8 \\
<200 cells/μL & 34 (40%) & 13 (48%) & 0.8 \\
Framingham risk score ≥ 10% & 14 (17%) & 8 (27%) & 0.28 \\
\hline
\end{tabular}
\caption{The clinical characteristics of the PAD and control group.}
\end{table}

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no differences between patients with HIV infection and healthy controls for body mass index, total cholesterol, HDL-cholesterol, fasting plasma glucose and creatine levels. Triglyceride levels, however, were significantly higher in HIV-positive patients (p<0.001). Arterial stiffness, measured by aortic pulse wave, was significantly increased compared to controls but was not correlated with parameters of HIV infection, such as viral load, duration of HIV infection or current CD4+ levels. Carotid intima-media thickness was increased compared with controls, but the differences were not statistically significant and there was no association with parameters of HIV infection or anti-retroviral treatment (duration of treatment, type of medication). Left ventricular diastolic dysfunction (LVDD) was correlated with HIV infection with a prevalence of 37% (n=16). After adjusting for age there was an independent association between aortic pulse wave velocity and LVDD suggesting that the arterial stiffness serve as an independent predictor of LVDD. Results are summarized in Table 2 below.23

Another cross-sectional study by Kwiatkowska et al. compared 111 patients infected with HIV with 40 age-gender matched healthy controls and found abnormal ankle-brachial index (ABI) values in 22.5% of the cohort subjects. The median ABI was significantly lower in the HIV-positive group and showed greater range (abnormally high or

<table>
<thead>
<tr>
<th>Patients with HIV infection</th>
<th>Healthy controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) N=43</td>
<td>37.8±13.9</td>
<td>37.8±12.7</td>
</tr>
<tr>
<td>Sex: males/females (%)</td>
<td>26 (60.5%)/17 (39.5%)</td>
<td>15 (60%)/10 (40%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6±3.7</td>
<td>22.8±1.2</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>14 (32.5%)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Duration of HIV infection (month)</td>
<td>58.8±45.6</td>
<td>-</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dl)</td>
<td>88.4±9.2</td>
<td>88.6±8.7</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>186.8±52.2</td>
<td>173.4±33.5</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>163.5±83.2</td>
<td>87.9±30.1</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>44.8±4</td>
<td>45.7±5</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.87±0.17</td>
<td>0.84±0.12</td>
</tr>
<tr>
<td>Viral load (copies/ml)</td>
<td>200055±77684.9</td>
<td>-</td>
</tr>
<tr>
<td>CD4+ (cells/mm³)</td>
<td>402.6±232.9</td>
<td>-</td>
</tr>
<tr>
<td>HIV specific treatment, n (%)</td>
<td>37 (86%)</td>
<td>-</td>
</tr>
<tr>
<td>ARVT exposure (month)</td>
<td>55.2±45.6</td>
<td>-</td>
</tr>
<tr>
<td>RTI exposure (month)</td>
<td>55.2±45.2</td>
<td>-</td>
</tr>
<tr>
<td>PI exposure (month)</td>
<td>32±20.4</td>
<td>-</td>
</tr>
</tbody>
</table>

*Data are means ± standard deviation or number (%)*

*Abbreviations: BMI = body mass index; ARVT = antiretroviral treatment; RTI = reverse transcriptase inhibitors; PI = protease inhibitors*

Table 2 – Clinical characteristics of the HIV-positive and control group.23 Reprinted with permission from Rights Link.
low values) when compared to the HIV-negative controls. Symptomatic PAD, defined by the presence of intermittent claudication, was diagnosed in 2 HIV-positive male patients. Other symptoms such as numbness, tingling, stabbing pain, and muscle cramps were observed in 28 patients but had no association with ABI values. There were no cases of low ABI (<1.0) observed in the control group. In the study cohort, 6 patients had borderline ABI (0.91-0.99) and 5 showed abnormally high ABI values (> 1.4). Among the HIV-positive patients with low ABI values (< 1.0), a family history of cardiovascular disease was observed (p=0.03). A comparison of the subgroup with abnormal ABI and those with normal values showed higher LDL, non-HDL cholesterol and CRP levels, lower HDL levels, and more frequent cases of metabolic syndrome, although these differences were not statistically significant.

Musculoskeletal

Osteoporosis

Musculoskeletal (MSK) symptomatology in HIV may present at any stage of the infection, however symptoms vary. While the nature of the virus and corresponding immune system consequences are key to understanding pathologies, ART-induced drug toxicity has also shown significant effects on the MSK symptoms.

A meta-analysis conducted by Pinzone et al. investigated the effect of bisphosphonates on bone mineral density (BMD) in HIV-positive adults. This study was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) and identified on Cochrane Central Register of Controlled Trials (CENTRAL), Medline, EMBASE, LILACS, AEGIS, NLM, and clinicaltrials.gov. Eight articles documented the outcomes of BMD changes measured by dual-energy X-ray absorptiometry (DXA) at the lumbar spine, femoral neck, and total hip in controlled, randomized trials. Five trials compared alendronate with placebo or no intervention while 3 trials used zoledronate. At both 48 weeks and 96 weeks, BMD was increased in both trial arms at the total hip (MD: 2.12%; 95% CI: 1.43-2.81, MD: 3.2%; 95% CI: 1.52-4.88, respectively) and lumbar spine (MD: 2.84%; 95% CI: 2.11-3.57, MD: 6.76%; 95% CI: 4.98-8.54, respectively). Bisphosphonates were well tolerated when given orally/IV.

Martin et al. conducted a 48-week, open-label, multi-national sub-study of the Second Line trial, a study that randomized participants with high HIV viral loads after administration of first-line therapy to second line treatment. This sub-study randomized 210 participants in the original study to compare changes, over 48 weeks, in bone mineral density (BMD) on second line treatment agents: lopinavir/ritonavir (LPV/r) and raltegravir (RAL) or LPV/r+2-3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTIs). Dual energy X-ray
absorptiometry (DXA) scans of the proximal femur and lumbar spine were performed at baseline and 48 weeks to determine the difference in mean change between the study arms. A McNemars test compared osteopenia and osteoporosis while linear regression compared BMD changes at baseline and 48 weeks. After 48 weeks, Martin et al. discovered BMD reductions of -5.2% at the proximal femur in the LPV/r+2-3 N(t)RTIs and by -2.9% in the LPV/r+RAL arm. Lumbar spine BMD in the LPV/r+2-3 N(t)RTIs reduced at week 48 by -4.2% and by -2.0% in the LPV/r+RAL arm. The data is outlined in Figure 5 below. Sex, BMI and smoking status were accounted for with covariate analysis. Osteopenia (7.6%) and osteoporosis (2.0%) differences showed no clinical significance after a McNemars test. Martin et al. concluded that reduced BMD was significantly associated with longer duration of tenofovir usage and a low baseline BMI at the end of 48 weeks. Also, regimens that included LPV/r and raltegravir combinations over LPV/r containing N(t)RTIs showed less bone loss after first line agents failed to suppress the virus.27

A five-year longitudinal study of 106 postmenopausal, HIV-positive and negative African American and Hispanic women was conducted by Yin et al. This study assessed the effects of HIV infection and HAART on trabecular and cortical bone. Both groups were similar in age, co-morbidities and present illnesses. HIV-positive and negative individuals underwent bone architecture and cortical and trabecular bone mineral density (vBMD) measured by high resolution peripheral quantitative computed tomography (HRpQCT). Dual-energy x-ray absorptiometry (DEXA) was used to look at areal bone mineral density (aBMD). HIV-positive women displayed lower aBMB levels in the lumbar region and hip, but higher C-telopeptide and N-telopeptide (bone resorption markers) indicating higher bone turnover. HIV-positive women also showed lower vBMD cortical thickness and area at the tibia (11-12%), but the radius of bone (vBMD) was similar to the control group. The porosity of bone was similar for both groups. All differences documented were deemed significant via SAS measurement. Figure 6 visually highlights the microarchitecture differences in both HIV-infected/non-infected participants in both the radius and tibia.26

![Figure 5. Mean percentage change (SE) from week 0-48 in BMD in the proximal femur and lumbar spine.27 Table created from data reported in study.](image)
Mora et al. conducted a retrospective study on 88 HIV-infected children and adolescents (4.8-22.1 years old, 43 boys and 45 girls) to assess the applicability of quantitative ultrasonography (QUS) for bone health assessment in HIV-infected youth. 70% percent of this population had HIV viral loads that were undetectable compared to 30% with viral loads ranging from 1000 to 10,000 copies per ml. QUS measurements were performed on the mid-shaft of the tibia and distal radius of the non-dominant arm- a total of three times to account for variability. Dual-energy x-ray absorptiometry (DXA) scans were conducted on the lumbar spine and whole skeleton. The researchers found that QUS measurements of the radius of the arm were associated with DXA measurements of the lumbar spine after correction for differences in sex and anthropometry (R values 0.57 to 0.60). QUS readings of the tibia were also associated with DXA measurements of the lumbar spine (R from 0.58 to 0.66). The Z scores for lumbar spine DXA measurements were lower than QUS Z score measurements of the radius of the arm and tibia which was anticipated as the QUS device measures the speed of sound in the cortex of long bones which the human skeleton contains about 88% cortical bone (P<0.0001).

A 30-patient retrospective study conducted by Aparicio et al. evaluated bone mineral density (BMD). Participants were asymptomatic, HIV-positive men assembled into 3 groups: 17 in the treatment group, who were on ART (with protease inhibitors) 2+ years leading up to the study, 13 individuals not taking ART, but HIV-positive (naïve group), and lastly a control, HIV-negative group. A nutritional questionnaire, DEXA lumbar and femur scan, viral load and CD4 counts, bone formation and resorption marker studies (osteocalcin levels, PTH, testosterone, calcium, urine deoxypyridinoline, Vitamin D) were obtained. Osteopenia was present in the naïve group (8/13, 61.5%) versus ART group (9/17, 53%). However, these values were not statistical significance. However, mean serum levels of vitamin D showed a deficiency in
the ART group (86% of patients) compared to the naïve group. This result was of significance (p=0.04). In addition, lower testosterone levels were also significantly related to lower bone mineral density suggesting hypogonadism may play a role, in addition to ART.29

**DISCUSSION**

**Onychomycosis**

In the pre-ART era, onychomycosis was reported to correlate with a CD4 count equivalent or less than 450 cells/mm.4 This value was also reported by Moreno-Coutino et al7 in 2012, suggesting no changes in the pre- versus post-ART era. With regards to organism of causation, studies have revealed Trichophyton rubrum and Candida albicans as the most common culprits in the post-ART data.5,7 Causative organisms were not reported in the pre-ART data. Proximal white subungual onychocytosis accounted for 88.7% of onychomycosis subtype in the pre-ART era4, whereas this subtype only constituted 8.33% in the post-ART study.5 Total dystrophic onychomycosis, which was not addressed in the pre-ART data, was most common (55%) in the post-ART data.4,5

Treatment modalities for onychomycosis in the pre-ART era included itraconazole, which was primarily used for T. rubrum infections and displayed the least side effects of all trizole agents.4 Terbinafine was also utilized for *Trichophyton*, *Epidermophyton*, and *Microsporum* infections.4 However, it is important to note the profound potential side effects of azole-mediated inhibition of cytochrome P450 system as well as hepatotoxicity. Alternative treatment options, such as Vicks VapoRub, display minimal side effects and drug interactions with concomitant antiviral treatment.6 Moreno-Coutino et al. also reported an improvement with and, in 2 cases, complete resolution of onychomycosis infection just with the initiation of ART.7 Because patients with advanced HIV often require multiple medications, it is important to explore other alternatives to the standard oral anti-fungal therapy prescribed for advanced onychomycosis.

**Plantar Verrucae**

Before 1995, the likelihood of patients with HIV presenting with plantar verrucae was 10.0 times more likely than those without HIV.4 This decreased to 5.2 in 2008.9 However, once age, sex, and race/ethnicity was adjusted in this analysis, the value was not statistically significant. Therefore, the pre- and post-ART data are consistent regarding the prevalence of plantar verrucae in this population. Johnston et al. provides explanation for these findings, such that the implementation of ART therapy has increased the life expectancy of HIV patients with HIV infection and therefore, it is expected that the prevalence of clinical manifestations would persist.9
It is also important to note that the HPV strains that have been characteristically associated with certain clinical morphologies are not typically seen in HIV-positive patients. King et al. reported all plantar verrucae samples typed as HPV-2/HPV-27/HPV-57 subsets. For example, HPV2, which has traditionally been associated with mosaic pattern, was exclusively seen in verrucae plantaris. These subsets have been correlated with longer duration of infection and poor response to treatment. A co-infection, which is a rare finding, was also found in one of the HIV-positive subjects in this study, where 12 separate warts were found to have both HPV-2 and HPV-27. Although King et al.’s results challenge current literature, the clinical type identification was solely based on evaluation by one podiatrist.

Kaposi Sarcoma

Prior to the initiation of ART, Kaposi sarcoma was the most common tumor in HIV-positive patients, which still holds true today. Previously, 1 in 3 HIV-positive patients developed this disease, but with the implementation of ART, the rate of KS has significantly decreased. Today, just 5-7% of HIV-positive individuals develop KS. In the pre-ART era, a typical presentation of KS included a papular or macular lesion of red, blue, or purple color on the foot. Wu et al in 2013 reported the most common locations of KS equally on the face, neck, and lower extremity.

Peripheral Neuropathy

Some studies estimate that HIV-DSP affects up to 35% of all HIV patients. Other studies have shown that HIV-DSP affects 30 to 60% of the HIV and AIDS population. The percentages seem to project towards the higher end when taking into account asymptomatic patients with estimates ranging from 50 to 60%. In the pre-ART era, estimates of prevalence of HIV-DSP were considerably lower with a ceiling of approximately 30%. With the arrival of ART, what was once considered solely an acute condition has transformed into a more chronic one. Therefore, ART equates to a higher life expectancy thus, it would be reasonable to justify this dramatic increase in prevalence with the innovation of HIV treatment. This highlights the importance of recognizing nervous system dysfunction in podiatric patients. To ignore DSP would be to ignore a disability that may be affecting a large percentage of HIV infected patients that a podiatrist may see. Clinicians should especially have a high index of suspicion in older patients, 1 to 3 years duration on ART, and in those that live in a more urban environment as these have shown to be independent factors correlated with HIV-DSP.

Early diagnosis of HIV-DSP is critical to initiate immediate intervention and to consider referral to a neurologist to reduce symptomology and improve quality of life. There are many peripheral neuropathy scales
described in the literature to aid in recognizing HIV-DSP. The SPNS (subjective peripheral neuropathy scale) is a quick and easy tool to use. However, Venkataramana et al. found the sensitivity of the SPNS to be 47%. This makes the SPNS ineffective as a screening tool. However, they did find the specificity to be much higher at 83% and the positive predictive value to be at 70%. Clinicians must keep in mind that a high positive predictive value can be deceiving due to its dependency on the prevalence of disease. Therefore, the SPNS should only be reserved for when in need of a quick assessment.

Another tool used to diagnose HIV-DSP that encompasses both subjective and objective findings is the BPNS (brief peripheral neuropathy scale). Objective measurements in the BPNS include evaluation of deep tendon reflexes and vibration sense. It would seem that the BPNS is a superior instrument compared to the SPNS due to its more rigorous nature. Indeed, Tumusiime et al. found a prevalence of 59% when examining the 507 subjects in their study using the BPNS. Venkataramana et al. discovered a prevalence of only 42.66% (32/75 subjects) when employing the SPNS. It is believed that up to 20% of patients with HIV-DSP are asymptomatic. The objective measurements in the BPNS may be more sensitive to asymptomatic subjects hence explaining the difference in prevalence compared to when utilizing the SPNS. This makes the BPNS an overall more powerful tool that is relatively easy to use and does not require fancy instrumentation.

In the pre-ART era, diagnosis of HIV-DSP was performed via invasive measures. These included NCV, nerve biopsy, and analysis of cerebrospinal fluid. Although these diagnostic measures remain viable and perhaps more specific, they hardly seem necessary due to their cumbersome nature. The BPNS and LEFS are practical and relatively easy tools to implement in practice.

HIV-DSP affects the functional capabilities of inflicted individuals diminishing their ability to perform ADL (activities of daily living). It is important to recognize the extent of the functional limitation in HIV-DSP inflicted persons. The LEFS (lower extremity functional scale) is an instrument used to determine the magnitude of any such limitation. It asks the subject to rate the level of difficulty in performing daily tasks such as bathing, putting on shoes and socks, climbing stairs, getting in and out of a car, etc. Tumusiime et al. found the LEFS to have a high intra- and inter-assessor reliability with slight modifications to some of the criteria to take into account cultural differences between the environment the LEFS originated for and the environment they were assessing.

Although HIV-DSP initially affects the lower extremity, it eventually makes its way proximally to the upper extremity. Persons with HIV-DSP perform poorly on neuropsychological tests that require a high
upper extremity motor capacity. Curiously, Fellows et al. found that persons with HIV-DSP limited to the lower extremity also performed poorly on psychomotor speed tests that required only upper extremity dexterity. This highlights the importance in identifying HIV infected individuals with DSP, assessing their functional limitation, and incorporating a treatment and rehabilitation plan.

Presently, many different treatment methods and drugs are used in the symptomatic management of HIV-DSP with little to no effect. Medications used include anticonvulsants, antidepressants, and analgesics. Although they have been shown to be clinically effective in treating other neuropathies, they unfortunately have not been shown to be superior to placebo interventions in treating peripheral neuropathy due to HIV. Unconventional treatment options that provide some relief include acupuncture/moxibustion and lower extremity splinting. Splinting specifically reduces pain, muscle cramps, and sleep quality in HIV-DSP affected people. Anastasi et al. found that acupuncture with moxibustion provides both immediate and long-term (9 weeks after treatment cessation) pain relief. Research studies that delve into the pathophysiology of HIV-DSP are needed to create a framework to aid pharmaceutical companies in designing effective drugs.

**Peripheral Arterial Disease**

The advent of anti-retroviral therapy (ART) has transformed infection with the human immune deficiency virus (HIV) into a chronic, manageable disease with a life expectancy approaching that of the general population. It has been reported that patients with HIV infection have an increase incidence of cardiovascular disease (CVD). The increased risk was initially found among patients without ART, but studies in the last two decades have found a correlation between CVD and ART. As CVD is a leading cause of cardiovascular mortality, it is imperative to identify patients with early atherosclerosis and to try to modify their CVD risk factors. Markers that could be used for early detection include arterial stiffness, carotid intima-media thickness, and the presence of peripheral arterial disease. Pre-ART data reported a prevalence of hypertension in HIV disease to be about 20-25%. Recent reports have found hypertension in up to 74% of patients on ART. Medications such as protease inhibitors can cause lipodystrophy and metabolic disorders, which may contribute to the increased prevalence, however this is only postulated and direct evidence has not been found.

Arterial stiffness is now considered to be an independent predictor for cardiovascular events and mortality. Aortic pulse wave velocity (PWV) can be used to assess arterial distensibility. Papita et al. found significantly increased PWV when compared to healthy controls matched for age, gender, and smoking status. When adjusting for age, there was an independent association between aortic PWV and left
ventricular diastolic dysfunction. This suggests that arterial stiffness could serve as an independent predictor of LVDD. The authors found no association, however, between PWV and parameters of HIV infection (duration of infection, viral load, CD4+ levels) or exposure to ART (duration of treatment or type of medication).23

Many clinical studies support the opinion that carotid intima-media thickness is a valuable predictor of coronary risk status and subsequent CVD.22,23 Papita et al. found cIMT thickness was increased compared with controls, but the differences were not statistically significant. There was no association found between cIMT and parameters of HIV infection or ART.23 Knudsen et al., however, found that 15% (n=15) had a high mean cIMT (> 900 um).22 Papita suggests that stronger association of HIV infection with IMT in the internal/bulb region compared to the common carotid may explain the discrepancies found in literature.23

Kwiatkowska et al. found abnormal ankle-brachial index (ABI) values in 22.5% of the cohort subjects. The ABI median in the HIV-positive group was significantly lower when compared to HIV-negative subjects.24 Qaqa et al. found a similar result in a prospective cross-sectional study with no controls. Of the 113 HIV-positive patients studied, 26.5% (n=30) were diagnosed with PAD.20 These findings contrast with a separate single institution cross-sectional study of 173 American patients by Qaqa et al. which found only 13.9% (n=24) patients had PAD.21 Knudsen et al. reported an even lower incidence of PAD, with only 4 patients having ABI less than 0.9.22 This wide discrepancy in prevalence of PAD is found throughout the literature. A possible explanation for this variation could be the heterogeneity of study designs. Kwiatkowska et al.24 controlled for confounding variables such as smoking, age and gender, whereas the two studies by Qaqa et al.21 on American patients did not. Due to the complicated multifactorial nature of cardiovascular disease, however, it important to have large sample sizes in order to adequately account for the various etiologies of CVD. All 4 papers conclude that furthermore robust studies are needed to explore the relationship between PAD and HIV infection.

**Osteopenia**

Bone mineral density (BMD) is the amount of minerals comprising bone, reflecting overall strength. Lower BMD’s are the major complication of ART, despite decreasing the amount of HIV virus in their bodies. This finding initiated further research on the effects of ART on bone mineral densities. Martin et al. challenged cross-sectional studies in the pre-ART era, which suggested the HIV virus and factors such as smoking and steroid use were the primary causative factors.4 Newer research has shown that, in fact, the initiation of ART can lead to significant decreases in the BMD’s of patients.27
Though osteopenia was slightly higher in naïve patients (61.5% vs. 57%) in Aparicio’s study, vitamin D, a biochemical marker of bone remodeling, was significantly decreased (p=0.04) in HIV-infected males on treatment. Because osteopenia and osteoporosis showed no clinical significance in this study, Aparicio et al. further compared sex-hormone deficiencies, as the subjects were all male. Testosterone levels were correlated with bone mineral density in the lumbar spine, suggesting that a degree of hypogonadism may also play a role in bone remodeling. These findings, in contrast with Martin et al., suggest that HIV may be one risk factor in bone disorders.

Since the discovery of ART, many different classes of HIV medicines have been created to attack different stages of the HIV life cycle. Martin et al. studied the effects of bone mineral density on HIV-positive individuals on HAART containing nucleotide reverse transcriptase inhibitors (N(t)RTI). The author concluded those medicines which contain N(t)RTI’s have an increase in BMD loss compared with those on a different class of HIV medications such as an integrase inhibitor. Drug-induced bone loss is believed to be multifactorial. Medications may affect bone remodeling by renal mechanisms or drug metabolites. This loss is exacerbated by a longer duration of usage and also BMI.

When BMD is lost, osteopenia and osteoporosis are more associated complications. There is an increased need for supplements in patients with bone loss, especially those who are immunosuppressed or taking ART. These supplements include Calcium and Vitamin D as suggested by Aparicio et al. However, there is evidence for the use of bisphosphonates in HIV-infected individuals. Typically, bisphosphonates are used to treat post-menopausal bone loss by blocking bone resorption via hydroxyapatite crystal binding, however, Pinzone et al. suggest this medication could be successful at increasing BMD. Two specific bisphosphonates, alendronate and zoledronate, when given orally/IV increased BMD at the lumbar spine and total hip in HIV-positive individuals on ART. Despite showing an increase in bone mineral density, successful understanding of the use of bisphosphonates and prevention of bone fracture has still yet to be determined.

In the reviewed literature, bone mineral density has been classically determined through dual-energy x-ray absorptiometry (DXA). However, DXA cannot differentiate between cortical bone and trabecular bone. High-resolution peripheral quantitative computed tomography (HRpQRT) is a non-invasive technology, which gives a three-dimensional measurement of BMD in which separate assessment of cortical and trabecular bone can be seen. Yin et al. were the first to use HRpQRT to examine bone microarchitecture in HIV-infected individuals. They found lower BMD at the spine, hip and ultra-distal radius with higher levels of bone resorption.
markers. HRpQRT only detected lower cortical thickness and area of the tibia. Similar bone size in both HIV-infected and non-infected, but lower cortical area and thinner cortex detected by HRpQRT, suggests that bone resorption may be higher in HIV-infected women during menopause. Among the women participants, many ART regimens consisted of different classes of medications. Though HRpQRT did not differ among the different treatment groups, Yin et al. concluded that “modest associations” were seen on HRpQRT with women taking HAART with tenofovir, suggesting exposure to this drug may result in greater microarchitectural deterioration, further validating Martin and Aparicio.

Quantitative ultrasonography (QUS) has also been studied as an alternative measure in bone mineral density/health via speed of sound measurements. Mora et al. evaluated QUS measurements of the whole skeleton, which were related to DXA measurements. This suggests QUS may be an additional tool for measuring bone health. The major issue with this form of bone assessment is operator variability. Since QUS can be used on multiple body sites with different approaches, and multiple operators recorded QUS measurements in this study, inter-operative reliability may pose problems.

LIMITATIONS

As any literature review, the various papers analyzed contained different study designs, and therefore each study holds different significance to our findings. Patient inclusion criteria is of paramount importance when comparing studies and deducing a correlation between multiple variables. This was mitigated, to a degree, with high sample size and well-matched controls. However, heterogeneity across all studies still existed, including inclusion criteria, sample sizes, modalities of evaluation of clinical parameters, and more.

CONCLUSION

Dermatologic, neurologic, vascular, and musculoskeletal manifestations of HIV in the lower extremity are considerably common and can be devastating to the immunocompromised if not recognized in a timely manner. Even with the implementation of ART in 1996, HIV-related morbidities still persist, and the podiatrist plays a key role in recognizing these diseases.

When evaluating the dermatologic aspect, the podiatrist can identify onychomycosis, most commonly total dystrophic onychomycosis, which can be indicative that an HIV-positive patient’s T cell count is below 450 cells/mm. It is also imperative to note rare subtypes of HPV that are common in this patient population, such as HPV-27 and HPV-57. Other co-
morbidities such as Kaposi sarcoma commonly present on the lower extremity, and therefore the podiatrist can potentially be the physician to identify such disease.

Neurologic manifestations can cause pain, paresthesia, numbness, diminished vibration perception, poor sleep quality, and decreased quality of life. HIV-DSP prevalence ranges from 50-60%\textsuperscript{15,18}, and diagnostic tests such as BPNS and LEFS are reliable tools to implement in practice.\textsuperscript{15,17}

Arterial stiffness measured by aortic pulse wave velocity was increased in HIV-positive patients.\textsuperscript{23} However, carotid intima-media thickness as well as prevalence of peripheral arterial disease was controversial with conflicting studies presented in literature.\textsuperscript{21,23,24} More studies with better control of variables are needed to elucidate relationship between HIV and PAD.

Decrease in bone mineral density is a significant complication of ART. This has been classically determined through dual-energy x-ray absorptiometry (DXA), however, this diagnostic tool is limited between cortical and trabecular bone. Other tests such as HRpQRT and QUS are more specific and provide a valuable alternative option to DXA.\textsuperscript{26,28} Bisphosphonates have been suggested in literature to slow osteopenia and prevent fracture.\textsuperscript{25}

It is also important to reflect on the changes in diseases as well as their presenting clinical picture in the post-ART era. These manifestations may potentially be alleviated via an early and strategically planned treatment and rehabilitation plan.

**AUTHORS’ CONTRIBUTIONS**

All authors participated equally in the conception of the research topic, literature review, and extraction of data. All authors agreed upon the final submission.

**STATEMENT OF COMPETING INTERESTS**

All authors declare they have no competing interests.

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Efficacy and Selection Criteria of the Cotton Osteotomy as an Adjunct Procedure in Flatfoot Correction

Zachery Weyandt, Charles Hu, Joshua Ouellette, Caroline Tippett, Joseph Zehentner

Abstract

Objective: The purpose of our study was to examine all current outcome studies of the Cotton osteotomy to present its efficacy and propose evidenced-based recommendations on its best suited selection criteria.

Study Design: Qualitative Systematic Review of Literature

Methods: Two English language literature searches were conducted using PubMed databases. After review of all the articles, five articles were selected based on abstract summary and specified inclusion/exclusion criteria.

Results: One retrospective case-matched control study and four retrospective case studies were identified. Out of these five studies, 185 feet were measured pre-operatively and again post-operatively to evaluate degree of flatfoot correction. Each study obtained their subjects through a specific set of selection criteria. All studies had a method of radiographically measuring the degree of flatfoot correction.

Conclusion: The analysis of all available outcome studies on the Cotton osteotomy demonstrated its effectiveness in addressing forefoot varus, forefoot supinatus, and medial column instability by specific radiographic parameters including Meary’s angle, MASA, and medial cuneiform proximal and distal articular surface angle. Articles reviewed supported the utilization of the Cotton osteotomy when patients presented with the following criteria: absence of arthritis, absence of medial column instability, symptomatic HAV deformity, and a deformity correctable within limits of a 5-8mm plantarflexory bone block.

Key Words: medial column opening wedge osteotomy, Cotton osteotomy, flatfoot

Level of Evidence: 4
INTRODUCTION

Flatfoot deformities are often accompanied by a forefoot varus or medial column instability. Compensatory forefoot varus occurs in flatfoot as the hindfoot pronates to preserve the plantigrade foot.\(^1\) This forefoot varus often presents after hindfoot flatfoot procedures are utilized, and can become fixed.\(^1\) Current research agrees with the Hansen and Greisberg et al. theory which suggests medial column instability and forefoot varus can lead to hindfoot deformity as well as lateral forefoot overload.\(^2,3\) This supports the importance of addressing the sagittal plane deformity of the medial column in conjunction with hindfoot procedures as part of treatment to the symptomatic flatfoot. Adding this component to the surgical plan removes varus of the forefoot and/or medial column instability and thereby decreases the chances of the reoccurrence of flatfoot.\(^2\)

The medial column is typically addressed in flatfoot reconstruction by one of two approaches: a medial column arthrodesis or a medial column opening wedge osteotomy (aka. Cotton osteotomy). Previous outcome evidence has shown the effectiveness of arthrodesis on forefoot varus and medial column instability, however, at the cost of motion that may be unnecessary in certain situations.\(^4\) The Cotton osteotomy has been proposed and studied to address the same sagittal plane deformity without sacrificing motion of the joint.\(^2\) In our study, a literature review was conducted analyzing studies reporting Cotton osteotomy outcomes as a part of the sagittal plane correction in flatfoot deformities, reducing forefoot varus or supinatus that meet certain criteria that possibly deem arthrodesis unnecessary.\(^1\) The purpose of our study is to examine all current outcome studies of the Cotton osteotomy to present its efficacy and propose evidenced-based recommendations on its best suited selection criteria.

METHODS

Two English language literature searches were conducted using Pubmed databases. The first search of Pubmed was completed for the MeSH terms “flatfoot/surgery” OR (“flatfoot” and “surgery”) AND “cotton osteotomy”. This search obtained 9 results. Inclusion criteria included articles published from 01/01/2004 to 12/31/2017, full-text articles, and articles written in English. This resulted in 8 articles that met the above inclusion criteria. Exclusion criteria consisted of articles not focused on the treatment outcome of the cotton osteotomy, articles not having a method of evaluating adverse events (delayed union, non-union, fifth metatarsal overload, pain, plantar fasciitis, neuritis and infection), articles not implicating a system to evaluate the degree of correction before and after treatment (Meary’s angle, MASA, angle of medial cuneiform articulation, etc) and articles obtained through
a previous search. After review of the articles, three articles were selected for further review based on the abstract summary and the inclusion/exclusion criteria.

The second search of Pubmed was completed for the MeSH terms “flatfoot/surgery” OR (“flatfoot” and “surgery”) AND (“opening wedge osteotomy” AND “medial cuneiform”). This search obtained 4 results. Inclusion criteria included articles published from 01/01/2004 to 12/31/2017, full-text articles, and articles written in English. All articles met the above inclusion criteria. Exclusion criteria consisted of articles not focused on the treatment outcome of the cotton osteotomy, articles not having a method of evaluating adverse events (delayed union, non-union, fifth metatarsal overload, pain, plantar fasciitis, neuritis and infection), articles not implicating a system to evaluate the degree of correction before and after treatment (Meary’s angle, MASA, angle of medial cuneiform articulation, etc) and articles obtained through a previous search. After a review of the articles obtained, two were selected for further review based on the abstract summary and the inclusion/exclusion criteria. Figure 1 provides a summary of these literature searches.

Figure 1: Flow chart depicting summary of methods
RESULTS

A total of 5 studies were found to describe the outcomes of the Cotton osteotomy as an adjunctive procedure for flatfoot correction. Overall there were 4 retrospective case series and 1 retrospective case-matched control study. Table 1 summarizes these studies.

The retrospective case-series study Hirose et al. found the Cotton osteotomy effectively corrected fixed forefoot varus when done as an adjunct to other hindfoot procedures of flatfoot in all patients. Contraindications consisted of severe instability of the 1st tarsometatarsal joint. There was statistically significant improvement in the following radiographic parameters: Meary’s angle (14º), calcaneal pitch (4º), and medial cuneiform-to-floor distance (7º). Greater improvement of Meary’s angle was found in a modified Hoke-Miller procedure in comparison to the Cotton. However, 2 non-unions and 1 infection resulted compared to no non-unions or infections with the Cotton. A single 3.5mm-4.0mm screw was utilized in all 16 Cotton procedures; one case of screw removal occurred due to a painful screw head. Hirose et al utilized an autologous iliac crest bone graft to implant in the medial cuneiform.5

Lutz et al. found statistically significant improvement in all measured parameters for the 81 feet included in this study. They expanded the use of the Cotton osteotomy in flatfoot procedures to include fixed forefoot varus, medial column instability, and 1st ray elevatus. Contraindications consisted of medial column arthritis and medial column instability associated with a painful hallux valgus deformity. They also followed up with a selected group of patients up to 2 years which showed statistically significant improvement persisted over time when compared to their initial post-op radiographs. There were no reported non-unions. Ten of 24 adverse effects were attributed to the Cotton procedure, including 3 painful medial cuneiform screws, 2 medial cuneiform exostosis, 1 painful sesamoid, 1 plantar fasciitis, 2 fifth metatarsal overloads, and 1 recurrent symptomatic flatfoot. Lutz et al. utilized an allogeneic iliac crest bone graft.2

Aiyer et al. was a retrospective case-matched control study of 56 cases including 28 that utilized the Cotton as an adjunctive procedure to flatfoot reconstruction and 28 that did not address the medial column. The Cotton was utilized for fixed forefoot varus with absence of medial column instability or midfoot arthritis. In this study, the Cotton had no statistically significant effect on Meary’s angle, however, improved a newly defined medial arch sag angle (MASA) by 6.5º. Analysis showed the main effect of the Cotton was to plantarflex the 1st tarsometatarsal joint by 5.9º. They also showed better plantarflexion at the TMT with the Evans calcaneal osteotomy (11.2º) compared to the MDCO (4.6º). There were no
cases of malunion or nonunion. Aiyer et al. utilized an allogeneic bone graft but did not define the anatomical origin.\(^1\)

Castaneda et al. analyzed 23 Cotton procedures without using fixation on 22 patients with fixed forefoot varus. They also introduced a newly defined parameter for radiographic analysis to assess medial column correction achieved by using the Cotton procedure. Castaneda et al. measured the angle on lateral radiographs of the proximal and lateral articular surfaces of the medial cuneiform. Improvement of this angle was found from \(1.0^\circ\) pre-operatively to \(8.4^\circ\) post-operatively. At later follow-ups, the correction was maintained at \(7.5^\circ\), concluding that this

<table>
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<tr>
<th>Author</th>
<th>Level of Evidence</th>
<th># of feet that underwent Cotton osteotomy</th>
<th>Radiographic Measurements that Showed Statistically Significant Improvement</th>
<th>Major Findings</th>
<th>Type of Graft</th>
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<tr>
<td>Hirose and Johnson (2004)</td>
<td>4 (retrospective case series)</td>
<td>16</td>
<td>-Lateral Talo-First metatarsal (14(^\circ))</td>
<td>Found the Cotton an effective means of forefoot varus correction. Greater improvement of Meary’s angle was found in a modified hoke-miller procedure in comparison to the cotton. However, 2 nonunions and 1 infection resulted compared to no nonunions or infections with the Cotton.</td>
<td>Autologoue ileial crest bone graft</td>
</tr>
<tr>
<td>Lutz and Myerson (2011)</td>
<td>4 (retrospective case series)</td>
<td>81</td>
<td>-Lateral Talus- 1st Metatarsal Angle (9.9(^\circ)) -Talus Declination Angle (28.5(^\circ)) -1st Metatarsal Declination Angle (21.8(^\circ)) -Medial Cuneiform Height (33.50mm) -Talocalcaneal (Kita’s) (65(^\circ)) -Calcaneal Pitch (19.9(^\circ)) -AP Talonaviclar (21.42(^\circ)) -AP Talus - 1st Metatarsal (-1.83(^\circ)) (all &lt;6 months post-op mean)</td>
<td>Found statistically significant improvement of all radiographic parameters at 6 months s/p. 24 feet had a greater than 2 year follow up which displayed no significant difference in measured angles. 10 out of 24 adverse surgical events were attributed to the Cotton. No nonunions or signs of 1st met-cuneiform OA were reported.</td>
<td>Allogeneic iliac crest bone graft</td>
</tr>
<tr>
<td>Aiyer et al (2016)</td>
<td>3 (retrospective matched control study)</td>
<td>28</td>
<td>-Medial Arch Sag Line (MASA) (6.5(^\circ) improvement)</td>
<td>Main effect of Cotton was to plantarflex the first TMT by 5.9(^\circ). Significant improvement of MASA by 6.5(^\circ) (P = .002). Combination of Cotton with Evans showed greatest improvement of first TMT plantarflexion. No cases of malunion or nonunion were reported.</td>
<td>Allogeneic bone graft</td>
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</table>
can be maintained even without fixation. Boney union occurred in all patients. Castaneda et al. utilized an allogeneic iliac crest bone graft.6

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Outcome</th>
<th>Method</th>
<th>Bone Source</th>
</tr>
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<tr>
<td>Castaneda et al (2012)</td>
<td>4 (retrospective case series)</td>
<td>23</td>
<td>Medial Cuneiform Proximal and Distal Articular surface angle (7.5° improvement)</td>
<td>Introduced new radiographic parameters to measure medial column correction as described above, which isolates Cotton osteotomy. Boney union reported in all patients.</td>
</tr>
<tr>
<td>Boffeli and Schnell (2017)</td>
<td>4 (retrospective case series)</td>
<td>37</td>
<td>Lateral Talus-1st Metatarsal Angle (Mean pre-op of -17.24° to mean post-op of 0.51°)</td>
<td>Successful correction of medial column in all patients. Fixation was used in 16 pis. One subject had delayed union at 4 months post op which was fixed by using a bone stimulator for 2 months. Two cases of neuritis in patients who had plate fixation. Groups with fixation and without fixation showed similar outcomes.</td>
</tr>
</tbody>
</table>

**Table 1: Results of studies describing Cotton osteotomy as adjunctive procedure**

Boffeli et al. analyzed a total of 37 feet from 32 patients that underwent the Cotton osteotomy to find statistically significant improvement in Meary’s angle of 17.75°. The Cotton was used for fixed

<table>
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<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>Hirose et al.</td>
<td>Fixed forefoot varus</td>
<td>Severe instability of 1st TMTJ</td>
</tr>
<tr>
<td>Lutz et al.</td>
<td>Fixed forefoot varus, MC instability, 1st ray elevatus</td>
<td>MC arthritis, MC instability associated with HAV</td>
</tr>
<tr>
<td>Aiyer et al.</td>
<td>Fixed forefoot varus</td>
<td>MC instability, midfoot arthritis</td>
</tr>
<tr>
<td>Castaneda et al.</td>
<td>Fixed forefoot varus</td>
<td>NONE</td>
</tr>
<tr>
<td>Boffeli et al.</td>
<td>Fixed forefoot varus, forefoot supinatus</td>
<td>MC instability, HAV, MC arthritis</td>
</tr>
</tbody>
</table>

**Table 2: Inclusion and exclusion criteria which deem the Cotton osteotomy necessary for each study.**
forefoot varus and forefoot supinatus. Contraindications included medial column instability, hallux valgus, and arthritis of the medial column. A single delayed union was reported, which healed with the use of a bone stimulator. No nonunions were reported. Boffeli et al. utilized an allogeneic iliac crest bone graft.7

DISCUSSION

All papers reviewed supported the effectiveness of the Cotton as an adjunctive procedure in flatfoot surgery. Three papers reported statistically significant improvement of Meary’s angle, among others, that they used to establish medial column correction.2,5,7 However, this parameter is unable to isolate the correction from the Cotton from the other rearfoot procedures in flatfoot reconstruction. Two papers newly described their own radiographical parameter that isolates medical column correction from the rearfoot correction.1,6 The MASA and the medial cuneiform proximal and distal articular surface angle observed significant improvement, demonstrating the Cotton’s effectiveness.

Table 2 summarizes each study’s inclusion and exclusion criteria for their use of the Cotton osteotomy. Although the criteria vary slightly between each study there is a general consensus. All 5 studies used fixed forefoot varus as an indication for the procedure. Lutz et al. included medial column instability and 1st ray elevatus as indications as well, however, it was not used in any other study. Boffeli et al. included forefoot supinatus, an acquired soft tissue adaptation where the forefoot is inverted on the rearfoot as defined by Evans and Catanzariti but again was not defined in any other study.8 Exclusion criteria or contraindications also vary by study but include MC arthritis, MC instability, and hallux abductovarum deformity.

Complications that can occur from the Cotton are irritation, pain, and/or neuritis from fixation. Hirose et al. reported one case of a painful screw head in which it had to be removed. Boffeli et al. reported 2 cases of sensory neuritis that occurred in his procedures that utilized fixation. It should be noted that both cases used plate fixation of a total 4 plates used in the study. In 2 papers (Aiyer et al. and Lutz et al.), it was stated that use of fixation in Cotton procedures was not routine and one paper (Castandeda et al.) stated that fixation was not used to avoid the complications of hardware and/or donor site morbidity. This is possibly due to the inherent stability of the graft in the medial cuneiform, which can be tested for security after its placement. Supported by evidence of these 3 papers as well Cotton osteotomy technical guides, fixation appears unnecessary if inherent stability of the wedge is present, which would eliminate any complication of hardware placement.1,2,3,6,9 Another aspect that should be considered when contemplating the use of fixation is the type of graft. It should be noted that 4 out of the 5
studies utilized a tricortical iliac crest bone
graft.\textsuperscript{2,5,6,7} Aiyer et. al chose not to define the
anatomical location of the graft, however did
specify that it was an allograft. This should be
considered due to the fact that a tricortical
graft may have more inherent stability at the
graft site than bicortical and fixation may
depend on the type of graft used.

In all 5 papers reviewed, all studies
reported no nonunions using the Cotton. Only
Boffeli et al. reported a single case of delayed
union that was treated with a bone stimulator,
which resolved at 6 months. In comparison,
nonunion rates in midfoot arthrodesis
procedures has been reported to be as high as
20%.\textsuperscript{2} The high rate of union in all Cotton
outcome studies demonstrates it’s high
reliability.

Cotton osteotomies also eliminate
shortening of the medial column. In fact using
the Cotton lengthens the medial column
increasing the length of the MLA, tightening
the plantar fascia.\textsuperscript{2} Utilizing the Cotton can
also decrease the time spent non-weight
bearing, making it possible to weight bear in a
surgical boot in 2-4 weeks compared to 6-8
weeks in arthrodesis.\textsuperscript{2,3}

Another advantage of the Cotton is the
ability to adjust the required amount of
plantarflexion more easily.\textsuperscript{2} A wedge can be
fashioned to fit the exact degrees of
plantarflexion needed at the TMT. In addition,
this plantarflexion comes at no expense of
mobility at medial column joints, which
would be sacrificed in medial column fusion.\textsuperscript{1}

\section*{CONCLUSION}

A review of the most current literature
reveals the Cotton osteotomy is an effective
and powerful sagittal plane procedure in
flatfoot correction when used as an adjunct in
flatfoot surgery. All papers reviewed
supported the use of the Cotton osteotomy
when intraoperative assessment presented
fixed forefoot varus after hindfoot procedures
for flatfoot correction that meet certain
criteria: absence of arthritis, absence of
medial column instability, or had a
symptomatic HAV deformity. The deformity
must be correctable within limits of a 5-8mm
plantarflexory bone block.\textsuperscript{10} When utilized,
all papers assessed and confirmed correction
of medial column sag and forefoot varus by
one or more of the following parameters:
Meary’s angle, MASA, and angle between the
proximal and distal articular surfaces of the
medial cuneiform.

\section*{AUTHORS’ CONTRIBUTIONS}

All authors participated equally in the
conception of the research topic, literature
review, and extraction of data. All authors
agreed upon the final submission.

\section*{STATEMENT OF COMPETING
INTERESTS}
All authors declare they have no competing interests.

REFERENCES


**Efficacy of Clostridial Collagenase: A Literature Review**

Brian Wolff, BA, Lauren Murphy, BS, Karla De La Mata, BS, Tinisha Ricks, BS, Jason Kaplan, BS

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**Abstract**

**Introduction:** The purpose of this study is to evaluate the efficacy of clostridial collagenase ointment (CCO) for the enzymatic debridement of lower extremity ulcers.

**Study Design:** Qualitative Systematic Review of Literature.

**Methods:** A Pubmed search was conducted: (collagenase debridement [MeSH Terms]) AND skin ulcers [MeSH Terms]. Inclusion criteria required articles to be written in English, published between 01/01/2002-12/12/2017, and conducted in human models. This yielded 30 articles. Exclusion criteria was applied and 24 articles were rejected: three were not published in English, eight were published before 2002, two combined collagenase with hyaluronic acid, one only evaluated the cost without discussing clinical trial(s), six either did not evaluated the use of collagenase or did not discuss its efficacy, three were review articles, and one did not study ulcers in the lower extremity. This yielded six articles for final review.

**Results:** Six were selected for final review. Three compared CCO to autolytic debridement. One compared CCO to saline moistened gauze (SMG). One combined CCO with negative pressure wound therapy (NPWT). One evaluated the use of Clostridial collagenase independently in a large retrospective analysis.

**Conclusion:** CCO reduces time to wound closure, decreases the costs associated with care of lower extremity ulcers, and did not have any reported adverse events.

**Key Words:**
Clostridial collagenase ointment, ulcers, lower extremity wound, enzymatic debridement

**Level of Evidence:** 4
INTRODUCTION

Background:
Lower extremity ulcers have numerous etiologies; a few of the most common including foot deformity, peripheral/diabetic neuropathy, and venous insufficiency. The economic burden of foot ulcers is substantial, with the average cost of treatment of a diabetic foot ulcer over a two year period in 2009 being $46,841. Decreasing the time a wound requires to heal both reduces economic burden and the likelihood of amputation. Standard wound care includes infection control, offloading, and debridement. Debridement techniques include sharp surgical, enzymatic, autolytic, and mechanical. Clostridium histolyticum derived collagenase is considered the “gold standard” in selective topical enzymatic debridement of necrotic tissue with Smith and Nephew’s Santyl being the only FDA approved collagenase ointment in the US market. It can be used in the pediatric, adult, and geriatric population.

Why do an enzymatic debridement:
Various modalities of debridement are widely implemented as a corner stone in wound treatment. Past research supports the use of enzymatic debridement as an essential component of wound bed preparation. Preparation of the wound bed includes reduction of inflammatory substances and bioburden, promotion of DNA synthesis, and elimination of the hypoxic environment; all of which encourages the migration and proliferation of keratinocytes and fibroblasts. The goals of enzymatic debridement are to encourage granulation, promote oxygen availability, and enhance re-vascularization and re-epithelialization of wounds. It removes necrotic tissue while preventing the increase of inflammatory cytokines (tumor necrosis factor-alpha and interleukin-6), metalloproteinases, and fibronectin.

How clostridial collagenase works:
The majority of debridement modalities are non-selective, meaning that viable tissue is removed along with necrotic tissue. Surgical debridement is the fastest of these non-selective modalities. Other non-selective modalities include mechanical and enzymatic (i.e. papain-urea, fibrinolysin, trypsin and streptodornase). The two types of selective debridement are autolytic and enzymatic (clostridial collagenase ointment (CCO)). Autolytic debridement utilizes an occlusive or semi-occlusive dressing that supports the body’s macrophages and endogenous proteolytic enzymes. Applying CCO to wounds has become popularized among patient populations where surgical debridement is not appropriate.

Clostridial Collagenase (CC) is a proteolytic enzyme that cleaves collagen through hydrolysis at the triple-helical region of collagen molecules. CC cleaves only denatured collagen because it is unable to break through the mucopolysaccharide sheath that surrounds viable collagen.
CC does not act upon factors that promote granulation: keratin, fat, fibrin, and growth factors. Additionally, CCO degrades devitalized collagen into peptide fragments that promote angiogenesis and endothelial proliferation. Furthermore, CCO plays a role in decreasing the potentiation of bacterial colonization by removing the necrotic tissue that would otherwise spur bacterial growth.

**Objective and Hypothesis:**

This qualitative systematic review of the literature aims to assess the efficacy of enzymatic wound debridement with *Clostridium histolyticum* derived collagenase in the treatment of lower extremity wounds. The authors hypothesize that the use of CCO reduces time to closure of wounds, decreases costs associated with wound care, and is not associated with any significant adverse effects.

**METHODS**

For this qualitative systematic review of the literature, a Pubmed search was conducted. The search utilized MeSH terms and the Boolean operator “AND”. The search was: (collagenase debridement [MeSH Terms]) AND skin ulcers [MeSH Terms]. This yielded 30 results. By including only articles in English, published between 01/01/2002-12/12/2017 and conducted in human models, the results were narrowed to 19 articles. 13 articles were excluded: two combined collagenase with hyaluronic acid, one only evaluated the cost without discussing clinical trial(s), six either did not evaluate the use of collagenase or did not discuss its efficacy, three were review articles and one did not investigate ulcers in the lower extremity. This yielded six articles for final review.

**RESULTS**

Marrazzi et al. performed a retrospective analysis that included 332 patient with chronic ulcers of various etiologies, treated with CCO in an outpatient
setting. The mean ulcer area was 18.2 cm$^2$ with granulation tissue not exceeding 80% of the wound bed. CCO was applied once daily until the ulcers fully healed, which took an average of 15.4 weeks. This study also utilized a silver sulfadiazine (SSD) dressing, which was applied every fourth day to prevent infection, while the CCO acted as a debriding agent on days one through three. The researchers found the ulcers with a mixed etiology healed the fastest (mean time to healing 9.2 weeks), followed by diabetic ulcers (16.6 weeks), pressure ulcers (17.1 weeks), arterial ulcers (17.8 weeks) and lastly venous ulcers (19.4 weeks). The researchers also found that smaller wounds correlated with shorter time to closure ($p<0.01$).

A randomized prospective analysis conducted by Galperin et al. observed the effect of CCO versus hydrogel dressing on ulcer size in 17 patients. At the start of the study, ulcer area in both groups were similar (8.1 cm$^2$ for CCO and 7.8 cm$^2$ for hydrogel). The change from baseline of wound area at the end of the fourth week showed a decrease of 70% in the CCO group vs 41% in the hydrogel group. The difference between these two groups was not found to be significant ($p>0.05$). However, when each group was independently compared to their respective baseline measurements following treatment, a significant reduction in wound size was seen in weeks one ($P=0.0300$), two ($P=0.001$), three ($P=0.0010$) and four ($P=0.0070$) in the CCO group. Whereas, the hydrogel group only had a significant change in week one ($P=0.0500$).

In a moderate sized randomized control trial (RCT) (n=48) Tallis et al. compared CCO to Saline Moisten Gauze (SMG) wet to dry dressings combined with sharp debridement in diabetic foot ulcers (DFU’s). The inclusion criteria included an ulcer area between 0.5-10 cm$^2$ for at least one month with neuropathy around the wound and adequate blood flow. All of the 48 participants received sharp debridement initially before the start of the randomized assigned treatment. 0.2mm (nickel thickness) CCO was applied once daily. The SMG group had dressing changes daily, with weekly sharp debridement. Treatment was given for four weeks, with an additional follow-up of up to eight weeks after the last treatment. If anyone in the CCO group required sharp debridement, they were removed from the study (one patient). The wounds were graded using a standardized wound assessment tool (modified Bates-Jensen Wound Assessment), which assigned a number of 1-5 (1 being the best condition, 5 being the worst condition) for eight subscales. Tallis et al. found CCO was equivalent to SMG in mean wound assessment score; but superior in decreasing the wound area at four weeks and continued throughout the next eight weeks (follow-up). Five stalled ulcers (defined as an ulcer that reduced less than 10% in size) were noted in the SMG group, making up about $\frac{1}{4}$ of the group. With this data Tallis et al. went on to perform an economic assessment comparing
cost of treatment of DFUs with CCO to SMG. The investigators concluded that SMG was significantly more expensive, due in large part to the increased time to wound closure associated with SMG.\textsuperscript{1}

Waycaster et al. evaluated the clinical and cost effectiveness of enzymatic debridement versus autolytic debridement. A three-stage Markov model was implemented following the execution of a randomized control trial that compared the use of CCO (n=14) to hydrogel dressings (n=13) in the maintenance of debridement and wound closure. The trial included 27 patients with stage III and IV pressure ulcers classified by the National Pressure Ulcer Advisory Panel (NPUAP). Stage III is defined as full thickness skin loss and Stage IV is defined as full thickness skin and tissue loss. The ulcers ranged in size from 1 cm\textsuperscript{2} to 64 cm\textsuperscript{2} in area, all of which greater than 85% necrotic tissue surface area. At minimum, dressings were changed daily without sharp debridement or cross-hatching. For analysis using the Markov model ulcers were placed in one of three categories, inflamed (necrotic) wound, proliferating (healing) wound and epithelialized (healed) wound. There were two transition periods between the three states corresponded to Phase I and Phase II of the 12-week clinical trial. At 42 days, the phase I primary outcome was complete debridement. Only those patients that successfully reached the phase I outcome continued onto phase II of the study. At 84 days, the phase II primary outcome was complete wound closure. Approximately 85% of the CCO group reached complete debridement during phase I, while only 29% of the hydrogel group completed this phase (p=0.03). During phase II, 69% of the CCO group achieved complete wound closure compared to only 21% of the hydrogel group (p=0.0213).\textsuperscript{10}

Cost effectiveness was estimated for a long-term care facility, in which the prevalence of pressure ulcers can be as high as 28%.\textsuperscript{10} The cost effectiveness ratio was calculated for each product based on the total cost and clinical benefit, defined as the number of epithelialized (healed) days over a one-year time span. Hydrogel dressings are more affordable but care utilizing the hydrogel dressings is 2.7 times higher and 1.5 times less effective as compared to CCO. Over a one-year span, the direct cost of CCO was $2003.00, which was $3,477.00 less than the cost of using hydrogel dressings. The hydrogel group only had 218 days of healed wound compared to 317 days of healed wound in the CCO group.\textsuperscript{10}

An RCT conducted by Konig et al., compared a moisture-activated polyacrylate pad (TenderWet®24) to CCO under sterile gauze. 17 patients received autolytic debridement (TenderWet®24) and 24 patients received CCO. The authors calculated in advance that at least 29 patients would be needed in each group to demonstrate superiority of one product over the other. In this underpowered RCT, it was found that there was “no statistically significant superiority of either product”. However, the
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<th><strong>Authors</strong></th>
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<th><strong>Type of Study</strong></th>
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<td>Marazzi et al.</td>
<td>Statistical evaluation was supported by Smith and Nephew. Authors had no conflict of interest</td>
<td>Retrospective analysis evaluating the effects of CCO on ulcers in outpatients</td>
<td>(246/332)</td>
<td>Average healing time 15.4 weeks with ulcers of mixed etiology having the shortest time to heal and venous ulcers having the longest time to heal</td>
<td>CCO is well accepted, has the potential to improve wound healing, and decreases time of wound closure</td>
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<td>Galperin et al.</td>
<td>Supported by Smith and Nephew (manufacturer of Santyl)</td>
<td>Randomized prospective analysis: CCO vs hydrogel</td>
<td>(17/17)</td>
<td>CCO increases the level of anxiety associated with inflammation resolution and decreases ulcer area</td>
<td>CCO alters the repair activity of collagen and extracellular matrix proteins by enhancing the production of anti-inflammation associated peptides</td>
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<td>Tullis et al.</td>
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<td>RCT: CCO vs saline moistened gauze used for wet to dry dressings</td>
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<td>CCO showed a “significantly better response rate”</td>
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<td>Waycaster et al.</td>
<td>Funded by Healthpoint Biotherapeutics (manufacturer of Santyl)</td>
<td>RCT: CCO vs autolytic debridement with economic analysis</td>
<td>(break down of location not explicitly stated, but does mention lower extremity ulcers in the inclusion criteria)</td>
<td>“Faster debridement associated with CCO therapy translates into better outcomes and a substantial total cost savings.”</td>
<td>In a long-term facility, CCO results in substantial cost savings</td>
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<td>Konig et al.</td>
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<td>(42/42)</td>
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<td>TenderWet 24 &quot;appeared to be more efficient&quot;</td>
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<td>McCallon et al.</td>
<td>Funded by unrestricted grant from Smith and Nephew. Grantor had no input on study design, data collection, or statistical analysis.</td>
<td>Retrospective analysis: NWPT alone vs NWPT + CCO</td>
<td>(6/114)</td>
<td>Overall change in BWAT score and decrease in necrotic tissue domain of BWAT</td>
<td>Use of CCO showed a statistically significant improvement in wound healing time</td>
</tr>
</tbody>
</table>

**Table 1: Summary of Article Reviewed**
authors go on to claim that autolytic debridement with TenderWet 24 “appeared to be more efficient”.

McCallon et al. conducted a retrospective analysis on 114 adult inpatients who presented with chronic pressure ulcers (duration > 30 days) at a long-term acute care hospital. Patients were all assessed to have stage III and stage IV chronic pressure ulcers (NPUAP guidelines). The wounds were also assessed with the Bates-Jensen Wound Assessment Tool (BWAT), which assesses wounds by 13 different parameters, each with five sub-categories. The mean initial wound area was > 50cm². The data demonstrated no significant differences with respect to: age, blood urea nitrogen, glucose, albumin, creatinine, hemoglobin, or the initial presentation of wound surface area for all participants within the study. Patients were divided into two treatment groups: 47 patients received only negative pressure wound therapy (NPWT), while 67 patients received CCO in addition to NPWT. The CCO group had significantly worse wounds on initial presentation as assessed by BWAT score (P=0.017). The CCO group demonstrated better overall improvement based on BWAT score (p=0.022) The addition of CCO to NPWT demonstrated an improvement in wound healing speeds established by the overall reduction in BWAT score.

**DISCUSSION**

Standard treatment of ulcers consists of ridding necrotic tissue, exudate, bacteria and other noxious agents from the wound bed, which supports faster healing by creating a more favorable environment. Sharp debridement is a viable option for removal of necrotic tissue. However, both autolytic and enzymatic debridement have been widely accepted and implemented in long-term facilities, where the expertise of a physician might not always be readily available to perform surgical debridement. Enzymatic debridement can prove to be easier to utilize and less expensive than other methods.

Waycaster et al. found the cost was higher in the autolytic (hydrogel) group compared to the enzymatic (CCO) group. They found the higher cost was due to the increased frequency of hydrogel dressing changes required. Tallis et al. found the cost of using SMG to be higher compared to CCO, not because the dressing needed to be changed more often, but because surgical debridement was still needed in combination with the SMG treatment. The overall cost effectiveness ratio was found to be $373.00 cheaper in the CCO group compared to the SMG group.

Tallis et al. not only found that using CCO was economical, but also found that CCO continued to work even after treatment
ceased, and called this “maintenance
debridement”. As collagenase cleaves the
triple helix, it releases breakdown products
that promote granulation tissue formation and
ultimately wound closure.\textsuperscript{1} Tallis et. al further
explore this unique mechanism of action by
evaluating the need for surgical debridement
in the CCO and SMG group. The SMG group
had to undergo six additional debridement
procedures over the course of the four week
treatment protocol. Wound closure proceeded
at a quicker rate, even in the one patient in the
CCO group who required surgical
debridement during the follow-up period.
CCO was also shown to resolve the
inflammatory stage of wound healing. Wound
healing was faster in the CCO group
compared to the SMG group.\textsuperscript{1} In cell culture
from diabetic foot wounds, Galperin et al.
measured an overall reduction in pro-
inflammatory markers, specifically TNF-
alpha and IL-6.\textsuperscript{9}

CCO can be used in isolation, but can
also be combined with other treatment and
dressing modalities to better expedite healing.
For instance, McCallon et al. combined CCO
with NPWT. It was found that using CCO in
combination with NPWT displayed a
demonstrable improvement in wound healing
time and a decrease in necrotic tissue vs
NPWT alone.\textsuperscript{11} Another common practice is
to combine CCO with dressings, which can
prove to be beneficial or disadvantageous in
certain cases. Dressing that contain potassium
and magnesium (light metals) enhance CCO’s
activity. Whereas, dressings that contain
iodine, silver, iron, or nickel (heavy metals)
were shown to inhibit CCO’s activity.\textsuperscript{2,12} To
prevent adverse interactions, Marazzi et al.
utilized CCO for three days and then used
silver sulfadiazine on the 4th day to avoid the
potential negative effects of combining these
two ointments.

Tallis et al. had no reports of adverse
events directly related to CCO use. CCO was
found to be a safe treatment for lower
extremity ulcers.\textsuperscript{1,6,7,9,10,11}

**CONCLUSION**

The use of enzymatic debridement
presents multiple advantages. It may act as an
alternative treatment option for patients who
are unable to undergo surgical debridement
due to vascular complications. When using
CCO, it is important to be aware of possible
interactions with other wound care products.
Heavy metals should be avoided in
combination with CCO.\textsuperscript{2} Debridement of
wounds with CCO stimulates the healing
process by decreasing wound bed
inflammation. The specific mechanism of
action of CCO may be to increase the
migration of fibroblasts and keratinocytes into
the wound bed.\textsuperscript{9, 12} Enhanced proliferation of
these cells work to modulate inflammation
and create a more favorable environment for
wound healing.\textsuperscript{9} Along with decreasing
inflammation, CCO removes necrotic tissue
that would otherwise inhibit granulation and
re-epithelialization, thus allowing for faster wound closure.

In conclusion, CCO reduces time to wound closure, decreases the costs associated with the care of lower extremity ulcers, and did not have any reported adverse events.

AUTHORS’ CONTRIBUTIONS

All five authors participated equally in the conception of the research topic, literature review, and extraction of data. All authors agreed upon the final submission.

STATEMENT OF COMPETING INTERESTS

All authors declare they have no competing interests.

REFERENCES


Efficacy and Safety Profile of Epinephrine use in Digital Blocks: A Review of the Literature

Amber Kavanagh BS, Thomas Ehlers BA, Sarah Taslima BA, MS, MBA

Abstract

Introduction: The use of epinephrine in digital nerve blocks is a complicated and controversial topic among physicians from many specialties. The current gold standard for creating a bloodless field is using a tourniquet and plain local anesthetic, but this technique is not without its drawbacks. Epinephrine use has many benefits over tourniquets, but it has been underutilized as a viable alternative in end-arterial circulations due to early work in the 20th century where it was demonized, due to poor research methods. Epinephrine is not without its drawbacks, but when compared to plain anesthetic, it has extraordinary potential.

Study Design: Qualitative Systematic Review of the Literature

Methods: Two literature searches were conducted using the PubMed database. Inclusion criteria consisted of all articles that were either prospective or retrospective studies, case series, or randomized controlled trials published after 1990 where epinephrine along with a local anesthetic was used in a digital surgery. Exclusion criteria consisted of systematic reviews, meta-analyses, case studies, epinephrine concentrations more dilute than 1:200,000, epinephrine injected in sites other than digits, and non-human animal subjects.

Results: A total of 119 potential articles were assessed for screening. Eleven articles fit the inclusion criteria and were assessed for negative outcomes when epinephrine is combined with a local anesthetic for a digital procedure. The measurable outcomes that proved to be significant in the assessed articles were: perfusion rates, if necrosis occurred, pain levels, blood loss, capillary blood gas values, and temperature. In all of the articles evaluated, there was no data to suggest that epinephrine caused harm in any of the patients evaluated with these parameters.

Discussion and Conclusion: Eleven studies on the use of local anesthetic with epinephrine in end-arterial circulations, including the fingers and toes, reported favorable results with no necrosis, ischemia, or gangrene. Two of the studies were specifically done on a patient population who had comorbidities, including diabetes, hypertension, and circulation disorders. In these high risk and vulnerable populations, epinephrine showed promise in that there were no signs of damage in 123 patients examined. When assessing perfusion through different modalities, epinephrine injections demonstrated an initial drop in perfusion rates, but not to dangerous levels, and these normalized within several hours. The vasodilatory effects of local anesthetics seem to balance out the potent vasoconstriction from epinephrine. The net effect of epinephrine is a bloodless field, less anesthetic needs to be used, and there is less post-procedure pain as compared to plain anesthetic with a tourniquet.

Keywords
Epinephrine, local anesthetic, digits, toes, fingers, digital nerve block, digital surgery

Level of Evidence: 4
INTRODUCTION

It is a common thought in podiatric, orthopedic, and plastic surgery to avoid the use of epinephrine in digits while using local anesthetics. Epinephrine, a potent vasoconstrictor is a non-selective adrenergic agonist, which causes the smooth muscle in the walls of blood vessels to contract. It is thought that injecting such a powerful agonist into an end-circulation area can cause ischemia, which can lead to necrosis and gangrene. While prolonged vasoconstriction can lead to necrosis; the short half-life, dilute nature of injectable epinephrine, and vasodilator properties of local anesthetics makes this unlikely. There have been multiple studies using photoelectric plethysmography reporting that the transient decrease in blood flow in digits returns to normal levels within 3 hours, with no complications seen.\(^1\sim^4\) The systemic effects of high doses of epinephrine include elevated heart rate, increased anxiety, palpitations, diaphoresis, and increased respiratory rate.\(^5\) These systemic effects are rare while injecting into digits unless the physician performs an accidental intra-arterial or intravenous injection.

Digital nerve blocks are fairly common in the aforementioned medical specialties as well as in the emergency department. Prospective patients may present with an infection, ingrown nail, contracture of digits, or with compound fractures. Whenever a procedure is indicated to correct the pathology, the area needs to be insensate so the patient can have their medical needs attended to. The debate lies whether to use a local anesthetic with epinephrine or a tourniquet to create a bloodless field, so the physician can work or operate with better vision.\(^5\) Tourniquets are currently the standard in most hospitals due to the fear of epinephrine use - but tourniquets are not without risks. While the epinephrine potential complications are well documented and discussed, the risks in tourniquet use are given comparatively less thought. Applying a tourniquet has a host of risks and potential complications associated with it, including potential muscle, vessel, or nerve injury; risks of using systemic anesthesia (and increased cost to patient); necrosis; reperfusion injuries; and the general trend of requiring more local anesthesia.\(^6\sim^8\)

The initial use of “pharmacological tourniquets” was pioneered in the early 1900’s by Dr. Heinrich Braun, which consisted of cocaine (the original local anesthetic and potent vasoconstrictor) mixed with epinephrine.\(^9\) Shortly after, procaine was introduced as a local anesthetic which was used very commonly (with and without epinephrine) with varying degrees of success.\(^10\) There are several case studies demonstrating digital necrosis with plain procaine (and too tight of a tourniquet) as well as with untitrated epinephrine added to the anesthetic.\(^11\sim^13\)
Procaine was later replaced by local anesthetics today, often times lidocaine.5

Much of the apprehension from using epinephrine in digital (or terminal arterial) injections is conjecture stemming from inadequate measuring capabilities of epinephrine in the early 1900s, and is not evidence based.10 Before standardizing local anesthetics (with or without epinephrine) in labeled vials, physicians used to use procaine HCL. Adding epinephrine to this made an “unstable mixture”, so the epinephrine was added just prior to injection by estimating a specific number of drops just prior to use.11-13 There were some cases of digital necrosis from the early 1900s, but the lack of regulations makes this no surprise. The early 20th century methods of procuring anesthetic are by today’s standards, reckless and dangerous, and gave epinephrine with local anesthetics an atrocious reputation.9,10 When used correctly (measuring out doses properly) - epinephrine has many benefits, most importantly: decreases the systemic absorption of the anesthetic which prolongs action and severely decreases systemic toxicity. Local anesthetic toxicity can be due to poor technique, overdose, or inadvertent intravascular injections – which is avoided by aspirating the area just prior to injection.1,2,4,5,7,8

Steinberg et al. performed a literature review and found that over 200,000 injections of lidocaine (1% or 2% with 1:100,000 or 1:200,000 epinephrine, 6 mL maximum) were given into the toes, forefoot, and foot without any reports of necrosis, ulcer, or damage to a digit - whereas cases of necrosis secondary to tourniquet (without epinephrine use) is not uncommon.5,10 The authors were very clear about their patients and noted that those with pre-gangrenous conditions (peripheral vascular disease, Raynaud’s, and hyperthyroidism) were not candidates for epinephrine due to increased risk of vasospasm, but they found that healthy patients dealt with the injection well (albeit it is a bit more painful than a plain injection due to the low pH of epinephrine) with fewer side effects than with a tourniquet.

There are many reports of self-injections with epinephrine auto injectors (Epipen®) into digits, with accidental sticks of the finger being most common.14,15 What is important to note, is that the concentration of Epipen®’s is 1:1,000 (1mg epinephrine per 1mL of solution) with 0.3mg of epinephrine being the actual dose given.16 To put that into perspective, that is 6,000x as much epinephrine as in a simple 1:100,000 solution in 5mL. To get 0.3mg of epinephrine diluted in local anesthetic at a 1:100,000 concentration, one would need 30,000mL - which is out of the realms of realistic possibility. In several studies, accidental Epipen® sticks in digits showed no digital necrosis, and only 30% of patients needed pharmacological intervention (phentolamine being the primary treatment option) at a concentration
significantly higher than used in local anesthetics.\textsuperscript{5,14,15} This indicates that the evidence against using epinephrine in digital blocks in healthy patients is weak and based off of assumptions and pre-clinical scientific research.

If necrosis were to occur, there are several simple treatment modalities (pharmacological and not) including warming the area, placing the affected limb in a dependent position, injecting 1mg of phentolamine in the area, or performing a chemical sympathectomy with plain lidocaine. These are all benign and easy to perform in the rare instance that ischemia or necrosis begins to affect the area.\textsuperscript{5--12} It is recommended that when performing digital blocks with epinephrine, to have some of these modalities nearby, in the event that perfusion is compromised more than desired.

This article aims to provide an in-depth review of available literature on the use of digital nerve blocks with epinephrine. This was done primarily by examining skin perfusion rates through various modalities after injection and monitoring for any ischemia or necrosis. Using epinephrine instead of a tourniquet provides an attractive alternative for not only the patient, but the clinician as well, due to a number of benefits, including no general anesthesia, procedures can be done in-office (and therefore lower cost), and there is no risk of tourniquet-related pathologies.

\textbf{METHODS}

Two independent searches of medical literature were performed using the PubMed database. The first query conducted was using “lidocaine epinephrine digital” which obtained 51 results. Inclusion criteria includes articles published after 1990, English language, full text articles, and studies in humans which reduced the number of articles to 33. Exclusion criteria included articles published before 1990, non-English articles, case studies, systematic reviews, any epinephrine concentrations more dilute than 1:200,000, epinephrine injected in sites other than digits, and non-human subjects. After review of the 33 articles, seven were selected for further review based on the exclusion criteria, therefore 44 total articles were excluded.

The second search was completed using the Boolean operator “OR” for the terms “Epinephrine digits” OR “Epinephrine and toes” which obtained 68 results. After application of the inclusion criteria (listed above), 37 articles remained. Applying exclusion criteria (listed above) to those articles, four were selected for further review with 64 total articles excluded. There were eleven articles reviewed for this literature analysis. A summary of the methods is depicted in Figure 1.
RESULTS

The PubMed Literature Search yielded a total of 119 articles for screening. Of the 119 articles, only eleven fit the inclusion criteria and were assessed. The outcomes of these articles are stated below.

Altinyazar et al. (2004) performed digital blocking using lidocaine with epinephrine in patients undergoing surgery for lesions on the digits or hallux. A total of 24 participants were recruited for the study. 15 patients underwent finger operations and nine had toe operations. Only healthy patients were included. Patient’s
received digital blocks containing 2% lidocaine with 1:100,000 epinephrine. Digital artery response was measured before and after the digital block with color Doppler ultrasound using a 5- to 12-MHz linear broadband transducer further analyzed with the Wilcoxon test. The parameters measured included peak systolic velocity (PSV), end diastolic velocity (EDV), and resistive index (RI). The study results showed that after digital block, PSV was significantly decreased and EDV was absent, indicating blood flow halted (p<0.05). After 60 minutes of anesthesia, the arterioles began to vasodilate, which restored blood flow to the local area indicated by an increase in PSV and EDV and a decrease in RI (p>0.05). These results were observed for all patients. The study found that 20 of the 24 patients had digital blood flow at the tenth minute after digital block was introduced. One patient had biphasic blood flow and three had dump flow at 60 minutes. Biphasic flow was observed for all patients at the 90th minute. All patients were followed up at ten days postoperatively and none showed any signs of complications related to local anesthesia or the surgical procedure. No sign of digital necrosis was observed and the authors concluded that the use of a digital block of 2% lidocaine with 1:100,000 epinephrine is safe in a selected patient population.³

Altinyazar et al. (2010) conducted a 44 patient study with stage III ingrown toenails. The participants were divided randomly into two groups: 22 patients received 2% plain lidocaine and the other 22 patients received 2% lidocaine with 1:100,000 epinephrine. Measurements for evaluation included pain, drainage, and peripheral tissue destruction postoperatively. A sterile rubber-band tourniquet was applied for all participants. When evaluating postoperative pain, all patients did not experience any pain at their first visit. For postoperative drainage, both groups experienced mild or moderate drainage, but neither experienced severe drainage. For recurrence, two participants in the 2% plain lidocaine group and one patient in the epinephrine group experienced recurrence, but this difference was statistically insignificant. Significant findings from this study include the number of postoperative days to alleviate drainage and heal peripheral tissue. Participants in the plain-lidocaine group took 19.0 ± 3.8 days and the epinephrine group took 11.1 ± 2.5 days. Furthermore, the study observed a statistically significant lower volume of anesthetic needed
when epinephrine was used versus with plain lidocaine. The study concluded that, “the use of epinephrine-containing local anesthetics may decrease the risk of damage related to volume injected” (1571).17

Chowdhry et al. conducted a retrospective review of 1111 cases involving digital and hand surgery. 500 participants received a digital block of 1% plain lidocaine with an average dose of 5.7 cc. Of these participants, 100 presented with PVD or had injuries that compromised the vasculature, so they were not injected with epinephrine. 611 participants received injections of 1% lidocaine with 1:100,000 epinephrine with an average dose of 4.33 cc. The procedures were used for traumatic crush injuries, lacerations, amputations, and fractures. The case reviewers observed if there were any complications in either group, including digital necrosis or structural injury. No necrosis, nerve injury or digital gangrene from the use of epinephrine was observed in these patients.18

Hafner et al. recruited 20 healthy participants for a prospective, double-blind, randomized, placebo-controlled study to observe adequate perfusion in digits via laser Doppler flowmetry. Each patient was injected with 6 ml ropivacaine (7.5 mg/ml), 1% plain lidocaine, and 1% lidocaine with 1:200,000 epinephrine (Xylocaine), and physiologic saline solution 0.9% in four fingers. Blood flux was recorded for each finger by computers and LDF values were monitored for 60 minutes. When ropivacaine was administered, an increase in mean blood perfusion was observed. When 1% lidocaine with 1:200,000 epinephrine was administered, there was a statistically significant decrease of perfusion by 60%. This was reversed after 24 minutes. Sustained analgesia was observed with ropivacaine as long as six hours after administration. Analgesia was observed with 1% plain lidocaine and was statistically significant after 32 minutes. With the addition of 1:200,000 epinephrine, the effect was significantly prolonged. The study results concluded that the use of 1:200,000 epinephrine is safe and that ropivacaine with an epinephrine additive is advantageous.19

Cordoba-Fernandez et al. conducted a controlled, prospective and randomized study with 44 healthy subjects with painful ingrown toenails. The study subjects were divided into two groups. In the
experimental group, 34 test subjects were injected with a solution of 2% mepivacaine with 1:100,000 epinephrine and surgery was operated without a tourniquet. In the control group 36 toes were injected with a solution of 2% mepivacaine without epinephrine and operated with a tourniquet. The researchers examined the rates of recurrence, as well as duration of anesthetic effect, post-op bleeding, and pain. A chi-square test was conducted to evaluate the results of the study, which did not show a statistically significant difference of recurrence for both groups. The results showed significant difference in bleeding between the two groups (94.4% of toes with abundant bleeding in the control group and 17.64% of toes in the experimental group, P<0.0001). Anesthetic effect was also higher in the experimental group (P=0.001). The study concluded that there is strong evidence for the efficacy of anesthetic digital block with epinephrine without tourniquet.20

Firoz et al. conducted a retrospective chart review of 63 patients that underwent Moh’s micrographic surgery in the digits, with the most common lesion removed being Squamous Cell Carcinoma. Prior to the surgery, a total of 59 fingers and four toes were injected with 0.5% lidocaine (buffered with sodium bicarbonate in a 1:10 ratio) with 1:200,000 epinephrine. An average of 6.92 mL was injected into each tumor site in a proximal to distal direction. Of the 63 patients, 33% had circulation disorders, 64% had hypertension, 28.6% were type II diabetics, and 51% were taking some sort of anti-coagulant. Post-operatively, most wounds were allowed to heal by secondary intention. There showed to be zero cases of digital necrosis as well as no failures in the skin grafts used.21

Sonmez et al. conducted a randomized controlled trial of 20 patients who underwent digital surgery. The study was conducted to measure fingertip capillary blood gas parameters immediately before and 15 minutes after digital blocks were administered. There were two patient groups with ten patients in each group. The first group was injected with 3mL of 2% plain lidocaine and the second group was injected with 3mL of 2% lidocaine with 1:80,000 epinephrine. These nerve blocks were used for the following surgeries: cross finger-flaps, pyogenic granuloma, tendon cyst, wart, ganglion, and giant cell tumor removal. Capillary blood was collected in a heparinized capillary tube from the finger pulp to
specifically measure pH, PCO2, PO2, HCO3, and SaO2. There was a statistically significant increase in pH from 7.395 to 7.403 (P=0.032) in the lidocaine with epinephrine group after injection. There was also a 7% decrease in PO2 and a 1% decrease in SaO2 in the lidocaine with epinephrine group, however these results were not statistically significant.22

Schnabl et al. conducted a randomized controlled study of 20 patients receiving injections into the digits. The study was done to test skin perfusion rates by measuring acral skin blood flux via laser Doppler flowmetry. The 20 patients were broken up into four groups where 6 mL injections were given into both the right and left hands in the middle and ring fingers by using the Oberst’s injection method. Group one was injected with 0.75% plain ropivicaine, group two was injected with 0.75% ropivicaine with 1:100,000 epinephrine, group three was injected with local tumescent anesthesia 0.15% TLA (ropivicaine, lidocaine, saline solution, and 1:100,000 epinephrine), and group four was a control where patients were injected with 2% plain lidocaine with 20 minutes of a tourniquet. Skin perfusion was measured before injection, at 1, 8, 16, 24, 32, 40, 48, 56, 60, 360, and 1440 minutes. At 60 minutes, group one had a perfusion change of +143.7%, group two had +16.8%, group three had +45.7%, and group four had +63.3%. At 1440 minutes, group one had a perfusion of +35.1% (p=0.03), group two measured -34.4% (p=0.05), group three was -31.9%, and group four measured -27.2%. Pain levels were also recorded in each patient at 0, 16, 32, 48, 60, 360, and 1400 minutes using the Visual Analog Scale (VAS).3

Calder et al. performed a randomized control trial of 44 volunteers who had one ring finger injected with 2cc of bupivacaine and the other injected with 2cc of bupivacaine with 1:200,000 epinephrine. After the injection, several parameters were measured, including: time for digits to return to normal pain, pressure, and touch sensation as well as fingertip temperature and capillary fill time. The findings indicated that the epinephrine increased the length of the bupivacaine action when measuring pain at onset, lasting 16.4 hours compared to 15.0 hours of plain bupivacaine (p=0.005). The return of touch sensation was felt at 17.3 hours for the epinephrine group and 15.6 hours for group one (p=0.004). Finally, the pressure sensation returned at 13.9 hours in the plain
group compared to 15.5 hours in the epinephrine group (p=0.004). There was also a hyperemia noted with temperature elevation of both the plain local anesthetic and with epinephrine (with lower temperature elevation with the epinephrine injection). There were no complications associated with either the plain bupivacaine or bupivacaine with epinephrine injections. No signs of ischemia or digital necrosis were noted to any of the digits after the procedures were completed.²⁴

Denkler evaluated the treatment of Dupuytren’s contracture in a standard hospital setting with local anesthetic (typically a 50:50 mixture of lidocaine and bupivacaine) and a tourniquet versus using a similar mixture of local anesthetic, but with a range of 1:100,000 to 1:100,000,000 epinephrine in the office. After 43 surgeries in the hospital with plain local anesthetic and 60 in the office setting with epinephrine added, there were similar post-operative improvements in range of motion of the metacarpophalangeal joints and interphalangeal joints as well as similar complications between the two groups. There were no cases of digital necrosis or gangrene and no signs of ischemia during any of the procedures with the epinephrine or the tourniquet.²⁵

Andrades et al. evaluated 43 patients with lesions in their fingers or toes who came into the emergency room. There were two groups, the first had digital blocks performed with 2% plain lidocaine and the second used 2% lidocaine with 1:100,000 epinephrine. The initial injection to numb the patient was 1.5 mL and after 10 minutes, the digits were re-evaluated to assess sensation level, and if needed, an extra 0.5 mL of anesthetic was injected. The researchers concluded that the group given lidocaine with epinephrine needed fewer injections and less overall anesthetic as compared to the plain lidocaine group. Only 4% of patients given epinephrine needed a second injection, while 24% of the plain lidocaine group required additional injections (p<0.05). Lidocaine with epinephrine had a longer lasting effect of 4.6 hours compared to 2.4 hours with plain lidocaine (p<0.05). The added epinephrine also had decreased overall pain on the VAS with a mean of 1.4, whereas the lidocaine plain group scored a mean of 4.1 (p<0.05). There were no systemic complications or signs of digital ischemia, gangrene, or necrosis in either of the two groups.²⁶
<table>
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<th>Study Design</th>
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<td>RCT</td>
<td>44 participants (all toes)</td>
<td>Group 1: 2% lidocaine plain Group 2: 2% lidocaine with 1:100,000 epinephrine</td>
<td>Pain level, drainage, and peripheral tissue destruction</td>
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<td>Chowdhry et al</td>
<td>Retrospective case review</td>
<td>1111 participants (all fingers)</td>
<td>Group 1: 1% lidocaine plain, Group 2: 1% lidocaine with 1:100,000 epinephrine</td>
<td>Necrosis, nerve injury</td>
<td>No necrosis, no nerve injuries</td>
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<tr>
<td>Hafner et al</td>
<td>RCT</td>
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<td>Bleeding amount, recurrence with chi-square test</td>
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<td>Study Type</td>
<td>Participants</td>
<td>Lidocaine with Epinephrine</td>
<td>Digital Necrosis</td>
<td>No Necrosis</td>
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<tr>
<td>Firoz et al</td>
<td>Retrospective Case Review</td>
<td>63 (59 fingers, 4 toes)</td>
<td>0.5% lidocaine with 1:200,000 epinephrine</td>
<td>Digital necrosis</td>
<td>No necrosis</td>
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<td>Sonmez et al</td>
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<td>Group 1: pH inc, 7% dec PO2, 1% dec SaO2 Group 2: inc PO2 and SaO2</td>
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<td>Schnabl et al</td>
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<td>Group 1: 0.75% ropivacaine plain Group 2: 0.75% ropivacaine with 1:100,000 epinephrine Group 3: 0.15% TLA (ropivacaine, lidocaine, saline solution, 1:100,000 epinephrine) Group 4: 2% lidocaine plain with 20 minutes tourniquet</td>
<td>Skin perfusion rates through acral skin blood flux via laser Doppler flowmetry</td>
<td>Perfusion at 60 mins: group 1 +143.7%, group 2 +16.8%, group 3 +45.7%, group 4 +63.3% at 1440 mins: group 1 +35.1%, group 2 -34.4%, group 3 -31.9%, group 4 -27.2%</td>
</tr>
<tr>
<td>Calder et al</td>
<td>RCT</td>
<td>44</td>
<td>Group 1: 2cc bupivacaine with 1:200,000 epinephrine Group 2: 2cc bupivacaine plain</td>
<td>Return to pain/pressure/sensation, fingertip temp, capillary fill time</td>
<td>Longer to return to normal in group 1 Temp: elevated in both (Group 2&gt;1), no necrosis</td>
</tr>
<tr>
<td>Denkler</td>
<td>Retrospective Case Review</td>
<td>103 (all fingers)</td>
<td>Group 1: 50:50 lidocaine and marcaine with tourniquet Group 2: 50:50 lidocaine and marcarine with 1:100,000-1:100,000,000 epinephrine</td>
<td>Digital necrosis, ischemia, ROM improvements</td>
<td>Improved ROM, no digital necrosis</td>
</tr>
<tr>
<td>Andrades et al</td>
<td>Case series</td>
<td>43</td>
<td>Group 1: 2% lidocaine plain Group 2: 2% lidocaine with 1:100,000 epinephrine</td>
<td>Pain level, Injection volume, digital necrosis</td>
<td>Group 2 needed fewer injections and experienced less pain No necrosis</td>
</tr>
</tbody>
</table>

Table 1: Summary of Results for each Study
DISCUSSION

Local anesthetic with epinephrine vs plain local anesthetic

The use of epinephrine in digital blocks comes with a variety of advantages as compared to injecting with local anesthetic alone. Some of the key differences are related to the ease of creating a bloodless field, lower anesthetic levels injected, and decreased pain ratings in patients overall. Altinyazar et al. reported an eight-day shorter duration for postoperative drainage of the surgical site with the use of epinephrine as compared to the plain lidocaine group. There was also a 1mL lower volume of anesthetic injected in the epinephrine group. Hafner et al. initially showed a laser Doppler flowmetry perfusion decrease of 60% (p<0.01) in the epinephrine group as compared to the plain ropivacaine group. However, this was reversed after 24 minutes and the vasoconstrictive effect could not be detected at all 48 minutes later. The analgesic effect of lidocaine was increased when epinephrine was added, contributing to prolonged pain relief. Cordoba-Fernandez et al. studied the effect of mepivacaine with epinephrine against plain mepivacaine and found that the addition of epinephrine decreased the level of abundant bleeding to 17.65% of patients, whereas the plain anesthetic group had abundant bleeding in 94.4% of patients (p<0.0001). The duration of anesthetic effect lasted longer in the epinephrine group as well (p=0.001).

Sonmez et al. demonstrated that the lidocaine with epinephrine group took about 3 hours longer to regain full sensation in the finger than the plain lidocaine group (p<0.001). The capillary blood gas values did not show any significant changes when comparing both groups together. Schnabl et al. showed no significant acral skin perfusion changes via laser Doppler flowmetry directly after injection of ropivacaine with epinephrine, increased perfusion at six hours, and decreased perfusion at 24 hours post-injection. This is in comparison to the plain ropivacaine group, which showed increased perfusion throughout all time intervals. The epinephrine group also exhibited an analgesic effect lasting 12 hours longer than the plain ropivacaine group. Calder et al. tested plain bupivacaine against bupivacaine with epinephrine, which revealed longer return to pain sensation (additional 1.4 hours, p=0.005), touch sensation (additional 1.7 hours, p=0.004), and pressure sensation (additional 1.6 hours, p=0.004) in the epinephrine group. Andrades et al. compared plain lidocaine against lidocaine with epinephrine and found that the epinephrine group required less reinforcement injections to acquire proper analgesic effect (4% of patients) compared to the plain lidocaine group (24% of patients, p<0.05). The mean pain score was on average three points higher on the VAS in the plain lidocaine group as well (p<0.05). The total time for loss of pain sensation was two hours longer in the plain lidocaine group (p<0.05).
Chowdhry et al. and Denkler simply commented on the fact that there was no necrosis or complications seen in either the plain anesthetic or epinephrine groups. From these results, it is evident that the experimental groups using epinephrine had less complications and more patient satisfaction than the plain anesthetic groups. Since epinephrine causes vasoconstriction, it maintains the local anesthetic in the procedure area giving it this longer lasting effect.

*Local anesthetic with epinephrine vs local anesthetic with tourniquet*

Currently the recommended and gold standard treatment for digital nerve blocks is using plain local anesthetic with the addition of a tourniquet to create a bloodless field. However, there have been several studies which specifically compared different outcomes using epinephrine versus a tourniquet in a digital nerve block. Cordoba-Fernandez et al. found that in hallucal procedures, as compared to tourniquets, epinephrine provided less bleeding in the area (P<0.001) as well as causing an increased duration of the anesthetic (P=0.001). Schnabl et al. completed a similar study and evaluated skin perfusion rates after injecting plain local anesthetic, local anesthetic with epinephrine, or plain local anesthetic with a tourniquet. The results were that the reduction in skin perfusion was similar with a tourniquet compared to using epinephrine, although the anesthetic wore off significantly faster than in the epinephrine group (P<0.001). There were also more complications in the tourniquet group, including paresthesia, hematoma, and minor motion deficits for up to 14 days after the procedure. Lastly, a study by Denkler, which evaluated surgeries on Dupuytren’s contracture, comparing the use of a tourniquet in a hospital setting (because patients cannot tolerate tourniquets on the arm without general anesthesia) with using epinephrine in an office setting. Both procedures had nearly identical results leading to improvements in range of motion - however, performing the operation in a hospital with a tourniquet and general anesthesia comes with increased risk and a significantly higher price as compared to an office setting.

Overall, the problems with tourniquets are usually underappreciated in comparison to those of epinephrine, as they are viewed as necessities in the surgical world. This method of creating a bloodless field is far from perfect however, with many potential complications including: reactive hyperemia which can cause increased bleeding leading to diminished anesthetic effect, hematoma formation, nerve or vessel damage, and edema secondary to lymphatic obstruction. While epinephrine is not a risk free modality either, it has much fewer complications and creates less bleeding with an increase in the local anesthetic duration. There is a risk for ischemia or necrosis from
using either option, but this is generally reversible with phentolamine in cases of epinephrine vasoconstriction.

Accidental EpiPen Injections

There have been a number of case studies and retrospective case series reviewing accidental injections of EpiPen into the digits. The concentration of epinephrine in these autoinjectors is 1:1,000, much more potent than the concentrations used in digital blocks prior to any type of procedure, which are on average a concentration of 1:100,000-1:200,000. Mrvos et al. collected case reports on 28 accidental injections of epinephrine auto-injectors with 23 of the cases being in the digits. Of these cases, four patients reported no effect and nine required no treatment. The patients who did require treatment, consisting of warm soaks and massage, were not at risk for digital injury and there were no cases of necrosis or infection.27 The symptoms reported in this retrospective review included swelling, pallor, pain, and erythema. Muck et al reported on six years of data for a total of 365 cases of epinephrine auto-injections into the hand, 127 of those involving a digit with complete follow-up. Vasodilatory intervention was only administered in 23% of patients, which consisted of nitroglycerin paste, local phentolamine injection, and local terbutaline. Ischemic events were documented in four patients. Local symptoms were observed to be pain, blanching, discoloration, numbness, ecchymosis, ischemia, and decreased capillary refill. In the end, all patients had complete resolution of symptoms and no cases of digital necrosis.14 Fitzcharles-Bowe et al. collected information on 59 incidents of accidental EpiPen injections from 1900-2005 to find that 32 of these cases had not required treatment. In the remaining cases that did require treatment, phentolamine was the most common substance used.15 This is the gold standard for reversal of the vasoconstrictive effects of epinephrine and has shown to reverse the pathology up to 13 hours after the accidental injection.28 This alpha blocker acts to relax the wall musculature of the blood vessels to ensure their vasodilation. It has been shown that 1 mg of phentolamine can reliably reverse the vasoconstrictive action in digits an average of 1 hour and 25 minutes post-injection.15 Since this agent is so well known for its ischemic reversal properties and has shown to have high rates of success when administered, physicians can feel comfortable that they have this as a back-up should there be any signs of ischemia when lower concentration epinephrine is used in digital blocks.

Contraindications

There are a number of known contraindications for the use of epinephrine in digital surgery or digital blocks. While some medical professionals use epinephrine often in digital surgery, most are in agreement that it should not be used in patients with any sort
of vascular compromising conditions. For hand injections, physicians will commonly use the Allen test to examine arterial blood flow before performing these injections. This test involves manually compressing both the radial (RA) and ulnar arteries (UA), followed by having the patient clench their fist as to expel blood from the hand. After this, the fist is opened and the UA is released so the physician can time the recovery of capillary blushing to the hand. The terminal arterioles in the fingers and toes are sensitive to vasoconstrictive agents in patients with peripheral vascular disease, cardiac problems, thromboangiitis obliterans, Raynaud’s, systemic sclerosis, scleroderma, nicotine consumption, diabetes, and microangiopathy. Out of the eleven studies in this systematic review, only two included a patient population with vascular compromise. Firoz et al. included 33.3% of patients with circulation disorders, 63.5% with hypertension, 28.6% with type II diabetes, 3.2% being smokers, and 50.8% having been on some type of anticoagulant. Denkler included 12 patients with hypertension, two smokers, three with coronary artery disease, one diabetic, and two patients who had stopped warfarin days before the operation. The researchers felt comfortable injecting epinephrine in these subjects because such a high number of them were taking anticoagulants, helping to relieve the dangers of vessel spasm or partially occluded vessels. To have studies conducted with these comorbidities is an accurate representation of the patient population most physicians deal with in their daily practice. There were no cases of digital necrosis, gangrene, or ischemia observed in these patients.

Adverse events

While there were no adverse events including cases of necrosis, ischemia, or gangrene in the studies we reviewed, there have been reported cases of digital injury with the use of digital nerve blocks, with or without the use of epinephrine. Denkler reports on a number of adverse events from the years 1880-1966, when there were much fewer regulations regarding injectables. Denkler found that there were 48 cases of digital necrosis, with only 21 of them involving epinephrine, and none of them utilizing lidocaine. Many of these were due to poor regulations, constrictive dressings, and a lack of understanding of potential medical issues that patients had. In modern times, there have been very few, if any, reported cases of non-reversible necrosis secondary to epinephrine. Other than the low risk of necrosis, potential adverse events include: increased pain of injection due to the low pH of epinephrine or accidentally injecting into a blood vessel. This risk of systemic injection is significantly decreased by aspirating before injecting to ensure the needle is not placed inside a blood vessel. While these events are certainly possible, they are very improbable, and not unique to epinephrine use.
CONCLUSION

When looking at the data that has been collected from the use of local anesthetics in combination with epinephrine, this technique has the potential to be more efficient in performing digital blocks before a variety of procedures. The results of the studies revealed no cases of digital necrosis, gangrene, or ischemia, in contrast to what has been stated in the literature of the past.

There are some limitations to this systematic review that was conducted on the use of epinephrine in combination with local anesthetics. Many of the studies claimed that they tested the use of epinephrine against a control group. The injections given in this “control group” were a plain form of local anesthetic in most cases, which in reality is not a proper control. These studies would have been stronger if they injected some sort of saline solution into the digit to observe what happens to blood flow, pain level, and the other measurable outcomes that were observed. Perhaps the injection of fluid into such a small space with compressible vessels and nerves alone accounts for some vasoconstriction and pain relief. Only one study used physiologic saline solution as a placebo to study the effects of fluid injection, which produced a small but prominent anesthetic effect.\(^{19}\)

The studies also varied in types of local anesthetics that were used. The different researchers chose to use a variety of these anesthetics including lidocaine, ropivacaine, mepivacaine, and bupivacaine. Since several local anesthetics were used, all with different times of onset and duration, it is difficult to compare across studies. The most common local anesthetic used in podiatric practice is lidocaine, however some of these choices come down to physician preference and type of procedure being done. Not only were different anesthetics used, but different volumes were given to obtain loss of sensation in the digit. Higher amounts of anesthetic injected could have an effect on vasodilation of vessels, altering the effect of epinephrine vasoconstriction in the same area.

Another limitation to this review, unique to the field of podiatry, was the small amount of studies involving epinephrine use in the toes. Of the eleven studies, only four included injections in the toes.\(^3, 17, 20, 21\) Most of the previous studies completed, especially in the dermatologic and plastics fields are conducted on the fingers. While many podiatrists state they use epinephrine in the office setting for digital blocks, there is limited evidence of no adverse events and there needs to be more studies reported on this topic. Although the fingers and toes both include end-arterials, the foot vessels are further from the heart and more commonly compromised by disease. This has been said to increase the risk for necrosis because of this already limited blood flow.
Most of the studies did not use a patient population that the average podiatrist will see in their office. Only two of the studies included patients with diabetes, circulation disorders, and nicotine consumption.\textsuperscript{21, 25} Since there are an increased number of patients who come to the podiatrist with these conditions, it is difficult to compare the results of this review, which mainly focused on healthy patients with no circulation compromise.

Lastly, the studies focused on different measuring parameters, making it hard to compare results to each other. Even in the studies that looked at Doppler flowmetry, different markers were examined such as PSV, EDV, and RI in one compared with LDF (laser Doppler flowmetry) values in another.\textsuperscript{3, 19, 23} Some studies simply looked at whether necrosis was present after injection with epinephrine. Even the pain level taken from patients was assessed differently in each experiment, with some coming from the VAS and others based on return of sensation in the digit.

With these limitations taken into account, the use of epinephrine in digital blocks is promising. It will aid in giving the physician a bloodless field, prolong loss of sensation, and decreased pain levels for the patient. These effects lead to a less complicated procedure, and ease the recovery process for the patient.

\textbf{AUTHORS’ CONTRIBUTIONS}

All authors participated equally in the conception of the research topic, literature review, and extraction of data. All authors agreed upon the final submission.

\textbf{STATEMENT OF COMPETING INTERESTS}

All authors declare they have no competing interests.

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