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A Note from the Editor

The evolution of medicine is contingent upon the capable minds of those practitioners within, and those theorist without, to pursue the ideals of science; testing every principle for validity, sustainability, and purpose. Should, at any time, these individuals become complacent in their aspirations to discover the truth, then the progression of medical practice fails, and disease becomes the victor. It is the hope, through diligent perseverance, that we as a medical community strive to explore the unexplored, and challenge the accepted. Through these attempts we sustain the foundation of evidenced based medicine, ensuring the best possible care by continuous efforts to improve. Displays of such efforts, evidenced from the most novice of research attempts to the most concrete multi-centered clinical trials, depend on the guidance and aid of the seasoned minds of science. Without the wisdom of these individuals, the recreation of the metaphorical wheel would be inevitable. To that note, I extend my gratitude to the current senior/faculty advisory board and peer reviewers for their endless efforts to publish a journal of supreme quality. Additionally, a journal is only as good as the works it contains, and one would be amiss if a special ‘thank you’ was not extended to the endless efforts of our authors.

It is my hope, as the 2013-2014 Editor-in-Chief of the New York College of Podiatric Medicine PMR, that the contents of this journal serve as a useful tool to employ the current practices of exceptional patient care for numerous pathologies. To overlook this central goal would undermine the primary focus of research. May you find the contents of this journal to be enlightening, inspiring, and helpful, as we all seek the common goal of optimal patient care.

J. Adrian Wright, AM
Editor-in-Chief
Literature Review of Verrucous Carcinoma of the Foot

Sarah Zottoli, MS, and Sarah Breakstone, MBS

Abstract

Introduction
Verrucous carcinoma can be found in many areas of the body and is an infrequent finding in the lower extremity. This low-grade, locally invasive clinicopathologic variant of squamous cell carcinoma has been linked to the human papilloma virus (HPV) and malignancy. Removal of verrucous carcinoma is recommended and can be accomplished utilizing many techniques.

Study Design
Systematic Review of the Literature

Methods
A PubMed search was performed using keywords. Articles were excluded if they were deemed irrelevant by their abstracts. Due to the rarity of this condition, there were no exclusions made based on publication year. In addition to case reports and case series, articles pertaining to common misdiagnoses and misused terminology were also included to help the reader correctly define verrucous carcinoma. Utilizing many papers allowed us to identify several characteristics of verrucous carcinoma presentation and assessed several criteria for diagnosis and treatment in twenty-three cases.

Results
Twenty-three cases were evaluated in this study. Verrucous carcinoma was found to be over three times more common in male patients, with the mean age of presentation being sixty-one years of age. The most common area of presentation on the foot was the plantar forefoot. Additionally, surgical excision predominated as the most common treatment, superseding amputation and cryotherapy. Furthermore, Mohs micrographic surgical technique was discussed as a viable treatment option. Radiation was not found to be a favorable option, with evidence strongly suggesting its role in malignant change.

Conclusion
Surgical excision and Mohs micrographic surgical technique are promising treatment methods for verrucous carcinoma. Utilizing the correct procedure when taking biopsies is very important, and obtaining a sample of appropriate depth and width is key to the correct diagnosis of verrucous carcinoma. We conclude that great care should be taken in obtaining adequate biopsies and that the follow-up time reported in many cases is insufficient in assessing the rate of reoccurrence.

Key Words
Verrucous carcinoma, Mohs, human papilloma virus (HPV), malignancy

Level of Evidence: 4
INTRODUCTION

Verrucous carcinoma is a term originally used by Lauren V. Ackerman over 60 years ago to describe an indolent and abnormal variant of squamous cell carcinoma in the oral cavity. He found that the cheek, mucosa, and lower gums were the most common location of these findings, with the condition predominately occurring in males. Additionally, a significant association between tobacco use and verrucous carcinoma was established.1

Depending on the anatomical site, there are three main forms of verrucous carcinoma: oral florid papilloma, giant condyloma acuminatum, and epithelioma cuniculatum.2 Furthermore, each of these forms can go by additional names, such as Ackerman tumor, Buschke-Loewenstein tumor, and carcinoma cuniculatum, respectively.3,4 Epithelioma cuniculatum pedis is a term referring to any squamous cell carcinoma of the foot. Verrucous carcinoma of the foot has greater penetration and destructive power than other forms of verrucous carcinoma.6 Most cases on the lower extremity present on the sole of the foot, particularly on high-pressure areas (Figure 1). Additionally, presentation on the toes is exceptionally rare.2

Verrucous carcinoma is commonly misdiagnosed because it can resemble a variety of other epidermal and dermal lesions. Some similarly presenting benign lesions are verruca plantaris and dermatitis. More aggressive lesions that can be misdiagnosed as verrucous carcinoma include squamous cell carcinoma and basal cell carcinoma.7 Case histories have shown that verrucous carcinoma is usually identified after a long-standing diagnosis of resistant verruca plantaris for over ten years.8

Treatment of verrucous carcinoma is often delayed in part due to misdiagnosis. Common presentation is a slowly enlarging warty tumor that may be greasy, foul-smelling, and produce a sebaceous discharge. One mitigating factor of a delayed diagnosis is that verrucous carcinoma rarely metastasizes.9 Verrucous carcinoma has a variety of histological characteristics that at first glance would seem to be helpful in the classification of this disease. Both exophytic and endophytic growth patterns with stroma containing inflammatory infiltrates are demonstrated in verrucous carcinoma. Additionally, keratin-filled cysts project deep into the dermis in rete ridges (Figure 2). Superficial areas of parakeratosis and hyperkeratosis are also present.6 Diagnosis is difficult to obtain with histopathology alone due to the sharing of these histological characteristics with many other diseases.

Prevalence of verrucous carcinoma in the mouth, larynx and perianal areas is much greater than other regions of the body. Fortunately, growth is slow and the spread to lymph nodes is rare.10,11 Distant metastasis is also infrequent, but metastasis does occur and can lead to loss of limb or other serious complications. Additionally, recurrence is relatively common and growth is relentless, which may result in extending deep into tissues.10 Thus, early proper diagnosis and treatment can be cost effective and potentially life saving.
In this paper, we will review several cases of verrucous carcinoma that present on the foot. This comprehensive literature review will focus on common presentations, treatment modalities, and diagnostic criteria.

METHODS

Two authors conducted independent literature searches utilizing the online database PubMed with keywords such as ‘verrucous carcinoma’ and ‘foot’. The initial search results with ‘verrucous carcinoma’ alone produced 1,559 articles. With the addition of the keyword ‘foot’, the search results were reduced to 122 articles. Based solely on title, 40 articles were selected and 18 of those were eliminated by their abstract not meeting our inclusion criteria. A total of 22 articles were selected and thoroughly reviewed.

RESULTS

The majority of literature pertaining to verrucous carcinoma is in the form of case reports and case series. The lack of available random control studies makes it difficult to assess the best treatment for removal. Additionally, the follow-up time post removal of lesions makes it difficult to assess the rate of recurrence.

The findings in the 23 cases reviewed, shown in Figure 3, indicate that the average age of the patient affected by verrucous carcinoma of the foot was 61. There was a dominance of male versus females with a ratio of 18:5. The verrucous carcinoma had a greater affinity of the right foot versus the left with a ratio of 15: 6. Only one case was reported to have affected both feet. Additionally, verrucous carcinoma was observed mostly on the forefoot plantar surfaces. The reports indicated a predominance of forefoot verses rearfoot at 16: 6 and plantar verses dorsal at 20: 3. Of the indicated cases there were 11 biopsies of a suspicious area obtained. Furthermore, 4 out of the 11 needed another biopsy to confirm the diagnosis of verrucous carcinoma. Additional diagnostic techniques used were MRI in 4 cases, CT scan in 2 case, bone scan in 3 cases, and radiography in 5 cases. Treatment with excision compared to amputation of the affected area occurred at a ratio of 16:8, respectively. Of the 16 excisions, 4 cases needed re-excision for verification of the diagnosis or to make sure they had excised adequate border. Cryotherapy was also a treatment modality that was utilized in 2 cases. Lastly, we found that there was an incidence of recurrence in 2 cases. We predict that this rate of recurrence may have been higher if follow-up periods were longer. Most cases had minimal follow up of a few months to one year, possibly leading to the low number of possible reoccurrences.
DISCUSSION

Diagnosis
The diagnosis of verrucous carcinoma can be rather challenging due to the rarity of the condition. It presents most commonly in men and usually between 40 and 60 years of age. Unlike squamous cell carcinoma, it is uncommon for verrucous carcinoma to form keratin pearls. Additionally, when utilizing biopsy as a diagnostic tool, samples are often taken that lack necessary depth and/or width. Comorbidities found in the cases reviewed were congestive heart failure, hypertension, and diabetes mellitus type II. However, we did not find supporting evidence that these health conditions have a positive correlation with developing verrucous carcinoma. Additionally, there are many differential diagnoses (Figure 4) and misdiagnoses reported.

Human Papilloma Virus Association
There appears to be an association between human papilloma virus (HPV) and verrucous carcinoma. It is now thought that HPV may facilitate the development of verrucous carcinoma in some patients. However, many verrucous carcinoma samples are negative for both low-grade (types 6 and 11) and high-grade (types 16 and 18) HPV DNA. Most cutaneous verrucous carcinoma occur on the sole of the foot in a weight-bearing area.

Radiotherapy Contraindication
Researchers believe that radiotherapy is contraindicated in the treatment of verrucous carcinoma. Radiation has been associated with malignant changes and is believed to make verrucous carcinoma more aggressive.

Treatment
Pain, cosmesis, and other complications support the removal of epithelioma cuniculatum. Although it rarely metastasizes, verrucous carcinoma is very locally invasive and destructive. The common treatments discussed in our literature review consisted of surgical excision, amputation and Mohs micrographic surgery. Success rates with Mohs surgery, a microscopically controlled dissection technique aimed at preserving as much good tissue as possible while obtaining tumor removal, have been reported as high as 98% when treating epithelioma cuniculatum. Other treatments that have shown less success are cryotherapy, grafting, curettage, electrodessication, and radiotherapy. Because of potential malignant changes and aggressiveness, care should be taken to assess for malignancy associated with verrucous carcinoma. There are hallmark
Clinical findings suggestive of malignant transformation such as new onset of pain, change in character, drainage, odor, and appearance of a mass.\textsuperscript{18} Despite the rare occurrence of malignant change, patients with verrucous carcinoma, especially with chronic wounds, should be assessed for malignant change. Many diagnostic tools have been used in making an accurate diagnosis such as biopsy, CT, MRI, X-ray, and bone scan.\textsuperscript{6,14,17}

**CONCLUSION**

Due to the fact that verrucous carcinoma is a rare finding on the lower extremity, obtaining a large sample size and conducting randomized control trials could present several challenges. However, considerably larger sample sizes would significantly increase the validity of reported successful treatment modalities and appropriate screening criteria. Further investigation is needed to adequately assess recurrence of verrucous carcinoma, incorporating longer follow-up time. Additionally, obtaining biopsies of sufficient depth and width is essential in making a proper diagnosis. No “gold standard” treatment is consistent throughout the literature, despite many techniques that have been utilized. In avoiding amputation, surgical excision and Mohs technique are common treatment methods with promising results in complete removal and avoiding recurrence.

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Table 1. Treatment Modalities and Reoccurrence Reported in Twenty-Three Cases of Verrucous Carcinoma.

<table>
<thead>
<tr>
<th>Source</th>
<th>Age</th>
<th>Excision</th>
<th>Re-Excision</th>
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<th>Amputation</th>
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Table 2. Reported Diagnostic Techniques of Verrucous Carcinoma.

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<th>Source</th>
<th>Age</th>
<th>MRI</th>
<th>CT Scan</th>
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Authors’ Contribution
SZ conceived the topic, participated in obtaining resources, and assisted in designing the study and drafting the manuscript. SB conceived the design of the study and participated in obtaining resources and drafting the manuscript. Both authors have read and approved the final manuscript for publication.

Statement of Competing Interests
The authors of this manuscript declare that they have no competing interests.

REFERENCES


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Complex Regional Pain Syndrome Type 1 in a Pediatric Patient: A Case Report of a 10-Year-Old Female Patient

Raymond Lee, BA and Dae Y. Lee, BS

Abstract

Introduction
The purpose of this article is to discuss Complex Regional Pain Syndrome (CRPS) and further increase awareness of CRPS as a diagnosis for persistent unilateral limb pain in pediatric patients. Pediatric CRPS differs from adult CRPS in various signs and symptoms. For this reason, it is important to recognize these differences when evaluating pediatric patients with persistent unilateral limb pain.

Study Design
Case Report

Methods
The inclusion criteria for this study necessitates that the patient be both pediatric and diagnosed with CRPS. All other possible etiologies for presenting symptomatology must be ruled out. Patients that are above the age of 18 or have any secondary diseases or conditions that could otherwise cause similar symptoms were excluded from the study.

Results
This article will offer a case presentation of a 10-year-old African American female pediatric patient with the symptomatology found in pediatric CRPS. The patient does not have any secondary diseases or conditions that would otherwise account for her underlying symptoms. Furthermore, this article will offer the most currently used modalities and methodologies for diagnosing, treating, and managing pediatric CRPS.

Conclusion
One of the major problems with pediatric CRPS is that it is often overlooked as a diagnosis for prolonged periods of time. This stalling of diagnosis leads to delayed treatment of the patient. Crucial to the diagnosis of CRPS in a pediatric patient is to recognize the different presentation from that of an adult patient. Early and correct diagnosis of pediatric CRPS is fundamental for shorter and more effective management of the problem.

Key Words
Complex Regional Pain Syndrome, Pediatrics, Children, Budapest Criteria, Reflex Sympathetic Dystrophy

Level of Evidence: 4
INTRODUCTION

Complex Regional Pain Syndrome (CRPS) is a painful disorder first described during the American Civil War by American Physician Silas Weir Mitchell. During the time, the disorder was referred to as “causalgia” by English Physician Robley Dunglison from the Greek words for heat (“caus” or “Kavaros”) and pain (“algia” or “ockyos”) because of its presentation as a debilitating “burning pain.” ¹ Throughout history, the syndrome continued to be referred to by many different names, including reflex sympathetic dystrophy, post-traumatic dystrophy, and Sudeck atrophy, reflecting an increasing awareness that the condition actually includes a wide range of disabilities and symptoms.² All of these disorders are now grouped under the name “Complex Regional Pain Syndrome” by the International Association for the Study of Pain (IASP).³

CRPS is described as a disorder affecting one extremity or more with characteristic excessive pain accompanying edema, limited range of

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<thead>
<tr>
<th></th>
<th>Adult CRPS</th>
<th>Pediatric CRPS</th>
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<tr>
<td>Gender</td>
<td>Female:Male 2.3</td>
<td>Female:Male 3:1</td>
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<tr>
<td>Median age of onset</td>
<td>37.7</td>
<td>8-16</td>
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<td>Affected area</td>
<td>Upper:Lower 2:1</td>
<td>Upper:Lower 1:5 with 75% predilection for the foot 1:4</td>
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<td>Resolution</td>
<td>74%, often spontaneously</td>
<td>92% with therapy</td>
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<td>Most common etiology</td>
<td>Fracture 46% Significant relation to history of major trauma</td>
<td>Minor trauma 80%</td>
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<tr>
<td>Presentation</td>
<td>· Increased warmth</td>
<td>· Decreased warmth</td>
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<td></td>
<td>· More edematous</td>
<td>· Less edematous</td>
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<td></td>
<td>· Pronounced neurologic symptoms</td>
<td>· Neurologic symptoms less pronounced</td>
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</table>
motion, vasomotor instability as well as skin changes.\textsuperscript{3} It is currently thought to be due to an abnormal host response to tissue injury, and is further categorized into two types: Type I is the condition in which there are no identifiable nerve lesions, and Type 2 is the condition in which there are nerve lesions in conjunction with the disorder. Based on the IASP, CRPS Type I occurs after an initial noxious stimulus occurs, leading to a condition where there is a disproportionate amount of pain compared to the stimulus, spontaneous pain, possible edema and possible abnormal sudomotor activity in the region of the pain.\textsuperscript{4} CRPS Type 2 occurs after an identifiable nerve injury occurs, leading to pain in the areas supplied by the affected nerve with similar symptoms of edema and abnormal sudomotor activity seen in Type 1. Because CRPS Type 2 is associated with a specific nerve injury and CRPS Type 1 is not, former names for the conditions were “causalgia” and “reflex sympathetic dystrophy, respectively.\textsuperscript{3}

It is important to recognize that CRPS occurs in both adult and pediatric patients, and as a result, the presentation of the condition differs between the two populations. Whereas adult CRPS often manifests in the upper extremities and occurs after a major traumatic event, pediatric CRPS has been documented to occur mostly in the lower extremities without any inciting trauma.

Early diagnosis and treatment of CRPS is considered one of the major factors in efficacy of treatment. Unfortunately, the significant differences between adult and pediatric CRPS often leads to delayed diagnosis of the condition in pediatric patients.

Diagnosis of CRPS is usually based only on history and physical findings. There are no specific lab findings for CRPS. However, lab work does serve an important role in ruling out other conditions that may cause symptoms that are also present in CRPS. As a result, CRPS is often diagnosed after a large number of clinical visits. The condition may then progress into a more severe state. All these aspects contribute to delayed treatment and overall reduced treatment efficacy. This article will analyze the differences between adult and pediatric CRPS, the signs, symptoms, method of diagnosing, and treatment of pediatric CRPS, and present a case of a 10-year-old pediatric patient seen at the Foot Center of New York diagnosed with pediatric CRPS.\textsuperscript{5}

**Epidemiology and Etiology**

In children, CRPS Type 1 is most commonly seen in females, with the incidence highest at or just before puberty. In a study by Sherry et al., who followed 103 children with CRPS, 87 were girls with a mean age of 13 years.\textsuperscript{5} A similar study by Low et al, found that in 20 pediatric patients with CRPS at the Pain Clinic in the Children’s Hospital at Westmead, 18 (90%) were female. In the study, the mean onset age for females and males was 12.1 and 8.9 years respectively.\textsuperscript{6}

Additionally, CRPS Type I seems to be more common amongst Caucasian children. Bernstein et al. reported that 18 of 23 pediatric patients with Type 1 CRPS were Caucasian, 4 were Hispanic and 1 was black.\textsuperscript{7} Wilder reported similar findings in both the Children’s Hospital in Boston and at the Mayo Clinic in Rochester.\textsuperscript{8} Allen et al. found parallel results in their retrospective study of 134 patients with CRPS.\textsuperscript{14} Additionally, Wilder reported that CRPS Type 2 is found to have nearly the same incidence in both boys and girls, and has been found in children as early as 3 years old.\textsuperscript{8}

Murray reported 46 pediatric CRPS patients with ages ranging from 8 to 15.2 of which 76% (35) were female. Fifty-four percent of the patients had a history of trauma. According to Murray, the average number of professionals seen by the patients before the diagnosis was 2.3, with a median diagnosis time of 12 weeks, median recovery time of 7 weeks, and a 27.5% relapse rate.\textsuperscript{9}

The pathophysiology of CRPS is unknown; there are various different theories on the causes of the symptoms seen in CRPS, including peripheral...
small fiber neuropathy, neurogenic inflammatory pain, and an autoimmune condition where anti-neuronal antibodies attack host nerve fibers. The central sensitization theory, a newer etiology recently proposed, introduces the idea that CRPS is the result of a period of intense or repetitive noxious stimulation leading to increased excitability of neurons, ultimately resulting in pain even with non-noxious stimuli. 6,10

Differential Diagnoses
There are multiple diagnoses that may present with similar symptomatology as pediatric CRPS, and so it is important to rule out these diagnoses. Differential diagnoses for CRPS include (1) trauma, (2) post-traumatic neuropathy, (3) inflammatory disorders, and (4) tumors.

Trauma (commonly presenting with edema, erythema and localized swelling) leads to pain secondary to tissue damage. Bony fractures or other soft tissue damage should be ruled out with diagnostic imaging modalities such as plain film radiographs, computed tomography scans, or magnetic resonance imaging.

Damage to peripheral nerves may present with similar “burning pains” that many CRPS patients suffer. However, unlike CRPS, post-traumatic neuropathy is usually localized to the affected area of trauma or the area respectively innervated by that nerve. Comparably, CRPS Type II may have a specific peripheral nerve lesion, but the affected areas usually spread beyond the distribution of the affected nerve.15

Inflammatory conditions (e.g., osteomyelitis, juvenile arthritis, rheumatoid arthritis, reactive arthritis, systemic lupus erythematosus and psoriatic ankylosis) and tumors also need to be ruled out prior to diagnosis of CRPS. Plain radiographs, bone scans and blood analysis should be performed if these diagnoses are suspected.

Table 2: Budapest Criteria for clinical diagnosis for CRPS

<table>
<thead>
<tr>
<th>Category</th>
<th>Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory</td>
<td>Hyperesthesia and/or allodynia</td>
</tr>
<tr>
<td>Vasomotor/Edema</td>
<td>Temperature asymmetry and/or skin color changes/asymmetry</td>
</tr>
<tr>
<td>Sudomotor</td>
<td>Edema and/or sweating changes/asymmetry</td>
</tr>
<tr>
<td>Motor/Trophic</td>
<td>Decreased range of motion and/or motor dysfunction and/or trophic changes.</td>
</tr>
</tbody>
</table>

Table 3: Categories of the Budapest Criteria
Diagnosis
Currently, the accepted methodology for diagnosing Complex Regional Pain Syndrome (CRPS) is through history and physical examination. The clinical diagnosis is made through satisfying a set of requirements set forth by the Budapest Criteria [Table 2]. Furthermore, distinguishing CRPS Type 1 from CRPS Type 2 is through assessing whether there is the presence of a nerve lesion.11 Some clinicians still use the International Association for Study of Pain (IASP) diagnostic criteria for diagnosis of CRPS, but a study by Norman et al. demonstrated that the IASP diagnostic criteria was significantly less specific than the Budapest diagnostic criteria (0.41 to 0.68) and has the potential for substantial false positives.12

It is important to rule out other possible diagnoses, and therefore additional studies are usually taken before the diagnosis is made. Complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum autoantibodies should be obtained to rule out possibilities of rheumatologic diseases or infections. However, once the clinical diagnosis of CRPS is made, no further studies are recommended as there are no confirmatory studies or lab evaluations. Once a diagnosis is made, it is recommended to begin treatment as immediately as possible. Delayed treatment could decrease efficacy of treatment and prolong the course of pain.

Three-phase bone scintigraphy may be a useful technical modality for supporting the diagnosis of CRPS.13 A retrospective chart review of 134 patients by Allen et al. found three-phase bone scan to be a helpful imaging technique to support the diagnosis of adult CRPS type I in 53% of the patients that had reported receiving bone scans.14 Similarly, several groups have argued that for pediatric CRPS patients, bone scans revealing diffusely increased uptake should be considered a necessary component for diagnosis of CRPS.8 However, it must be noted that while bone scanning in adult CRPS patients will reveal diffuse hyperperfusion, bone scanning in pediatric CRPS patients does not necessarily always produce similar results. Sometimes, bone scans in pediatric CRPS patients show results indicating normal bone, which may delay the clinicians’ diagnosis. For this reason, three-phase bone scan should not be used as the sole evidence for confirming a positive diagnosis.

Other imaging modalities can also be used, such as magnetic resonance imaging and plain radiography, to help rule out other possible differential diagnoses. Rho et al. argued that magnetic resonance imaging is often “necessary” to rule out other possible pathologies as the source of pain. Additionally, plain radiographs may be useful in supporting the diagnosis of CRPS because it would reveal “patchy osteoporosis and periarticular osteopenia” that can be seen as early as two weeks after onset of symptoms.15

Thermography can also be useful in confirming the diagnosis of pediatric CRPS. Most pediatric CRPS patients present with asymmetry in temperature of the lower extremities, with the affected limb commonly being colder. A difference of 1.0°C is considered significant, and often a significant difference between the affected and unaffected limbs could be useful in helping the clinician consider the diagnosis of CRPS.15

Treatment
Treatment of CRPS involves multiple modalities with the goal of complete reduction of pain, and if that is not possible, control of pain to allow for normal daily life-style. These modalities include pharmacological methods and physical therapy, as well as psychological assessments.

Although there are no definitive drugs that have been found effective in mitigating CRPS symptoms, pain medications have been cited by various authors as being an integral part in the management process for CRPS.68 Low et. al. used analgesic medications in conjunction with physiotherapy for treatment for pediatric CRPS cases, and he found that compliance to therapy
was often difficult without the administration of some form of pain-relieving medication. Multiple authors used amitriptyline and gabapentin and reported good results in conjunction with physical therapy. However, it is important to note that there are few well-designed studies regarding medication for pediatric CRPS, and therefore the usefulness of pain medications for treatment of this condition is still widely controversial.

Adding to the controversy surrounding pharmacological treatment of CRPS is a study done by Sherry et al., whose study of 103 children with CRPS revealed that 95 children (92%) became symptom free after the initial round of physical therapy alone, without any pharmacological treatments. Bernstein et al. found similar results in a study of 23 pediatric CRPS patients, where they found long-lasting reduction of CRPS symptomatology in all but one patient with physical therapy alone. Currently, physical therapy is considered to be the most effective treatment for CRPS, with controversy revolving around whether there should be adjunctive use of pharmacological modalities.

Finally, there has been some speculation that pediatric CRPS has a psychological component as well. Various authors, including Sherry et al., Low et al., Wilder et al., and Rho et al., found that a large number of children of CRPS have similar psychological characteristics. In a study of 46 pediatric CRPS cases, Murray found that 25% of the children had psychological issues that could have possibly contributed to the manifestation and severity of their condition. Murray et al. identified these children with having “high achieving” personalities in either academics or sports. Although there are some critiques to the use of psychological intervention as appropriate treatment for CRPS, some clinicians feel that psychological approaches to treating CRPS can be useful as an adjunct to physical therapy.

CASE REPORT

Ten year old female African American patient, henceforth called NG, presented with her mother to the Foot Center of New York on 11/9/2011 with a chief complaint of a severe, sharp shooting pain on the entire left foot and ankle. NG stated that the pain started in a precipitous manner 2 months earlier at a vacation when she was “walking a lot in flip flops.” She denies any event of specific traumatic event to the area but may have “turned her ankle” before the pain started. The pain was localized to the left lateral ankle initially but had spread to the entire left foot and ankle over 2 days. Severity of pain had not changed for the last 2 months.

The mother stated that her daughter’s foot was initially “red and swollen” but this had reduced over time. The mother also stated that she noted the muscles of her daughter’s foot sometimes “spasmed.” The mother stated that her daughter would not let anything touch her left foot and had not been able to wash her left foot because the touch of the washcloth or even water was too painful to bear. The patient slept with her left foot resting on a pillow at night without anything covering her foot. NG had been ambulating in crutches for the last 6 weeks because she was “unable to put any weight on the foot.”

When the pain first started on the vacation, NG was evaluated in the emergency room. Radiographs were taken but no clear pathology was evident. When she returned home from the vacation, her pediatrician referred her to a podiatrist for the pain. On 10/6/2011, an MRI was ordered that was unremarkable for any joint effusion, bursitis, fracture, or tarsal coalition. The
podiatrist placed NG in a CAM walker but she was unable to tolerate it for more than a few minutes as the pain was even worse in the splint. Patient was then referred to the Foot Center of New York.

The most notable finding on physical examination was the asymmetric appearance and temperature of the two feet. The skin of the left foot was scaly and dry and showed dystrophic changes, whereas the skin of the right foot presented without any notable sign of abnormality. The temperature on the right foot was 82.7 degrees Fahrenheit and 75.9 degrees Fahrenheit on the left foot. The patient appeared anxious and presented with “protective posture.”

Palpation of vascular status on left foot was difficult due to pain upon even light touch of the skin. A Doppler examination was performed and revealed normal pulses bilaterally. Capillary refill time was 1 second at the tip of all digits.

Upon neurological examination, no significant abnormality was noted. Protective sensation was intact bilaterally using Semmes-Weinstein monofilament test, but the patient stated that she felt the monofilament less on her left foot. Patellar and Achilles reflexes were 2/4 bilaterally. The plantar reflex showed plantarflexion of the hallux bilaterally. Lasegue test was performed and produced negative results for nerve impingement. The patient stated that she could not actively move her left ankle or foot.

Review of the radiographs of the left foot revealed a patchy osteoporosis that, in conjunction with the history and physical findings, suggested a possible diagnosis of CRPS. The case was discussed with the pediatrician and a referral was made to a pediatric neurologist.

NG was evaluated by a pediatric neurologist the following week. The neurologist agreed with our clinical impression and prescribed Neurontin to the patient. NG was referred to physical therapy at the Foot Center of New York on 12/1/2011 until she could be admitted to Columbia Presbyterian Pediatric Pain Management Center for intensive physical therapy regimen and behavioral modification therapy from mid-January to early May 2012.

Through the therapy regimen, NG slowly regained daily activity with incrementally reduced pain. She was able to tolerate putting on and off a sock on the left foot by early February. She was able to tolerate slippers, walk a small distance with the assist of a walker, and kick a ball with the left foot. From March to April, she advanced from a walker to a cane to independent walking without any assistive device. Pain level was minimal in April but she was still not able to tolerate a regular closed toe shoe. In May, she could walk normally without pain in regular shoe gear and was discharged from Columbia Presbyterian Pediatric Pain Management Center. There has been no relapse to date.

DISCUSSION

Although CRPS in adult patients was already recognized in the American Civil War, it was not until the 1970s when CRPS was mentioned and diagnosed in pediatric patients. It is important to note that there is currently an increasing number of pediatric patients presenting with CRPS, but the symptoms are significantly different from its appearance in adults.

Pediatric CRPS differs strikingly from adult CRPS in both presentation and response to treatment. Whereas adult CRPS usually presents with a history of significant major trauma preceding the condition, pediatric patients with CRPS usually do not report a history of any major trauma involvement. Additionally adult CRPS seems to present with more upper extremity involvement, CRPS in children has been documented to more commonly manifest in the lower extremities with a predilection for the foot. Low et al.’s study of 20 pediatric patients with CRPS reported that 17 children (85%) had lower
limb affected.\textsuperscript{6}

Since CRPS in children had not been discussed until early in the 1970s, there is still a lack in awareness of pediatric CRPS in differential diagnosis which may lead to delayed diagnosis and treatment. Murray estimated that the median time to diagnosis pediatric CRPS to be 12 weeks, with 15\% of these children taking over 12 months to diagnose. Additionally, Murray et al. reported that over 50\% of the pediatric CRPS patients had inappropriate treatments such as limb immobilization, which may exacerbate the condition in CRPS.\textsuperscript{9} Similarly, Low et al. reported that the mean time to diagnose pediatric CRPS was 13.6 weeks, with the longest recorded time to be 41 weeks.\textsuperscript{6} Allen et al. reported that patients on average see 4.8 different physicians before referral to pain centers.\textsuperscript{14} This delay in diagnosis is concerning because early recognition and treatment of the condition is believed to be one of the major factors in increased treatment efficacy and decreased treatment time needed.\textsuperscript{6}

Similar to many cases discussed by the various mentioned authors, NG presented with symptoms including (1) manifestation in lower extremity and foot, (2) occurrence during pre-adolescent age or at puberty, (3) unilateral presentation, (4) significant decrease in temperature of affected extremity, and (5) patchy osteoporosis found in the radiograph. It took 8 weeks to diagnose NG with CRPS, and it required 4 clinical visits before the diagnosis for CRPS was considered. An important aspect of CRPS treatment is early and proper diagnosis so that there is not a delay in correct treatment. As seen with NG and multiple cases in Murray’s research, improper diagnosis of the condition led to treatment options that were unsuitable for the condition, specifically immobilization with any splinting device.\textsuperscript{9}

As mentioned earlier in this article, there are currently many different treatment options for CRPS, and there is still much controversy regarding what is the best protocol for management of the condition. It has been indicated by various authors that physiotherapy is one of the more effective treatment options for CRPS, with an estimated recovery time of seven weeks.\textsuperscript{6,8,9} As seen with NG, her recovery time following intensive physical therapy was estimated around 18 weeks, and we believe that this prolonged recovery time might be secondary to her condition being diagnosed in a more progressed state. With regards to pharmaceutical intervention, analgesic medication in conjunction with physiotherapy was useful in improving compliance in NG, and so there should be further studies evaluating the use of analgesics for management of pediatric CRPS.

There have been several debates by multiple authors about a possible psychological component in pediatric CRPS. Although this is just a small correlation, it is an interesting finding that may play a significant role in helping diagnose pediatric CRPS in the future. If there is an identifiable correlation between psychology and pediatric CRPS, it may be possible to use psychological evaluation as a means to screen for patients at risk for pediatric CRPS. This increased awareness of patients at risk would be beneficial as it would alert physicians that pediatric CRPS can be a likely diagnosis, and thus decrease the chance of delayed diagnosis of the condition. Therefore, we believe that there should be further studies evaluating the possible psychological components of pediatric CRPS.

Finally, as mentioned before, most studies indicate that pediatric CRPS symptomatology manifests more commonly in the lower extremities and feet. This increased predilection of lower extremity involvement in pediatric CRPS indicates that podiatry plays a crucial role in recognizing the condition earlier on, so patients may receive a timely referral for management.
CONCLUSION

Pediatric CRPS is starting to become more recognized since the 1970s, but there still needs to be an increased awareness of CRPS in pediatric patients. Understanding more about the characteristics associated with CRPS in pediatric patients will expedite a more accurate diagnosis and treatment of the condition. Despite all the modalities that may be used to help with the diagnosis of CRPS, it is important to emphasize the fact that the gold standard for diagnosing CRPS is through history and physical examination. All lab work, imaging modalities and tests are useful in ruling out other potential diagnoses. Additionally, since pediatric CRPS manifestations are more credited to occur in the lower extremities, podiatrists have a critical role in identifying children with CRPS for timely intervention.

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AUTHORS’ CONTRIBUTION
RL and DL both conceived the topic and design of the study. RL independently performed a literature search, drafted the abstract, introduction, epidemiology, etiology, diagnosis, differential diagnosis, treatment and discussion. DL independently performed a literature search, participated in adding additional information to all sections, and constructed the tables referenced throughout the study. Both authors read and approved the final manuscript.

COMPETING INTERESTS
Both authors of this case report declare that they have no competing interests.

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Abstract

Introduction
The purpose of this study is to review clinical treatment in the most recent case reports of adult patients diagnosed with tuberculous osteomyelitis of the foot or ankle bones.

Study Design
Qualitative systematic review of the literature

Methods
The authors utilized search databases PubMed and Google Scholar to obtain relevant articles fitting in the construct of this study’s design and purpose. Keywords employed included ‘tuberculosis of foot and ankle’, ‘tuberculous osteomyelitis’, and ‘extraspinal tuberculosis’. A total of 44 abstracts were selected for further review. On the application of inclusion and exclusion criteria, 13 total articles were evaluated and reviewed for the purpose of this study.

Results
The authors found that while tubercular osteomyelitis may have variable presentations, high clinical suspicion can be achieved with histopathologic study in conglomeration with other diagnostic features found via microbiologic culture, Ziehl-Neelsen staining, and increased inflammatory blood markers. The most clinically significant diagnostic tools were histopathologic studies as well as cultured bone biopsies. Normal chest radiographs were found in the majority of cases and therefore cannot be used to rule out the possibility of extra-pulmonary TB. It was evident in the reviewing of the case reports that anti-tuberculin therapy is effective at treating osteoarticular tuberculosis infections.

Conclusion
This systematic review lends to a specific clinical timeline and approach regarding the presentation, radiographic manifestations, methods of diagnosis, treatment, and outcome of patients with suspected TB osteomyelitis of the foot and ankle.

Key Words
*tuberculosis, osteomyelitis, foot, ankle, osteoarticular*

*Level of Evidence: 4*
INTRODUCTION

Tuberculosis, a disease transmitted via respiratory fluid that manifests itself through granulomatous inflammation leading to ulceration and a loss of vital function, has been implicated as the cause of death in 8.6 million people worldwide in 2012. This exists despite efforts at eradication or attempts to control severe spread in populations of lower socioeconomic classification, who present with the highest incidence amongst economic groups. This figure has been on the rise in foreign-born persons residing in the United States, accounting for as much as 50% of all tuberculosis-related deaths.

The presentation of tuberculosis, as indicated by positive cultures of Mycobacterium tuberculosis, are widely varied and extend from the typical intra-pulmonary presentation to extra-pulmonary, the latter including soft tissue and bony articulations. Circumstantially, both manifestations are on the rise, likely due to an increase in multi-drug resistant forms of M. tuberculosis in concurrence with an overall aging population. Extrapulmonary tuberculosis has been reported in 10-15% of all TB infections and osteoarticular tuberculosis accounts for 1-3% of all tuberculosis cases in the Western world; the latter accounting for 16-25% of all TB mortality figures and occurring most often in weight-bearing joints.

A positive diagnosis of tuberculosis, particularly in populations presenting with extra-pulmonary manifestations, is quite difficult to ascertain and is often misdiagnosed. As such, extra-pulmonary diagnoses are often delayed, opening the door to increased spread and damage from the bacteria’s inflammatory consequences leading to a loss of function with potential limb loss in addition to increased severity with common comorbidities and sequelae including, but not limited to, rheumatoid arthritis, septic arthritis, and osteomyelitis. A seldom-recognized phenomenon with dire consequences, extra-pulmonary tuberculosis manifested in bones and joints, must be recognized in a timely manner by the attending caregiver. Herein, a review of recent case reports of 14 patients diagnosed and ultimately treated for tuberculosis osteomyelitis of the foot and ankle are presented.

METHODS

All three authors performed literature searches using the online search databases PubMed and Google Scholar. Search terms included, ‘tuberculosis AND ankle’, ‘tuberculosis AND foot’, ‘tuberculosis of foot and ankle’, ‘extraspinal tuberculosis’, and ‘tuberculous osteomyelitis’. Google Scholar returned a total of 10,200 results, in which it was evident that the first 70 merited further inspection of abstracts, being that they concerned tuberculous osteomyelitis of the foot or ankle. Of these, 21 abstracts were selected for further detailed review. Based on inclusion criteria set forth by the authors, papers satisfying the following conditions were included: written in English or with viable translation, case reports published 2008 or later, and bony manifestations of infection in adults 20 and older. Based on exclusion criteria established by the authors, articles containing any of the following characteristics were excluded: articles published before 2008, written in another language with no viable translation, soft tissue lesions of the disease, and articles that concerned patients under 20 years old. When applying these criteria, 6 papers were retained and included in this review via Google Scholar. PubMed returned a total of 664 articles, of which the abstracts of 23 were selected for a further detailed review. Applying the aforementioned inclusion and exclusion criteria while also accounting for overlap between the search databases, 7 unique articles were retained from the PubMed database and included.
in this review, resulting in a total of 13 articles. These 13 studies had a total compilation of 14 cases.

RESULTS

Patient Presentation
The mean age investigated was 43.8 years old and the median age was 44. There were 9 males and 5 females. Individuals’ ethnicity reported included Yemenite, Hispanic, Somalian, South Asian, and Caucasian. These individuals were evaluated for this review on the following criteria: age, sex, chief complaint, history of chief complaint, previous treatment administered for said complaint, past medical history, initial clinical examination, and concurrent lab tests and imaging. Evaluation included the foot and ankle in each case. Of these, 12 presented with pain, 11 presented with swelling, 3 presented with ulceration, 2 presented with erythema, 2 presented with tenderness upon deep palpation, 2 presented with range of motion reduction, and 1 presented with purulent drainage. In addition, 4 cases reported difficulty upon ambulation, while 6 cases reported the onset of progressively worsening symptoms beginning only after trauma to the foot or ankle that had been previously unresolved.

Diagnostic Imaging
The most common radiological features reported were cortical erosion, periarticular osteopenia, and narrowing of the joint spaces. The appearance of these three features, known as “Phimester’s Triad”, are classic to osteoarticular tuberculosis but are not diagnostic and do not always appear in unison. Also reported were soft tissue swelling, synovitis, tenosynovitis, and in one case, bony spur growth. 9 When used, MRI consistently showed bone edema with hypointense T1-weighted and hyperintense T2-weighted images, shown in Figure 1. 4,6-7,9-11 Bone scintography, only used in three of the cases, showed increased bone turnover, increased vascularity and focal increases in infected areas. 5,11-12 When present, lytic lesions appeared either in delineated or non-delineated forms, thus adding bone cysts or osteolytic tumors to the differential diagnosis. 5,7,11,13-15 This is illustrated in Figure 2.

Radiological features of osteoarticular tuberculosis are nonspecific but are used in correlation with other tests to achieve diagnosis. 2-15 Features reported such as lytic lesions, bone edema and periarticular osteoporosis are differential of many possibilities, such as osteosarcoma, osteomyelitis, rheumatoid arthritis, septic arthritis or degenerative joint disease. If tuberculosis is suspected, however, a specimen for histopathological study should be sought. The advantage of imaging with CT or MRI was often noted with regard to guidance in obtaining adequate biopsy specimens when plain radiography did not provide clear demarcations of infected areas. 15-17 One study did report two CT-
guided biopsies that failed to provide sufficient material for analysis. CT and MRI also provided better imaging in regards to localizing and delineating the extent of surrounding soft tissue damage such as tenosynovitis and synovial thickening.

Osteoarticular Tuberculosis is difficult to detect early by radiography. Sandher et al. found that 50% bone loss must occur before radiological changes are identified. In one case of TB in the midfoot, plain radiography revealed only minor degenerative changes, yet 10 weeks later films showed significant midfoot erosion. Diversely, MRI may show early signs of the disease such as abscess formation or bone edema, but ultimately pathology is needed for diagnosis. In a suspected case of multifocal tuberculosis, skeletal scintography allows for identification of hot focal areas before symptoms may occur at those lesions. While useful in diagnosis and delineating the extent of the disease, radiography may also be used in monitoring recovery and follow-up. Bone regeneration and full repair of lytic lesions were reported on follow-ups after anti-tubercular regimens.

Methods of Diagnosis

Hematological investigations can be useful in that they may uncover inflammatory markers that may signify possible infection; these investigations were reported in 11 out of 14 cases. More specifically, tests for erythrocyte sedimentation rate (ESR) were reported 11 times, and tests for C-reactive protein (CRP) were reported 9 times. Of the studies that conducted these investigations, approximately 73% of cases had an elevated ESR, along with 89% of cases reporting an elevated CRP. Only one case had normal findings of both ESR and CRP. These tests, however, can be falsely negative, are generally not specific, and cannot by themselves deduce a diagnosis of tuberculosis.

Every case reviewed presented some sort of method for obtaining specimens for testing. These

Figure 2. Left: Non-delineated lesion of distal right fibula. Right: delineated lesion of distal left tibia.
included invasive procedures such as intraoperative biopsy via curettage or debridement if necessary, intraoperative drainage, and less invasive procedures such as fine needle aspiration of affected areas. Aspiration sufficed in only two cases, and generally was inconclusive, thus favoring a more invasive procedure. Still, it is recommended that fluid aspiration and biopsy both be done in order to make a definitive diagnosis. Specimens attained during these procedures were then tested in a variety of methods, all of which are shown in Table 1 and will now be discussed in detail.

Ziehl-Neelsen (ZN) staining of aspirate, otherwise known as acid fast staining, revealed acid fast bacilli in only 2 of 11 cases in which it was conducted. Several studies attribute this to the paucibacillary nature of the disease, as well as the infection’s propensity to infect tissue rather than fluid. Microbiology culture was positive for TB only in the instances in which bone biopsy specimens were used, with one exception where synovial fluid aspirate yielded positive growth on culture. In only one instance was culture negative via a bone specimen. Any other specimen, be it urine, blood, or swab of a superficial cutaneous ulcer, was always negative on culture. Again, this could be attributed to the paucibacillary nature of this disease. While a positive bone culture is effective at diagnosing tuberculous osteomyelitis, it could take two to three weeks to obtain a result. In such cases clinicians need to evaluate other tests and procedures to achieve clinical suspicion and start treatment immediately to avoid complications as the infection progresses.

Chest x-ray, when conducted, was found to be abnormal in only 18% of cases. Conversely, PPD, or the Mantoux Test, was found to be positive in 75% of cases in which it was reported. Thus, based on the case reports studied, positive PPD is easily more common in tuberculous osteomyelitis than is an abnormal chest x-ray.

By far and away, the most effective diagnostic procedure throughout the cases reviewed were histopathological studies of obtained specimens. In all cases in which histopathological studies
were conducted, slides revealed tuberculosis-like findings described as follows: epitheloid granulomas with caseous necrosis, Langhan’s type giant cells, and Koch’s bacillus. Epitheloid granulomas and Langhan’s type giant cells are shown in Figure 3. It should be noted that although these features are generally hallmarks of tuberculosis, other conditions may present with similar findings. For instance, tertiary syphilis presents with necrotizing granulomas, sarcoidosis with epitheloid granulomas and Langhan’s giant cells. Thus, other factors may be considered in the diagnosis of TB such as a positive PPD test.

On occasion TB infection was either confirmed based on the patient’s response to anti-tuberculin therapy, or via a positive polymerase chain reaction assay and cytology for tuberculosis.

**Treatment & Outcome**

Once a diagnosis was achieved, or at least a high clinical suspicion, all patients underwent a similar treatment regimen and had similar outcomes. All patients were given all or part of an established “empiric” anti-tuberculin therapy. This consisted of pharmaceuticals, immobilization, and surgical correction following debridement of lesion if necessary. All cases followed the Directly Observed Treatment/Short Course plan, otherwise known as DOTS, which was established and undertaken by both by the Department of Health and the World Health Organization. This ensures consistent follow-up visits while on drug therapy.

Generally, the treatment regimen consisted of combinations of the following drugs: Rifampicin (or Rifampin), Isoniazid, Pyrazinamide, and Ethambutol, or RIPE. Prophylactic pyridoxine (vitamin B6) was given in two cases to offset the potential advent of peripheral neuropathy and CNS toxicity associated with isoniazid treatment. Of the 14 patient cases reviewed, five did not provide detailed drug regimens, citing either overall RIPE treatment for periods ranging from 12-18 months, or antituberculin chemotherapy. All other cases provided detailed drug regimens in which specific drugs were taken for specific amounts of time outlined in Graph 1. Additionally four case reports prescribed either an immobilization cast or a non-weight bearing crutch following debridement of lesion.

In three cases, surgery was needed as a result of radical debridement of the lesion that necessitated intraoperative fixing. One patient required arthrodesis of the ankle, or ankle fusion following debridement of lesion that caused loss of motion.
and extensive ankle joint destruction. \(^8\) Another patient required subsequent bone grafting following surgical sequestrectomy and debridement of lesion. \(^{14}\) A third patient required a transmalleolar screw implantation to compensate for the transmalleolar surgical approach the clinicians took in order to assess and debride the suspected lesion. \(^{13}\)

Eight case reports reported conducting follow up radiography on their patients. Five of these studies’ x-rays revealed healing of previously infected bone lesions citing remineralization with sclerosis of margins, \(^{14-15}\) consolidation of lytic lesion, \(^{11}\) bone regeneration and repair of osteolytic lesions, \(^{5}\) and re-ossification of bone. \(^{19}\) Two other cases used their follow up x-rays to rule out further bony destruction. \(^{6,13}\) One case conducted a follow up MRI, which revealed complete resolution of edema within the area of the previously held lesion. \(^4\) Every case reviewed for this study claimed complete patient recovery upon follow up and reported no indications of recurrence. The one outlier claimed loss of overall ankle range of motion post treatment attributed to the duration and extent of that individual’s infection. \(^8\)

**DISCUSSION**

Tuberculous infection of the lower ankle and foot is a significant sub-category of all extrapulmonary tuberculous diagnoses but has remained elusive due to the wide range of diseases it mimics.
including pyogenic or rheumatoid arthritis, Kaposi’s sarcoma, osteochondrosis, bone tumors, osteoarthritis, amyloidosis, pigmented villonodular synovitis, actinomycosis, fungal osteomyelitis, gout, and sarcoidosis. It is, therefore, obvious that a very common feature of extrapulmonary tuberculosis and, in particular osteoarticular tuberculosis, is a delay in treatment due to misdiagnosis or late patient presentation. Because tuberculous infection of the bones and joints of the foot can be so detrimental, it is a concern that must be in the arsenal of differential diagnoses of the caregiver.

Several factors should be taken into account in the diagnosis of tuberculous osteomyelitis of the foot and ankle. Aforementioned radiological findings can be helpful, but are not specific for diagnosis of tuberculosis. ESR and CRP are often elevated in these patients, but are also not specific markers for disease. ZN staining, when positive, as well as positive PPD tests can both help in making a diagnosis. The best diagnostic evidence for tuberculosis infection is the analysis of histopathologic slides, which reveal markers for the disease. PCR can be used to confirm the diagnosis, but this is usually carried out once high clinical suspicion for TB is attained. It is evident that the diagnosis of tuberculous osteomyelitis in the foot and ankle is often achieved by correlating radiologic, clinical, and histological findings.

Although tuberculous osteomyelitis is a rare disease, review of the literature and case reports maintains that definitive diagnosis is based on histopathological features of obtained specimens. Early diagnosis remains difficult due to the variety of non-specific signs or symptoms such as lytic lesions, cortical erosion and edema at the site of infection, as well as a systemic increase in inflammatory markers. Although useful in delineating extent and demarcations of the disease, radiographic imaging is not diagnostic. A normal chest x-ray should not be grounds for dismissing the possibility of osteomyelitic tuberculous infection. Hematological tests for inflammatory markers can be helpful but not necessary for diagnosis as the majority of patients had increased ESR and C-reactive protein levels. Microbiologic culture of bone biopsy specimens were positive for Mycobacterium in all but one case. In all cases reviewed, anti-tuberculin therapy was effective, irrespective of the minor differences in treatment regimens as shown in graph 1. Full recovery of bone and full range of motion at infected joints is expected as was reported in all but one case report; where the long duration and extent of tuberculous infection is believed to have resulted in loss of ankle range of motion.

CONCLUSION

It is apparent that tuberculous osteomyelitis of the foot and ankle bones does not lend itself to a clear cut and immediate diagnosis, though that would be in the best interest of the patients infected. Clinicians must assess possible patient history of trauma, immunosuppression, and presenting symptoms. All of these factors can present in many different conditions and further tests must be conducted to achieve high clinical suspicion. Radiographic manifestations are noteworthy, but cannot be specified to the disease. Therefore, a combination of methods was undertaken in all cases to further elucidate the patients’ conditions such as ZN staining, PPD testing, microbiologic culture, and hematologic as well as histologic investigation. The most sensitive diagnostic methods were histological studies as well as microbiologic culture of bone specimens obtained in biopsy. Overall treatment between cases shared more commonalities than not, involving similar combinations and timelines of empiric anti-tuberculin chemotherapy regimens consisting of RIPE. All patients were infection-free following treatment denoting that diagnosis and proper
treatment, will successfully mitigate the possible destructive forces of TB osteomyelitis should it go unrecognized or untreated. Because of the successful treatment method outlined within the case reports that combines histopathological studies with RIPE treatment, the primary issue in this disease is the time in which it takes to successfully obtain a diagnosis. Future studies should focus on calling attention to populations at risk while also working towards a more rapid diagnosis using tools that are commonly employed during the patient’s initial visit such as radiographic imaging combined with PPD testing. At the very least, these modalities can raise clinical suspicion of an elusive yet preventable disease that already has a treatment regimen prescribed to it.

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COMPETING INTERESTS
J.L., D.M., and Z.S. declare that they have no competing interests in regards to this manuscript.

AUTHORS’ CONTRIBUTIONS
J.L., D.M., and Z.S. worked together in all aspects of this study including, but not limited to the following: construction of study design, gathering relevant case information, and the analysis and review of said information. All authors read and approved the final manuscript.

REFERENCES


The Effect of Plantar Pressure on Ulcer Formation in Diabetic Patients

Sarah Mohamed, BA, Mehwish Seyal, BS, Augini Sidhom, BS

Abstract

Introduction
The purpose of this paper is to review the effect of plantar pressure on ulcer formation in diabetics.

Study Design
Systematic Review of the Literature

Methods
A search was done on PubMed, Medline and JAPMA with the key search words ‘plantar pressure and ulcers in diabetics’. A second search was done with the keywords ‘diabetic pressure ulcers’. Articles that looked at the relationship between diabetic patients and ulcer formation were read and analyzed. The search was done for full text availability on PubMed and PubMed Central. Some of the articles were not accessible through PubMed Central, so these articles were obtained directly from the respective full text journals: Journal of Diabetes Care, JAMA, JAPMA, Diabetic Medicine, BMC Endocrine Disorders, and Clinical Biomechanics. The inclusion criteria: studies on diabetic patients, and studies assessing peak plantar pressure and peak shear stress. Exclusion criteria: any studies done on cadavers.

Results
The authors found that peak plantar pressures play an important role in the formation of ulcers in diabetic patients, especially those with peripheral neuropathy. Peak plantar pressure in diabetic patients with neuropathy was greatest in the forefoot due to the exposed pressure levels during the propulsive phase of gait. As a result of this increased pressure, the forefoot is the site where the majority of diabetic pressure ulcers occur. Additionally, it was found that in diabetic patients with a history of ulceration, there is a high risk of ulcer re-occurrence due to disuse and atrophy of the muscles. Also, it was found that a high rate of ulceration occurs under the 4th and 5th metatarsal heads. This high rate of ulceration is due to peripheral neuropathy and lack of nociceptive feedback in diabetic patients.

Conclusion
The objective of this review was to see the effects of shear plantar forces on diabetic feet. It was found that the incidence of ulcers is higher in diabetic patients with neuropathy due to the increased shear forces causing micro tears in the skin. These micro tears result in hyperkeratosis formation second to a state of persistent inflammation. Further research assessing the effects of plantar pressures on ulcer formation would allow for more effective and preventative treatment plans for diabetic patients.

Key Words
plantar pressure, ulceration, diabetes
Level of Evidence: 4
INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that is increasing in prevalence each year in the U.S.\textsuperscript{1,5,7} Patients with DM have an increased risk of peripheral neuropathy as well as a greater risk of ulcer formation under the metatarsal heads. It is estimated that about 15% of Americans who are diagnosed with DM and symmetric peripheral neuropathy will have at least one foot ulcer in their lifetime.\textsuperscript{3} In the USA there are 25.8 million people suffering from diabetes of which, about 2.5 million suffer from ulcers. An estimated six billion dollars a year is spent on treatment of ulcerations in DM patients.\textsuperscript{7,11,12} There are numerous pressure variables that contribute to the formation of ulcers in diabetic patients. Understanding these variables, and how to minimize them, would help to better control and prevent diabetic ulcer formation. Peripheral neuropathy and mechanical stress distribution on the soles of the feet have been shown to be the two main factors contributing to diabetic foot ulcers (DFU).\textsuperscript{6} Diabetic peripheral neuropathy is one of the complications of uncontrolled diabetes which manifests as the loss of sensory and motor function, especially in the lower limbs, which is evidenced in the biomechanics of a diabetic foot.\textsuperscript{2} Plantar shear is a good indicator of callus formation which results in higher incidence of ulcer formation. During a single stance phase, there are areas of the plantar foot, which experience two forces in opposite directions from an accelerating propulsive phase to a decelerating contact phase. The foot experiences anteroposterior (AP) and mediolateral (ML) forces, thus making shear forces an important factor in the prediction of ulcer formation.\textsuperscript{9}

METHODS

A search was preformed on PubMed, Medline and JAPMA for all the articles between 1997-2013 with the key search words ‘plantar pressure and ulcers in diabetics’ and ‘diabetic foot ulcers’. Out of the total 745 articles that were found, 27 articles were selected for the initial review. From the 27 articles, 12 articles were selected based on the inclusion and exclusion criteria. The inclusion criteria for the study consisted of: studies preformed on diabetic patients assessing peak plantar pressures and peak shear stress. Exclusion criteria included any studies done on cadavers.

RESULTS

A common studied factor in diabetic foot ulcer formation has been the Peak Plantar Pressure (PPP).\textsuperscript{7} The PPP is the greatest amount of pressure in which the bottom of the foot is exposed. PPP has been found to be a variable playing a large role in the formation of diabetic ulcers.\textsuperscript{7} A study done by Petaky et al, found that diabetic patients without peripheral neuropathy or peripheral vascular disease, had increased peak plantar pressures in the big toe, and the 5th metatarsal head compared to the non-diabetic control group.\textsuperscript{4} The PPP has been observed to be greater in the diabetic patients with peripheral neuropathy compared to diabetics without peripheral neuropathy. It was observed that while walking barefoot there is anterior displacement of PPP and a reduced contact plantar surface. The PPP was greatest in the forefoot. This has been observed as the most common site of ulcer formation in diabetics.\textsuperscript{4,7}

In a study done by Guldemond et al, it was found that the forefoot plantar pressures were greater in the 1\textsuperscript{st} MT and the 5\textsuperscript{th} MT area.\textsuperscript{5} This finding of greatest forefoot pressure in the 1\textsuperscript{st} and 5\textsuperscript{th} MT plantar regions agrees with the findings of Petaky et al.

Caselli et al. performed a 30 month prospective study in which the forefoot and rearfoot PPP were measured in diabetic patients with varying degrees of peripheral neuropathy. In addition, the forefoot to rearfoot PPP was obtained. It was found that the PPP in the forefoot increased in a
linear fashion to the severity of neuropathy. Both the forefoot and the rearfoot PPP were greater in the moderate to severe neuropathic diabetic patients compared to the mild and non-neuropathic diabetic patients. In addition, the forefoot to rearfoot ratio (F/R ratio) was greatly increased in those patients with severe peripheral neuropathy. Foot ulcers developed in 19% of the feet, with 98% of the ulcers occurring in the forefoot. It was found that the F/R ratio was a good predictor of ulcer formation. The F/R ratio was increased only in patients with severe diabetic neuropathy. This suggests that during off-loading, diabetic patients, especially those with neuropathy, experience greater forefoot PPP compared to rearfoot PPP and experience an imbalance which may be related to the formation of the plantar ulcers in these patients.

In order to see the effects of diabetic neuropathy on the plantar distribution of pressures in a diabetic foot, a cross sectional study was performed by Bacarin et al. Three groups were selected which included a control group of 20 asymptomatic people, 17 people with diabetic neuropathy (DN) and 10 people with diabetic neuropathy and a history of at least one foot ulcer (DNU). A barefoot gait analysis was performed, and the pressure distribution measured based on five areas of the foot labelled as: M1 rearfoot, M2 midfoot, M3 lateral forefoot, M4 medial forefoot, M5 rearfoot. It was discovered that in people with DNU there was an overload of pressure on the midfoot and the lateral foot. The pressure gradient in those areas was higher in people in the DNU group than the control group. This change in biomechanics is the result of a compensatory mechanism which occurs during ulcer healing, and not only changes the way the foot functions, but leads to an increased risk of re-occurrence. High re-occurrence is thought to be due to disuse atrophy.

Metin et al. studied the effects of plantar pressure and shear forces in a study, which included fifteen people with no clinical symptoms and twenty people with diabetic neuropathy (DN). The patients were allowed to walk barefoot on a custom built shear and pressure platform and the data was collected using variables like peak AP, RES, and STI. It was found that the peak AP and resultant (RES) magnitudes were higher in diabetic group respectively. Also, the shear-time integral (STI) for both AP and RES was dramatically higher in diabetic patients. It was also noted from the previous studies that the application of frictional shear force of increasing magnitude can lead to lichenification and hyperkeratosis formation. Shear forces will not only improve our understanding of hyperkeratotic lesion formation, but also ulcer formation. A better knowledge of such mechanisms would lead to improvements in wound care treatment and prevention.

Metin Yavuz studied the plantar shear values in three different groups: diabetic patients with neuropathy, diabetic patients without neuropathy and healthy patients. He conducted an experiment with 39 subjects, 28 diabetic patients, and 11 healthy volunteers. The diabetic patients were further divided into two groups: 14 with...
neuropathy, and 14 individuals without neuropathy. Neuropathy was assessed using a biothesiometer and a vibration perception threshold of 25V was used. Data analysis was performed using ANOVA. A major difference was found between the three groups, with neuropathic diabetic patients having significantly higher peak shear, shear-time integral (STI) and pressure-time-integral (PTI). According to their findings, the two factors that should be evaluated in patients with peripheral neuropathy are peak shear and shear time integral magnitudes. The authors of the study strongly suggested that these factors should be evaluated to better understand and develop strategies for the management of neuropathic diabetic patients.

In another study done by Stess et al, 97 diabetic participants were selected. In the study, 34 of the patients did not have neuropathy and 14 patients had neuropathy but did not have a history of ulcers. The remaining patients had both peripheral neuropathy and plantar ulcers. The factors evaluated were: maximum pressure picture (MPP), pressure-time integral (PTI), and force-time integral (FTI). The results indicated a statistically significant increase in MPP and PTI in DU as compared to the control. The most significant increase was observed under the 4th and 5th metatarsal heads.

Based on the studies mentioned above, it has been found that the elevated incidence of ulcer formation in diabetics is a result of unequal pressure distribution. Consistent results are found to show that the incidence is higher in the forefoot compared to the rearfoot. The highest incidence rate of ulcer formation has been seen under the 4th and 5th metatarsal heads. Diabetic patients also have increased shear time interval and peak shear. Patients with diabetic neuropathy are prone to recurrent ulcer formation. Further knowledge and research regarding shear force distribution and its effects on diabetic ulcer formation would allow us to treat and prevent ulcers in diabetic patients more effectively.

The findings of increased peak plantar pressures in diabetic patients, and its correlation to ulcer formation suggest that the treatment of diabetic patients should incorporate decreased loading of the foot. The increased forefoot pressures compared to rearfoot pressures indicates that possible measures to prevent ulcer formation should be aimed at off-loading the forefoot more so than the rearfoot. In addition, the greatest pressure was found to be at the fourth and fifth metatarsal heads, therefore, it may be possible to reduce the risk of ulcer formation by using orthotics to limit the weight bearing forces on those areas. A two hour repositioning schedule is considered the minimum interval for patients at risk of ulcer formation.

However, a question that remains unclear is the plantar pressure threshold that would put the diabetic patient at risk of ulcer formation. As seen in the paper by Stess et al, they found the possible threshold to be 40 N/cm2 in diabetics with peripheral neuropathy, however, this is lower than the 98 N/cm2 threshold found in an earlier paper by Duckworth et al. Therefore, further studies should be aimed at determining what is the maximum plantar pressure that a diabetic patient with and without neuropathy can be exposed to before ulcers form.

DISCUSSION AND CONCLUSION

Based on the studies presented in this review, there is a positive correlation between plantar ulcer formation in diabetics and peak plantar pressure. It was shown that those patients who had diabetes and peripheral neuropathy had a greater risk of developing ulcers compared to diabetic patients without peripheral neuropathy. The peak plantar pressure was found to be greatest in the forefoot compared to the rearfoot in the area under the metatarsal heads. This abnormal distribution results in micro tears which can result in hyperkeratosis and callus formation. The highest increase in MPP was seen in the 4th
and 5th metatarsals, which is consistent with the highest rate of ulceration observed in the 4th and 5th metatarsals. There were also gait changes observed in diabetic ulcer patients and has been associated with peripheral neuropathy. Neuropathy causes atrophy of the muscles which causes the gait of the diabetic patient to be more supinatory, thus making them more prone to the ulceration of 4th and 5th metatarsals. Current research attempts at determining a pressure threshold for ulcer formation have failed to capture substantial sample sizes. It is suggested that these small population sizes may contribute to the variability in current research findings. Future research attempts, assessing larger populations, may yield more concrete evidence for a definitive threshold for ulcer formation.

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AUTHORS’ CONTRIBUTIONS
SM, MS, AS contributed equally in drafting the manuscript by writing their part for each section.

STATEMENT OF COMPETING INTEREST
The authors declare that they have no competing interest.

REFERENCES
Abstract

Introduction
The two goals of this study were to: provide pertinent knowledge regarding both the history and etiology of Down Syndrome (DS), and to elaborate on the podiatric medical conditions that are more prevalent within the DS population. Individuals with DS are a vulnerable population that requires extensive medical interventions to achieve an acceptable quality of life. While beset with numerous medical conditions the individuals with DS currently are expected to live well into their sixth decade of life. The development of treatment protocols and educational materials concerning this population would help hone the skills of podiatric physicians. It is the responsibility of podiatric physicians to apply their specialized knowledge to alleviate the suffering of this discrete subset of the population.

Study Design
Systematic Review of the Literature

Methods

Results
Individuals with DS have a plethora of medical issues, some within and some beyond the scope of podiatry. Common pathologies that present with a higher prevalence than the general population include metatarsus primus adductus, pes planus, tailors bunion, onychomycosis, onychocryptosis, tinea pedis, and xerosis.

Conclusion
A patient with DS represents both an obligation and opportunity to podiatric physicians. Through our specialized training and continued professional development we will be able to reduce the suffering and increase the quality of life in these individuals.

Key Words
Down syndrome, DS, pronation, underserved population, podiatric profile

Level of Evidence: 4
INTRODUCTION

The two goals of this study were to: provide pertinent knowledge regarding both the history and etiology of Down Syndrome (DS), and to elaborate on the podiatric medical conditions that are more prevalent within the DS population. Individuals with DS are a vulnerable population requiring extensive medical interventions to achieve an acceptable quality of life. While beset with numerous medical conditions, the individuals with DS currently are expected to live well into their sixth decade of life. This is due to a multitude of factors mostly correlated to better medical care and access to services. Some may think of the patient with DS as too complicated to be generalized. In many respects these individuals are indeed correct. In the global assessment of DS, one set treatment for all associated pathologies is practically impossible. However, if the associated pathologies are divided into narrow fields respective to different specialties, a group effort of the medical team may be employed to render more effective treatment.

The chronic and non-curative status of DS and all of its associated comorbidities requires a specialized understanding of the underlying general health issues that afflict these individuals. The development of treatment protocols and educational materials concerning this population would help hone the skills of podiatric physicians. It is the responsibility of podiatric physicians to apply their specialized knowledge to alleviate the suffering of this discrete subset of the population.

METHODS


The search was preformed utilizing “All fields” to ensure a broad sampling of the literature. There were a number of exclusionary criteria. Articles older than 1950, except historical inclusions, were excluded. Results were sorted by relevance and reviewed by the authors. The total number of articles was initially reduced to 94 and after eliminating redundant or mis-indexed copies of articles, the total number was finally reduced to 40 articles for inclusion. The inclusion criteria were based on reading and critiquing the abstracts, then assessing their relevance to podiatry and Down syndrome.

RESULTS

Historical Background

Utilizing today’s tremendous medicine resources allows researchers to elucidate their most thought provoking questions. In many ways, the evolution of knowledge and terminology within the medical literature is highly fascinating. This is very apparent with the development of the classification of DS.

The first clinical classification of DS was by Langdon Down in 1866 through his observations within a London hospital. As insightful as Dr. Down’s thoughts were, a more definitive classification for DS took many more years to develop. The first person to posit DS as a chromosomal alteration was Waardenburg based on the observation of Brushfield spots found within the eyes of individuals with DS. In the following decades Lejeune, a geneticist,
confirmed the hunch of Waardenburg and DS became defined as a trisomy of the 21st chromosome. Further work in the field of genetics eventually correlated advanced maternal age with an increase in the incidence of DS. Recently it has been demonstrated that not only does risk increase proportionally with maternal age, but with paternal age as well. Work has continued to define the genetic components of DS. It has been shown that the 21q22 locus of the 21st chromosome contains many of the genes that code for the disease associated with DS. More than 90% of individuals with DS get an extra chromosome that is of maternal origin; meanwhile, less than 10% from paternal origin.

Genetics of DS

The aneuploidy condition known as trisomy 21 has three varieties, all of which result in the phenotype of DS. The most common instance, by far, is a full trisomy 21, in which each and every somatic cell has an extra 21st chromosome. The other two trisomy 21 conditions are mosaic trisomy (2-4%) and Robertsonian translocation (3-4%). In Mosaic trisomy and Robertsonian translocations the mosaic genotype may have reduced or absent symptoms that are present. Thus, not every cell within the body contains an extra copy of the 21st chromosome. To our knowledge, there is currently no study that dissects the differences in these genotypes with regard to podiatric conditions.

Quality of Life

The prevalence of individuals with DS in the US is 1:691. This prevalence translates to almost 400,000 or more individuals within the United States living with DS. A short time ago this large population of individuals with DS was simply not present in the current numbers seen today. Children with DS were reported to only live until the meager age of 9 in 1929, which crept up to a nominal age range of 12-15 in 1947. People with DS in the recent past did not have a lengthy life expectancy that many people enjoy today.

Much of their artificially low life expectancy in the early 1930s was due to their marginalization within the community, coupled with lack of appropriate medical care. There are many afflictions that acted to augment the early demise of these individuals. The complications range from seemingly insignificant to debilitating. One notable complication is hearing loss second to otitis media infection. As neonates, most DS patients have abnormal thyroid function, which needs correction to reduce further intellectual disability. In addition, these individuals are prone to leukemia, having been found to have higher NK cell levels when compared to average adults. Adults also experience a blunted HR response during upright tilting of their head, indicating reduced sympathoexcitation. Despite these complications, advances in medicine allow these individuals to live into their 60s and 70s.

At first glance these recent gains in life expectancy are promising, however, the phenotype of individuals with DS typically changes as their age advances. The increased life expectancy has been obtained by the management of their early and chronic medical conditions. Current research suggests that the appearance of deleterious issues presenting later in life is due to genotypic alterations that were not present at birth.

Premature aging in individuals with DS appears in many ways. This population experiences both a higher prevalence and earlier onset of osteoarthritis. Additionally, individuals with DS have a higher BMI than age matched controls. The added stress due to excessive weight on compromised joints results in rapid degeneration of joint surfaces. Finally, this population is also
subject to a higher incidence of Alzheimer’s type dementia. 23

Gait, Deformity, Predilections

On average, infants with DS start walking a full year later than their peers.24 The lack of load bearing stress on developing bones may contribute to later bony deformities. Their issues continue into adulthood, as this population was also found to have poorer static equilibrium while standing.25 Initially it was thought that this poor static equilibrium was due to the hypotonic characteristic of these individuals, but it has been experimentally determined that individuals with DS exhibit the same muscle strength as matched controls.26 However, hypotonia cannot be the sole reason for poor static equilibrium; the defect must be a synergy between deformity and later developed hypertonia.

DS gait has been described as ‘Chaplinesque’, due to external rotation of their hips with increased knee flexion.27 These individuals also have increased ankle range of motion.28 Hypermobility of the ankles predisposes these individuals to many acquired deformities throughout their life. During walking they exhibit greater hip and knee flexion throughout stance phase, and plantarflexion of the ankle (dropfoot) during initial contact.28 Plantarflexion during initial contact may occur due to inherent joint sublaxity and muscle hypotonia.29 Adults with DS have a notably widened base of gait.29 The overall effect of these issues culminates in reduced gait stability and increased energy cost for movement.29-30

The most common orthopedic alterations found in an individual with DS are: bony deformity of the forefoot, flat foot, calcaneal valgus, knee valgus, and pronated flat foot.31 Interestingly, current literature regarding shoe wear suggests that individuals with DS are wearing shoes that are simply too large.32-33 Many of individuals with DS wear larger shoes due to the splaying of their foot because of their orthopedic alterations. Some of these orthopedic alterations include: metatarsus primus adductus, pes planus, and tailors bunion.33

This population also experiences onychomycosis, onychocryptosis, tinea pedis, and xerosis in a higher prevalence than the general population.34 The increased prevalence of lower extremity medical conditions in the DS population suggests a need for more podiatric physician involvement.

Interventions and Implications

Other specialties have instituted paradigms that have resulted in increasing the quality of life and decreasing the suffering of individuals with DS. There is great support for programs that aim to improve the cardiovascular fitness of individuals with DS.35 There have been positive objective outcomes in intervention programs concerning strength, balance, and cardiac output of individuals with DS.36-39 Many of these programs are not novel inventions, but merely modified versions of existing protocols. Such protocols should also be incorporated for podiatry as well.

These outcomes have been used to improve the quality of life in these individuals to increase their autonomy through retained function.36 Essentially the longer the function is retained the better quality of life the patients will experience. The individuals with DS are not alone but are only one discrete population of intellectually disabled individuals with a heightened prevalence for lower extremity pathologies. The total physical activities of individuals with Down syndrome, Prader Willi syndrome, and Williams syndrome have been found to be similar.40 The protocols established for the treatment of DS in strength, balance, and cardiac output are analogous to many of those with severe intellectual disabilities.
DISCUSSION AND CONCLUSION

Individuals with Down Syndrome may have notable deficits in intellectual capacity, however, these deficits need not resign these individuals to suboptimal healthcare. With the combined efforts of the medical community in varying different specialties, we can hope to achieve a fluid model of management care that meets the demanding needs of these individuals. Such a model would aid in prolonging the autonomy of DS patients, and in so doing, diminish the financial burden that may result otherwise. It is not suggested, however, that such a model or protocol for the treatment of DS will be easy, but rather, will sustain a parameter within healthcare to prevent what can be prevented, and provide the best quality of life possible for these individuals.

AUTHORS’ CONTRIBUTIONS
NS conceived the topic. NS, SK, KK, and RT all performed a portion of the literature review and drafted the manuscript. All four authors have read the draft manuscript for submission.

STATEMENT OF COMPETING INTERESTS
The authors declare that they have no competing interests.

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Review of Treatment Modalities for Talar Osteochondral Defects Found in Adults

Jeremy Dublon, BS, Shruti Patel, MS, Brandon Ewald, BS, Brian Tuminski, BS

Abstract

Introduction
The purpose of this study is to review current classifications and treatment options for talar osteochondral defects in adult patients and to look at the pros and cons of the classifications and therapies to see if there is a need for improvement.

Methods
Review of the literature was performed by doing an online database search systematically and manually. Inclusion criteria: human subjects over the age of 19 years old, English written articles, and full text available articles. 21 articles were included with a timeframe from 1986-2013. Exclusion criteria included pediatric subjects younger than 19 years of age. Cadaveric or animal studies were not included because of clinical implications that may or may not occur in human patients.

Results
Since the Berndt and Harty classification, newer classifications have been created based on current diagnostic imaging such as CT-scans, MRI, or intra-operative grading. Currently, newer classifications are not universally used, but some of them do account for subchondral cysts or have incorporated different stages depending on the quality of the cartilage which is not integrated in the Berndt and Harty classification. Treatments which are being used today depend on the grade of talar osteochondral defect and include the gold standard arthroscopy and bone stimulation, retrograde drilling and bone grafting, tibial wedge osteotomies, mosaicplasty, and matrix-induced autologous chondrocyte implantation. Authors noted newer therapies need to be further researched. Currently, there is no gold standard replacement for cartilage. Gaining access to the talar osteochondral lesion can be difficult. The gold standard therapy of arthroscopy and bone stimulation is not always effective.

Discussion and Conclusions
There is no one classification which always accurately correlates the staging of the talar osteochondral defect with treatment that is implanted or vice versa, but some classifications are better for describing certain types of lesions than others. Newer therapies that are being used today such as mosaicplasty and various types of bone grafts still need to be further researched with longer evaluation of outcomes before these can be considered a high level of evidence-based medicine. Overall, future treatments must incorporate not only rapid healing of the defect, but should also encourage the regrowth of hyaline cartilage if damaged or prevent further impairment so that patients are able to get back to their daily activities with minimal repercussions.

Key Words
Osteochondral defects/lesions, Talus/talar
Level of Evidence: 4
INTRODUCTION

An osteochondral lesion of the talus (OLT) is defined as an injury to the talar dome that results in partial or total separation of the articular cartilage or subchondral bone. Numerous terms such as osteochondral defect, chondral defect, talar dome lesion or osteochondritis dissecans have been used interchangeably to describe the phenomenon of articular cartilage separation that can occur in varying degrees from underlying subchondral bone.

Although initially observed by Alexander Monro in 1738 as loose osteocartilaginous bodies resulting from subsequent trauma, Konig is cited as the originator of the term “osteochondritis dissecans,” in 1888. Konig used this term to describe loose bodies of osteocartilaginous material seen in joints attributed to necrosis.

While Konig observed these defects in larger joints, observation in the ankle is often credited to Kappis, who in 1922 used osteochondritis dissecans to describe his findings. Rendu, in 1932, went on to describe a case in which he discovered intra-articular fractures of the talar dome that were consistent with those reported earlier by Kappis and Monro.

It wasn’t until 1959 that the term “transchondral fracture” was coined by Berndt and Harty, who published a review of all literature pertaining to transchondral fractures of the talus from 1856 through 1956. From their review, a classification system was developed that has become the gold standard for radiographic imaging, staging, and treatment in regard to OLTs.

Etiology

As it stands today, talar bone bruising and osteochondral defects are becoming increasingly recognized in ankle trauma. A bone bruise is a subchondral osseous fracture of the cancellous microarchitecture typically associated with local hemorrhage and edema. When evaluating osteochondral lesions of the talus, it is important to recognize the difference between bone bruising and true osteochondral defects or fractures. Osteochondral defects and bone bruising can be distinguished by the presence of, or the absence of, breaks in the subchondral bone plate; when overlying cartilage or subchondral bone plate loses continuity, it is then termed an OCD or osteochondral fracture.

While Kappis and Konig initially attributed the formation of OCD lesions to ischemic necrosis of underlying subchondral bone, leading to eventual deviation of the fragment from its surrounding articular cartilage, more recent research has shown that nearly 85% of the population presenting with osteochondral lesions have been subject to traumatic events. Because it has been shown that the ankle joint is one of the most frequently injured joints in sporting activities in the general population, a correlation between talar dome lesions and athletic populations in the second to fourth decade of life has been suggested. The literature reports that 25-30% of people sustaining ankle sprain injuries develop chronic pain and dysfunction resulting in further investigation, while repeated trauma and associated instability increases the incidence of chondral defects. Aside from ankle sprain injuries, direct non-penetrating trauma to the lateral or medial malleoli, talus and tibial plafond have been shown to induce OLTs analogous to those reported in the knee involving the patella and femoral condyles.

Although the traumatic mechanism of injury is widely considered to be the most prevalent and accepted cause of OLT, a small subset of OLTs of differing origin have been described by Ferkel and Scranton. In a case study observed by Woods and Harris, a set of identical twins developed OLTs without traumatic etiology.
suggesting that genetics might play a role in development of OLTs.\textsuperscript{25} In addition to traumatic and genetic etiology, Conway proposed that perhaps embolism of the epiphyseal arteries accompanied by low grade infection present in the ankle may also be a cause of OLT.\textsuperscript{26}

All theories presented thus far have included a component of local ischemia and associated underlying necrosis, although not necessarily as the primary cause. As the chondral segment is devoid of blood supply, it slowly lyses from the underlying subchondral bone and may induce the formation of a distinct intra-articular fragment. Despite its limitations, the trauma theory remains the most popular and plausible explanation for the formation of OLTs. Regardless of the mechanism, an OLT suggests a distinct episode of macrotrauma, or repetitive microtrauma. The development of an OLT increases the risk of talar dome ischemia in affected individuals, which in turn encourages osteonecrotic processes leading to subchondral fracture and cartilaginous collapse with the ultimate sequela being alteration of joint mechanics.\textsuperscript{27}

**Prevalence**

Although ankle injuries are relatively common, it is estimated that one ankle inversion injury occurs per every 10,000 persons per day, the actual prevalence of OLTs is relatively low, and thus not completely understood.\textsuperscript{28} Although the talus is the third most common location for osteochondral lesions following the knee and elbow joints, OLTs only represent 4\% of all osteochondral lesions.\textsuperscript{29,30} According to Flick and Gould, incidence of OLT is only 0.09\% of all fractures and only 1\% of talus fractures.\textsuperscript{31} It is bilateral in 10\% of reported cases.\textsuperscript{32}

Historically, it was believed that a majority of OLTs occurred anterolaterally and posteromedially. Nishimura and colleagues sought to identify 4 patterns of OLTs on MRI. They found that the most common locations were anterolateral and posteromedial, however Elias, Jung and Raikin went on to invalidate this theory.\textsuperscript{33} In a retrospective study of 428 OLTs, they developed a nine zone grid which not only showed that central medial lesions were most common, they were often found to be the largest.\textsuperscript{34} This information confirmed an earlier study conducted by Elias which showed 66\% of talar dome lesions occurring in a cadaveric study were medially located.\textsuperscript{35} Elias, Raikin and Jung even went on to propose a potential mechanism for the prevalence of medial talar dome lesions, suggesting that a correlation existed between inversion ankle sprains and traumatic impact between the talar dome and the tibial plafond.\textsuperscript{35} In support of the traumatic theory of OLT formation, Flick and Gould would go on to say that 98\% of lateral lesions and 70\% of medial lesions were the results of trauma. That is not to say, however, that lateral lesions are more prevalent than medial lesions, simply that they are more likely to be a result of trauma.\textsuperscript{31}

**Clinical Presentation**

Typically, patients with OLTs will initially present with signs and symptoms analogous to an ankle sprain. They will complain of generalized ankle pain, swelling, and possible clicking or catching with range of motion of the ankle. The patient may even present with decreased or painful range of motion. If the patient notes a history of ankle trauma, or ankle sprain, and they have not responded appropriately to conservative treatment after 6-8 weeks, there should be suspicion of OLT.\textsuperscript{36} During the physical exam, palpation will typically elicit pain at the anterior margins of the joint, however absence of palpable pain does not rule out possible OLT. Dorsiflexion and plantarflexion of the ankle may be limited and also display a popping, clicking, or catching which may signify
a defect. Ankle effusion may also be noted. Since the Berndt Harty article, a plethora of literature has been written and reviewed ranging from case studies to proposed mechanisms of injury and etiology and treatments. Because of the complexity and partially unknown nature of this particular topic, it is important to continue our efforts to aggregate information. It is the goal of this article to give an in-depth overview of the most current and relevant information available on osteochondral lesions of the talus.

Classification

A classification system for osteochondral lesions of the talus was first proposed by Berndt and Harty in 1959 and continues to be the most widely accepted. This system divided lateral and medial lesions into four classes based on a literature review of transchondral fractures of the talus from 1856 to 1956 along with their own data obtained through the use of 15 cadaveric specimens. Berndt-Harty described characteristics of lateral and medial lesions as follows: for lateral stage one lesions, the lesion is found in the middle or anterior half of the lateral margin of the talus, and damage is limited to the talar lesion itself and the lateral collateral ligament. Lateral lesions are produced by strong inversion of a dorsiflexed ankle. Lateral lesions are typically wafer-shaped and shallow.

For medial lesions, some cases were accompanied by a lack of trauma, and lesions were generally found in the posterior half of the medial margin of the talus. The mechanism of injury for medial lesions is that of inversion, plantarflexion, and lateral rotation of the tibia on the talus. Medial lesions are typically cup-shaped and deep. Stage 1 lesions are those produced whereby the lateral talar margin is compressed against the fibula. In these lesions, the articular surface of the talar dome remains intact, however the subchondral bone is compressed (Table 1). In stage 2 lesions, avulsion of the talar dome fragment begins to occur in such a way that a fragment of cartilage is partially detached. In stage 3, the lesion is completely detached yet remains in place within a “crater”. In stage four, the completely detached osteochondral fragment is displaced within the ankle mortise and able to float within the joint space.

The advantages of the Berndt and Hardy classification system are its simplicity and widespread use. However, newer classification systems have been proposed based on imaging modalities that have since emerged.

Objective

The objective of this review is to determine current classifications and treatments for talar osteochondral lesions in adults and to compare them to what has been traditionally done in the past to see if there is a need for further improvement on how to treat these osteochondral defects.

METHODS

Independent online database searches were performed and categorized into either a systematic search or a manual search. The systematic search was done using PubMed search strings with Boolean operators which included the following search phrases: “Osteochondral Defects,” “Osteochondral Lesions,” “Talus,” “Talar,” “Treatment,” and “Classification.” In addition, MesH terms: “Adults,” “Human,” and “English” were used. The search yielded 430 results, of which 13 articles were selected for inclusion. Manual searches for other articles were performed within the Journal of Foot and Ankle Surgery and Google scholar. This search yielded 19 articles, but only 8 were eligible to be part of
the review. Overall, a total of 21 articles from 1986-2013 were included in the literature review. Search methods have been summarized in Figure 1. Inclusion criteria required adult and human subjects being 19 years and older. Full text available articles were also another requirement.

Exclusion criteria included pediatric subjects younger than 19 years of age. Cadaveric or animals studies were not included because of clinical implications that may or may not occur in human patients.

Primary outcomes were to evaluate newer classifications since the Berndt and Harty classification and what treatment is currently being used today of osteochondral lesions of the talus. Secondary outcome was looking at the need for newer treatments for these lesions.

**RESULTS**

**Newer Classifications**

Many newer classification systems have been introduced based on current imaging modalities such as MRI and CT scan. Others have been based on what is seen arthroscopically. Research has also focused on examining the correlation between what is seen on MRI and through arthroscopy.

Loomer proposed a fifth stage to Berndt and Harty’s original classification in 1993. This new stage is characterized by the presence of a subchondral, radiolucent cyst seen on CT scan. A classification system based on CT scan was developed by Ferkel and Sgaglione in 1990. Their classification is similar to that of Berndt and

Figure 1. Acquisition of studies based on inclusion and exclusion criteria.
Harty, however they divided stage II into two substages: stage IIA and stage IIB. Stage IIA consists of cystic lesions with a communication to the surface, whereas stage IIB consists of open surfaces lesions with an overlying fragment. 39

A classification scheme based on MRI was proposed by Anderson in 1989.14 For Anderson’s classification, stage 1 is defined as bone marrow edema. Stage 2a represents a subchondral cyst. Stage 2b represents an incomplete separation of an osteochondral fragment. Stage 3 represents fluid around an undetached, non-displaced osteochondral fragment. Stage 4 represents a displaced osteochondral fragment.14

Hepple et al introduced another MRI classification system in 1999 based on the Berndt and Harty classification. 40 Stage 1 represents damage of the articular cartilage only. Stage 2A represents cartilage injury with underlying bony fracture and surrounding edema. Stage 2B is the same as 2A without surrounding edema. Stage 3 represents a detached, non-displaced bony fragment. Stage 4 represents a detached and displaced fragment with uncovered subchondral bone. Stage 5 represents subchondral cyst formation.40

In 1999, Taranow described the MRI classification system that was developed at the University of Pittsburgh Medical Center. Cartilage is classified as: grade A (viable) or grade B (nonviable).41 The bony component is described from stage 1 to 4. Stage 1 is subchondral compression or bone bruise. Stage 2 consists of subchondral cysts which are not seen acutely. Stage 3 consists of lesions that are partially detached fragments in situ. Stage 4 consists of displaced fragments.41

Pritsch et al were the first to classify osteochondral lesions of the talus according to arthroscopic findings.42 In this system, stage 1 is designated by overlying cartilage that is intact. Stage 2 represents soft overlying cartilage, Stage 3 represents frayed overlying cartilage.42

In 1995, Cheng et al described arthroscopic findings in more detail as follows. In stage 1,

### Table 1: Berndt and Harty Classification

| Stage 1 | • Lateral Talar margin compressed against fibula  
|         | • Talar articular surface of Talar Dome intact  
|         | • Subchondral bone compression |
| Stage 2 | • Avulsion of Talar Dome with partial tearing of cartilage |
| Stage 3 | • Detached, non-displaced osteochondral lesion |
| Stage 4 | • Displaced osteochondral lesion in ankle mortise and is able to float in joint space |

articular cartilage is intense but morphologically intact. In stage 2, fibrillation or fissuring of the cartilage is present. In stage 3, either an osteochondral flap is present or bone is exposed. In stage 4, the osteochondral fragment is loose yet non-displaced. In stage 5, the osteochondral fragment is both detached and displaced. This staging system focuses entirely on the articular cartilage, as the bony component of the defect is not exposed arthroscopically.

Current Treatments

The gold standard for treatment of primary talar osteochondral defects is arthroscopic debridement and bone marrow stimulation, and this is still being used today. The success of this treatment, utilizing either the anterior or posterior approach, has been shown to maintain radiographic osteoarthritis grade postoperatively compared to preoperatively in 67% of 50. The rest of the patients in that study by Van Bergen et al went up one grade in 33% of patients within the 12-year mean follow up time. Another study showed retrograde drilling was more successful in improving patients’ articular cartilage condition using the Pritsch classification when compared to a transmalleolar drilling technique. Transmalleolar drilling comes with some limitations such as damaging the intact tibial cartilage with a Kirschner wire, or there may be no improvement noted on MRI.

In a study by Anders et al, patients with Berndt and Harty stage I and II lesions treated with fluoroscopy-guided retrograde core drilling and bone grafting, had better outcomes than stage III lesions because of the difference in intact versus a cracked cartilage surfaces. This technique encompassed exposing the lesion by plantar flexion while using the Pritsch classification to stage the lesion. A Kirschner wire was placed trans-talar and subchondral bone was drilled. Lastly, an autologous cancellous bone cylinder was placed under the chondral roof. Those authors deemed that this treatment is not recommended for stage III lesions because of the quality of cartilage.

Another study that used a similar retrograde drilling technique emphasized the importance of using a stepwise approach to correctly identify the integrity of cartilage. The authors also agreed this procedure can be used in the presence of intact cartilage with necrosis of the bone seen on MRI. A study conducted by Taranow et al. showed a mean improvement of 25 points in American Orthopedic Foot and Ankle Society (AOFAS) scores in a mean of 24 months postoperative in 16 patients with this technique.

Various techniques are being used to stimulate bone so that patients can heal faster. When dealing with larger lesions 1.5cm or greater, bone marrow stimulating method may not be useful. Defects that leave a cortical diameter that is greater than 75% cannot always be left open because they can lead to an “open-section effect” which are subject to torsional problems when loaded, thus authors Seo et al. decided to use bone cement composed of hydroxyapatite after arthroscopy to fill the gap where the previously located cyst was in a 43-year-old patient. Seo et al. The 43-year-old patient was evaluated at 3 months and 6 months post–operatively. No damage was noted to the surrounding vessels. The patient did not have any complaints of pain or limitations with range of motion. Osteochondral autologous transplantation (OATs) has been used to repair medium to large voids. The OATs procedure has shown in a study by Imhoff and colleagues that at 84 months there was significant improvement in AOFAS, Tegner, and VAS scores. The OATs procedure has been reported to be successful, but failures have been noted. These failures may lead to arthrodesis, which was noted in 3 out of 9 patients in a study by Gross and colleagues.
Surgical techniques analyzed by Verghese, Morgan, and Perera point out that osteotomies can help increase exposure that is needed to visualize the talus. The location of the osteotomy is dependent on the site of the lesion. For instance, medial osteotomies are more frequently used for medial lesions that are central or posteriorly located on the talus, and distal fibular osteotomies are used for lateral talus lesions. Other types of osteotomies may be needed and involve various osteotomies of the tibia. Tibial wedge osteotomies performed on 16 patients with Loomer classified radiographic lesions have shown significant AOFAS Ankle Hindfoot score improvement from 1 year post-operatively when compared preoperatively ($p=0.001$). Dobbs et al (2011) reported a case study in which a surgical osteotomy consisting of a distal tibial chevron (wedge) osteotomy with cadaveric allograft was used to fill the void for a centrally located talar dome lesion.

An alternative surgical procedure which does not involve a malleolar osteotomy includes using Matrix-Induced Autologous Chondrocyte Implantation (MACI). This technique has shown significant improvement ($p=0.002$) in physical functioning with a SF36 evaluation and significant AOFAS hindfoot scores post-operatively in a retrospective study of 10 patients with previously failed conservative therapy and unsuccessful arthroscopic debridement. These authors used the Cheng-Ferkel grading system for classifying the talar lesions.

**Need for Future Treatments**

New treatments for osteochondral defects of the talus are aimed at improving the pathogenesis of the disease as well as decreasing the morbidity associated with previous treatment modalities.

Currently, the gold standard for treatment of osteochondral defects is bone marrow stimulation with arthroscopic debridement of the defect. Osteochondral defects are difficult to treat since there is no source of stem cells for type II hyaline cartilage. As the understanding of osteochondral defects progresses, treatment modalities continuously change. Newer treatment options for talar dome lesions include mosaicplasty implantation, retrograde drilling, and the use of manipulated allografts and autografts. However, some of these treatments may not allow the use of arthroscopy. Without the ability to access the talar dome with arthroscopy, open arthrotomy would be required to reach any area of the talar dome that is not adequately exposed through end range of motion at the tibiotalar articulation. For lateral lesions that are not exposed through plantar flexion, a vertical anterolateral arthotomy is necessary. One can typically gain adequate access to the lateral defect through plantar flexion because the anatomy of the talus allows for the “rolling down” of the dome for enough exposure.

For medial lesions it is often necessary to perform a medial malleolar osteotomy, beginning at the most medial aspect of the malleolus and ending at the junction of the medial plafond. Once there is adequate exposure of the defect, the area is debrided using a curette to properly define where dead tissue ends and healthy viable tissue begins. The idea of removing a part of cartilage from one area of the body and placing it where there is an osteochondral defect is not new. The techniques by which implantation is achieved have changed dramatically. It was originally believed that if the surgeon was able to harvest a large specimen of articular cartilage from the donor site, the long term outcome would be improved. Today however, the opposite is true for osteochondral lesions of the talus. Mosaicplasty has become increasingly popular because of the ability to contour the articular surface to its most natural congruency on the talus, as well as decreasing the morbidity associated with harvest at the donor site. Most importantly, mosaicplasty allows for
transplantation of hyaline cartilage. Treatment consists of first exposing the defect in a proper manner similar to other non-arthroscopic treatment modalities. Once the area of defect is adequately exposed, the area is first debrided properly and measured. Next, a miniarthrotomy is performed on the ipsilateral knee to gain exposure to the harvest site. The mosaicplasty is achieved by harvesting cores of chondral bone from healthy non-weight-bearing knee articular cartilage and implanting those cores into identically shaped cores removed from the talus. In an article by Hangody, et al, 94% of 36 cases studied showed good to excellent long-term results between two and seven years post-op using the Hannover scoring system. Additionally, in all 36 cases, the patients admitted to no long-term donor site morbidity. A prospective study was done using mosaicplasty and a medial malleolar osteotomy for osteochondral defects with subchondral cyst formation in the talus greater than 1.5 cm in diameter in 32 patients. After a 2-year follow-up in those patients, the AOFAS score increased from 59.12 ± 7.72 to 87.94 ± 3.55, which was statistically significant. Mosaicplasty is a viable treatment option if conservative surgical treatment is not effective.

Capitalizing on today’s technological advancements, retrograde drilling has allowed surgeons the ability to attack the osteochondral defect from within. Using the aid of fluoroscopy and dyes, the drill is advanced through the sinus tarsi and into the talar neck in a posteromedial dorsal direction targeted to the medial aspect of the talar dome. The final few millimeters of drilling are done under continuous fluoroscopy to ensure that the healthy articular surface is not damaged. Retrograde drilling only allows for treatment of medial OLT’s because access is gained through the sinus tarsi, thus negating the ability to target lateral lesions. Once the proper debridement has been completed, it is possible to add bone graft to the defect, typically obtained from the Calcaneus. Following implementation of the bone graft, dyes are used to ensure proper packing of the area. Future modifications to this form of OLT management may include the use of cartilaginous growth factors being incorporated into the graft as well as the dyes used for imaging. In an article by Taranow et al, the others describe the process of retrograde drilling as management of medial osteochondral defects in sixteen patients.

DISCUSSION

A classification system that can dictate treatment protocol based upon the staging of the lesion would be ideal. Newer classification systems discussed previously have not been used as extensively as that of Berndt and Harty, especially in terms of treatment recommendation. McGahan and Pinney attempted to correlate the results of different treatment modalities with lesion grade using the Berndt-Harty system as well as their own method of classification. For marrow stimulation, they found that some studies reported better results for lower grade lesions whereas other studies found no correlation between lesion grade and results. For osteochondral autografts, they found little evidence to correlate outcome with lesion grade. They found insufficient evidence to support the use of osteochondral allograft or autologous chondrocyte implantation for osteochondral talar lesions of any grade. As previously mentioned, Anders et al found that retrograde drilling is inappropriate for stage 3 lesions. Choi et al argue that there are ages and symptom differences between osteochondral and chondral type lesions that occur in the talus which are not reflected in the Berndt and Harty classification. Future studies may further evaluate treatment outcomes in regard to lesion grade.
Newer treatment modalities have yet to be studied over a long period of time to justify their use as empirical. Mosaicplasty as a treatment for OCD’s of the talar dome has been preferred over the traditional arthroscopic debridement because of the greater congruency achieved. However, one negative of using the mosaicplasty modality is the fact that healthy cores must be taken from the ipsilateral non-weight-bearing articular surface in the knee. This presents another potential site for morbidity. Compared with retrograde drilling, mosaicplasty has the added benefit of being able to attack defects on the lateral surface of the talar dome. Retrograde drilling only allows for a subset of OCD’s, and is better suited for full thickness defects, eliminating its use for Stage 1 Berndt-Hardy lesions. The benefit of using retrograde drilling, however, is the notion that you are entering the talus through a small incision of a non-weight-bearing area. This reduces the need for arthrootomy or osteotomy and diminishes the likelihood of having the fibrocartilage replaced at the articular surface.

The main goal for treatment of osteochondral defects is to return the joint back to its original quality of function. This implies that treatment should be focused on repair of the articular cartilage resulting in the formation of type II hyaline cartilage throughout the defect. Using particulated juvenile allograft allows for the introduction of newer chondrocytes which in theory are better suited for chondral repair. Having a greater concentration of younger chondrocytes aids in repair by allowing younger chondrocytes to escape the extracellular matrix and take up hold in adjacent tissues to repair defects. This method of treating chondral defects eliminates the need to harvest healthy tissue from a donor site elsewhere on the patient, decreasing any potential morbidity associated with harvesting. Moreover, using juvenile allograft allows the surgeon to use a single stage method of treatment because there is no need to enter the joint initially to remove any specimen compared with the MACI technique. Matrix-induced autograft chondrocyte implantation does have the most potential as a long-term treatment modality in that the techniques and principles utilized with MACI can be implemented with other modalities to increase the long-term performance of the chondral implant within a weight bearing articular surface.

Having the ability to remove native cells from a patient and grow a specialized implant to be introduced back into the patient, has the potential to lead to many types of new treatment avenues. These newer and ever improving treatments for osteochondral defects of the talus help to decrease the morbidity associated with previous treatments and quickly return function to the ankle joint of patients with osteochondral defects of the talus.

One of the advantages of this study is that a variety of studies were evaluated in this literature review, including some of the latest therapies that could be the future of treating osteochondral lesions in the talus. Furthermore, this study aims to hone in on the adult population. Studies were only included if they were conducted in humans. Another advantage of this study shows there is a need to expand upon Berndt and Harty’s classification.

A limitation of this present study is that it did not identify from the available evidence which intervention is most fitting for the treatment of talar osteochondral defects in the talus. Another disadvantage to this study is that various treatments were discussed, but not all were based on which technique would be best depending on where the defect was located.

CONCLUSION

The current gold standard of treatment of osteochondral defects of the talar dome is
arthroscopy and bone stimulation. This has been practiced around the world longer than any other form of treatment for this pathology. Furthermore, there is no one classification which always accurately correlates the staging of the defect with the treatment that is implemented. Therefore, there is a need to use some of these newer classification systems because they cannot always be staged accurately by the Berndt and Harty classification. Present treatments focus on decreasing the morbidity associated with current treatments. Although debridement with mechanical chondral stimulation is effective to healing the defect, the resulting tissue type is less suited for articular compression than native hyaline cartilage. Thus, the focus of future treatments must incorporate not only rapid healing of the defect, but also encourage the regrowth of type II hyaline cartilage to help return patients back to their peak quality of life.

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AUTHORS’ CONTRIBUTIONS
All authors conceived the design of the study. JD conceived the topic of the study, drafted the new treatment section, and made all revisions throughout the peer review process. SP independently performed a literature search using PubMed, created the flow chart depicting search criteria, and drafted the current treatment section. BE drafted the background section of the study. BT drafted the current and new classification sections. All authors read and approved the final manuscript.

STATEMENT OF COMPETING INTEREST
The authors declare that they have no competing interests.

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Efficacy of Topical Agents (SA, 5-FU, and IMQ) for Treatment of Verruca Plantaris: A Systematic Review

Aaron Bradley, BS, Danielle Boyle, BS, and Michael Rossidis, BS

Abstract

Introduction
Conventional treatments for Verruca Plantaris are often challenging and painful being that these modalities obliterate infected keratinocytes by chemical or physical destruction. A literature review was conducted to assess and evaluate the efficacy of topical agents, specifically Salicylic Acid (SA), 5-Flurouracil (5-FU), and Imiquoid (IMQ), on the treatment of Verruca Plantaris (VP).

Study Design
Qualitative Systematic Review of the Literature

Methods
An English language literature search was conducted using the PubMed, Cochrane databases, and a review of textbook articles. Studies which contained HIV + or immunocompromised subjects or subjects who were prescribed immunosuppressants were excluded from this review. Other exclusions included non-English articles or articles published prior to 2000. Inclusion criteria consists of adults and children, HIV– and immunocompetent patients, and terms “Verruca Plantaris” OR “Plantar Warts.”

Results
Ten articles were obtained through the PubMed and Cochrane database that met the criteria for the study.

Conclusion
Treatment of VP was enhanced when the regimen included topical agents, such as 5-FU and IMQ, coupled with a keratinolytic agent, such as SA. These novel topical agents were able to decrease clearance time, when compared to conventional treatments, and were found to be most effective when coupled together. Future randomized controlled trials comparing the efficacy of 5FU/SA and imiquimod/SA on the treatment of recurrent plantar warts should take into account a standardized time frame of sustained clearance and potential adverse side effects. Moreover, such future studies may assist practitioners in determining the proper treatment for each individual patient.

Key Words
Verruca, 5-FU, IMQ
Level of Evidence: 4
INTRODUCTION

Verruca Plantaris (VP), or plantar wart, is a common condition seen routinely throughout practice-based medicine. It is a well-circumscribed hyperkeratotic lesion that appears on the sole of the foot, often identified by its cauliflower-like appearance. Verrucae are caused by the human papillomavirus (HPV). Specifically, HPV serotype 1, 2 and 4 are most commonly responsible for verrucae on the plantar surface of the feet. Given that humans are the primary reservoir for this precarious, highly contagious virus, a systematic review and treatment of VP is a central public health concern.

In fact, prevalence rates suggest that virtually every individual will be infected with VP at least once within his or her lifetime. These lesions are often painful and can make daily activities, such as walking, feel unbearable.

The diagnosis of this condition is often straightforward and concrete, but treatment for specific cases varies tremendously. Typically, the first line of treatment includes keratinolytic topical agents, such as salicylic acid; and cryotherapy, with liquid nitrogen. However, if the plantar wart still persists, alternative treatment options including invasive surgical excision or surgical curettage are employed. Despite their...
continued use, these treatment modalities only destroy the keratinocytes infected by HPV without completely inhibiting the replication of HPV, which can be present in surrounding tissue. This presents a problematic treatment approach as it can cause the plantar warts to resurface and become a recurring issue.¹⁸

The first line agent, liquid nitrogen, is one of the most common cryogens for treating plantar warts. Its mechanism of action is vaporizing the infected cells at a temperature of -196 °C. This cold temperature causes ice formation within the cell, which leads to damage by changing the osmotic gradient, disrupting intracellular structures, and damaging the cell’s membrane. These processes lead to a local inflammation that causes necrotic destruction of the HPV-infected keratinocytes. This immune reaction that is caused by the cryogen is short lived, and is one reason that cryotherapy does not work well with treating reoccurring warts. As one can imagine, this process is non-specific and could cause widespread damage to the local area, causing pain, erythema, blistering, and nail dystrophy, if treating periungual warts.²²

In light of the adverse side effects associated with cryotherapy and surgery, it may be beneficial for practitioners to consider the efficacy of less...
invasive treatments. Topical agents such as 5-Flurouracil (5-FU) and imiquimod (IMQ) provide a less intrusive, more potent form of treatment, which also provide mechanisms to eliminate the root cause of VP.

5-FU, an antimetabolite, interferes with DNA and RNA replication by acting as a suicide inhibitor of thymidylate synthase, an essential enzyme for the replication and proliferation of the HPV virus. This inhibition blocks the synthesis of thymidine, a nucleoside necessary for DNA replication, and triggers the keratinocytes infected with HPV to undergo cell death.

Alternatively, IMQ, an immune response modifier, acts by inducing the production of non-specific immune factors, such as tumor necrosis factor alpha, and interferons alpha, beta, and gamma. In addition, IMQ induces the production of specific immune factors, such as cytotoxic T cells. The creation of this specific immunological memory is thought to aid in the eradication of chronic recurrent VP.

Indeed, recent research suggests that both 5-FU and IMQ, when coupled with a keratolytic agent such as salicylic acid, are more effective at achieving complete resolution in various skin conditions such as Actinic Keratosis (AK), basal cell carcinoma, and squamous cell carcinoma, compared to the use of 5-FU or IMQ alone. In addition, VP has histologic resemblances to AK, benign and malignant skin conditions, as well as similar primary treatment approaches. Given these similarities, it is plausible that this coupled approach may be beneficial to eradicate troublesome cases of VP.

In light of the need for alternative treatment options for VP and the promising findings garnered by the use of coupled topical agents and SA, this manuscript aims to review the literature regarding the efficacy of 5-FQ, SA, and IMQ for the treatment of Verruca Plantaris. More specifically, this manuscript aims to review the literature by focusing on the analysis of the different methods by which these agents are being used today, how they can be used in the future, and evaluate the side effects they may have on patients.

METHODS

Three searches of the primary literature were performed using the Pubmed database. The initial search employed the Boolean operator "and" for the terms "Verruca Plantaris" OR "Plantar Warts"
AND "5-fluouracil." The first search yielded 11 articles. The second search employed the Boolean operators "or" and "and" for the terms "Verruca Plantaris" OR "Plantar Warts" AND "Salicylic Acid". The second search yielded 39 articles. The third search employed the boolean operators "or" and "and" for the terms "Verruca Plantaris" OR "Planter Warts" AND "Imiquimod". The third search yielded 15 articles. Exclusion criteria consisted of articles with HIV+ or immunocompromised subjects, or subjects who were prescribed immunosuppressants, as well as non-English articles and articles published prior to 2000. Inclusion criteria consisted of: HIV- and immunosuppressant patients, adults and children, and terms “Verruca Plantaris” OR “Plantar Warts.” The total number of articles found using the Pubmed Database was 55 articles. After evaluating the papers for proper exclusionary properties, 87% of the articles were excluded from review, resulting in 7 final articles chosen from the PubMed database.

Three searches of the primary literature were also performed using the Cochrane database. The initial search employed the Boolean operators “or” and “and” for the terms "Verruca Plantaris" OR "Plantar Warts" AND "5-fluouracil". The first search yielded 12 articles. The second search employed the Boolean operators "or" and "and" for the terms "Verruca Plantaris" OR "Plantar Warts" AND "Salicylic Acid". The second search yielded 1 article. The third search employed the Boolean operators "or" and "and" for the terms "Verruca Plantaris" OR "Planter Warts" AND "Imiquimod". The third search yielded 1 article. The Cochrane database search yielded 14 total articles. After applying the exclusion/inclusion criteria, 79% of the articles were excluded from review, resulting in 3 final articles chosen from the Cochrane database. In total, 10 articles met inclusion criteria for qualitative review.

Table 1: Comparison of Successful Treatment regimens for Recalcitrant VP using IMQ

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<td>Previous Unsuccessful Treatments</td>
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<td>40% Salicylic Acid and Podophyllin, Cryotherapy, Topical Glutaraldehyde,</td>
<td>Cryotherapy, Topical Cantharadin, Bleomycin Injections, Paring with Topical SA and 5-FU under duct tape occlusion</td>
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<td>Successful Treatments</td>
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<tr>
<td>-Concentration</td>
<td>5% IMQ</td>
<td>5% IMQ</td>
<td>5% IMQ</td>
</tr>
<tr>
<td>-Application</td>
<td>3 X per wk</td>
<td>3 X wk after paring</td>
<td>Left on foot for 3 day intervals</td>
</tr>
<tr>
<td>-Occulsion</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>-Clearance</td>
<td>14 wks</td>
<td>8 wks</td>
<td>6 wks</td>
</tr>
<tr>
<td>-Sustained Cure Rate</td>
<td>confirmed 3 mon later</td>
<td>confirmed 1 yr later</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Note: Data derived from literature referenced in the manuscript, citations shown in the table entries.
Table 2: Comparison of Different Topical Treatment Regimens for VP and the Clearance Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Topical Agent(s)</th>
<th>Results (Months of Treatment vs. % Clearance*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>SA+5% 5-FU (coupled)</td>
<td>2.5 Months 40%</td>
</tr>
<tr>
<td>7</td>
<td>SA</td>
<td>3 Months 14%</td>
</tr>
<tr>
<td>3</td>
<td>SA</td>
<td>6 Months 31%</td>
</tr>
<tr>
<td>6</td>
<td>5-FU SA IMQ</td>
<td>Avg. Results of 2.5 Months: 5-FU-46% SA-60% IMQ-12%</td>
</tr>
<tr>
<td>5</td>
<td>5-FU IMQ</td>
<td>12 Months 5-FU-57% IMQ-85%</td>
</tr>
</tbody>
</table>

*Note. Data derived from literature referenced in the manuscript, citations shown in the table entries

"Clearance is defined here as complete eradication without indication of sustained cured rate

Table 3: Adverse Effects of Treatment.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Acute Adverse Side Effects</th>
<th>Chronic Adverse Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young, S., et al [21]</td>
<td>5-FU- N/A SA- N/A IMQ- N/A 5-FU &amp; SA- Yes</td>
<td>5-FU- N/A SA- N/A IMQ- N/A 5-FU &amp; SA- No</td>
</tr>
<tr>
<td>Lopez-Gimenez. (9)</td>
<td>5-FU- N/A SA- N/A IMQ- Yes 5-FU &amp; SA- N/A</td>
<td>5-FU- N/A SA- N/A IMQ- No 5-FU &amp; SA- N/A</td>
</tr>
<tr>
<td>Samrao, A. [13]</td>
<td>5-FU- N/A SA- N/A IMQ- No 5-FU &amp; SA- N/A</td>
<td>5-FU- N/A SA- N/A IMQ- Yes* 5-FU &amp; SA- N/A</td>
</tr>
<tr>
<td>Cockayne, S (3)</td>
<td>5-FU- Yes SA- Yes IMQ- N/A 5-FU &amp; SA- N/A</td>
<td>5-FU- No SA- No IMQ- N/A 5-FU &amp; SA- N/A</td>
</tr>
</tbody>
</table>
DISCUSSION

Distinction between Non-Recurent and Recurrent Verruca Plantaris

Non-recurrent VP are usually harmless plantar warts that either resolve spontaneously or achieve complete eradication with a sustained cure rate when treated with Salicylic acid or cryotherapy. Recurrent, or recalcitrant, VP are plantar warts that do not resolve spontaneously or achieve complete eradication and a sustained cure rate when treated with first line treatment modalities. This occurs because recalcitrant VP will infect more keratinocytes and surrounding tissues with HPV. Subsequently, recurrent VP can be painful, troublesome and more difficult to effectively treat.

It is important to understand the distinction between a VP that is recurrent and non-recurrent when gathering data on topical agents. The studies that treated recalcitrant VP had a lower percentage of clearance, compared to non-recalcitrant VP. When taking into account the definitions of recurrent VP and non-recurrent VP, it makes sense that it was more difficult to achieve clearance when treating a recurrent VP, but when searching previous studies these definitions were often absent or overlooked. Given that recalcitrant VP requires prolonged application of topical agents, it takes longer for total eradication to occur. As a consequence, observed results may not fully capture the efficacy of topical treatments on recalcitrant VP, thereby creating artificially low clearance rates. Future research may aim to more accurately assess this treatment modality by distinguishing between recurrent and non-recurrent VP and conducting longer follow-ups with subjects.

Efficacy of Topical Treatment Regimens for Verruca Plantaris

Topical keratolytic agent: Salicylic Acid

Le Cleach and colleagues evaluated a multicenter, randomized, pragmatic trial and found that the treatment of Verruca Plantaris with 50% Salicylic Acid applied once daily for a maximum of 8 weeks yielded a 14% clearance after 3 months of treatment. In 2011, a RCT found that 29 out of the 95 patients, 31%, in the salicylic acid group had complete clearance when assessed after the 6-month treatment. Based on these studies, salicylic acid alone does not appear to be a viable and effective treatment regimen, when taking into account its clearance rates. This can be due to the mechanism of salicylic acid, which aims to directly destroy the keratinocytes that it encounters. Therefore, for a sustained cure of VP to be obtained with the use of salicylic acid, eradication of every single cell infected with HPV would need to occur. This can lead to the unnecessary killing of perfectly healthy keratinocytes in hopes of removing all the diseased ones.

Topical antimetabolite: 5-FU

Salk and colleagues found complete eradication of VP with high sustained cure rates using 5% 5-FU with tape occlusion. Nineteen out of the twenty patients (95%) randomized to 5% 5-FU with tape occlusion had complete eradication of VP within three months of treatment. Three patients had recurrence at 6-month follow-up, an 84% sustained cure rate. Although this trial demonstrated the efficacy of topical 5-FU, the recurrence rate of 16% after a mere six months needs to be taken into account when deciding which topical treatment option is best for the long-term management of Verruca Plantaris.
Despite these promising findings, the small sample size (n=40) makes it scientifically difficult to extrapolate these results and implement these findings into all treatment regimens. Notably, this illustrates the need for more RCTs comparing topical 5-FU and other promising topical agents, such as IMQ, in the treatment of VP. 5-FU’s ability to inhibit DNA and RNA synthesis prevents the proliferation and propagation of the HPV within infected cells. Additionally, the effects of this inhibition are more pronounced on HPV infected cells, given that these cells grow more rapidly and incorporate fluorouracil at an increased rate as compared to healthy tissue. Thus, application of 5-FU has less destructive effects on healthy surrounding tissue.

Topical Immunomodulator: IMQ

Recent studies have suggested that the use of IMQ can be effective in the clearance of recalcitrant VP. In Mitsuishi et al. (table 1), a patient with a 15-year history of recalcitrant VP was successfully treated with topical 5% IMQ applied three times per week at night. The complete eradication time was 14 weeks and the sustained cure rate was confirmed 3 months later. In Yesudian et al., a patient with a 15 year history of recalcitrant VP was successfully treated with topical 5% IMQ applied 3 X per week after paring. The VP was cleared in 8 weeks and complete resolution was confirmed a year later. The clearance achieved supports the use of IMQ for the resolution of recalcitrant VP. However, the inconsistency of the collected data of these case reports illustrates the need for a randomized-controlled trial to validate these findings.

The exact mechanism of IMQ is unclear, but IMQ’s ability to stimulate a specific immunological response that targets only the cells infected with HPV limits the destruction of healthy tissue. Furthermore, induction of cytotoxic T cells initiates an immunological memory directed against this specific HPV responsible for VP. This allows the immune system to continuously scan the entire body, and selectively destroy cells infected with this HPV.

Coupling of Topical Agents

Various methods were used to assess the efficacy of topical agents in the studies under review. Young and colleagues found that coupling .5% 5-FU with 40% SA had a 100% clearance rate over 14-60 days. Conversely, other studies that only applied 5-FU over 6 weeks had 19% clearance and SA over a 3-week period had only 14% clearance. These findings are significant because when coupled together the two topical agents seem to have a faster healing time. The synergistic relationship between the SA and 5-FU properties have a multiplicative effect, which will increase healing time. Additionally, SA destroys the thick keratinization pattern, a common characteristic of VP. This allows the 5-FU to penetrate the deep layers of the epithelium and inhibit the mitotic divisions of the VP. The coupling of the topical agents should be investigated more to validate the finding of the Young, Simon et al study.

In Tucker et al., (table 2), a patient with a history of recalcitrant VP was unsuccessfully treated with the use of cryotherapy, topical salicylic acid and 5-FU under duct tape occlusion. Subsequently, the patient was treated with topical IMQ under a 40% salicylic acid pad, which was covered under a duct tape occlusion. After 3 days, the pad and occlusion were removed, the patient debrided the VP, and then reapplied topical IMQ and a 40% salicylic acid pad under a duct tape occlusion. This strict regimen resolved the VP within 6 weeks. Complete resolution was not addressed. This regimen suggests a promising possibility of the use of topical IMQ coupled with SA when treating difficult and problematic cases of Verruca Plantaris.
Measurement of Clearance

Clearance is defined as the complete eradication without indication of future recurrence. However, variability in the amount of time to measure clearance (e.g., only 4 weeks compared to one year) creates inconsistencies in this body of literature, which may blemish the observed results of topical agent clearance. Kwok et al. averaged all the studies that used all three topical agents separately and found the percentage of clearance to be IMQ-12%, 5-FU 46%, and SA 60% within 8 weeks.6 These results are consistent with the findings of Kwok et al. review, which also confirmed that within the first 8 weeks SA always had faster cure rates for the clearance of VP.

In contrast, two case studies of Yesudian, P. D. et al. and Mitsuishi, T. indicate 100% sustained clearance for IMQ after a 1 year follow up.12,21 This suggests the immunological memory and true efficacy of IMQ to sustain VP clearance as opposed to treating the presenting VP with SA alone, which only sustains clearance for 4 weeks.21 However, issues of patient compliance may undermine these results, as the results did not include a randomized study with multiple subjects. It is important for future research to incorporate sustained results with IMQ to further investigate the efficacy of IMQ because of the immunological memory effects and sustained healing rate post 6 months. These gaps in the literature show the important points that need to be considered when reviewing the true efficacy of the topical agents.

Adverse Effects of Topical Agents

A significant finding within the Young, S., et al. study states that with the application of 5-FU coupled with SA, subjects showed signs of dermatitis (Table 3).23 This finding is inconsistent with previous research, which suggests that typical adverse affects from 5-FU include hyperpigmentation, erythema, erosion, onycholysis, and onychodystrophy, but not dermatitis.3 In light of this disparity, future studies may aim to investigate whether dermatitis is a normal adverse effect when combing 5-FU and SA as a treatment plan.

This review yielded conflicting findings in the consideration of adverse effects when using IMQ alone. One study consisting of 5 subjects for treatment indicated that the use of IMQ alone was associated with no adverse effects.8 However, this small sample size may limit the validity of this notion. The other study had a larger sample size and resulted in both chronic and acute adverse effects including erythema, burning, pain, erosion, flu-like symptoms, and ulceration.14 Such inconsistencies in findings, along with the scarcity of data in this regard, emphasize the need for more studies to quantify whether the treatment of IMQ causes chronic or acute adverse effects on patients.

Limitations

Despite the important findings yielded by this literature review, it is not without its limitations. Firstly, this review consisted of limited search terms such as “Verruca Plantaris,” which narrowed the amount of articles to two articles. Even with the addition of alternative search terms, such as “Plantar Warts”, the search ultimately only yielded a minute amount of articles.

Additionally, all of the studies under review utilized different methods to carry out the research. Variability in methodology makes it difficult to accurately compare results. Undoubtedly, greater research is needed to alleviate some of the gaps in the current literature. Presently these gaps include a lack of studies that combine all three topical agents as a treatment method, insufficient data on treatment modalities coupling a keratinolytic agent with topical 5-FU
or IMQ, and a lack of consistency when defining both the type of VP and the clearance rate. Also, randomized controlled trials on the use of IMQ as a treatment for VP need to be performed in order to find a correlation between the individual results found in the case studies. Raising awareness about other treatment methods and generating recommendations from the Food and Drug Administration regarding the use of some of these agents for VP may help to substantiate the empirical evidence of this treatment approach.

**CONCLUSION**

Ultimately, this review suggests that the efficacy of SA, 5-FU and IMQ for the treatment of VP is marked by faster clearance times when compared to conventional methods of VP clearance. After evaluation of these three topical agents, findings suggest that the fastest clearance times and minimal adverse effects came when 0.5% 5-FU and 40% SA were used in conjunction with each other. Additionally, for sustained clearance of recalcitrant VP, IMQ was most profound. Nonetheless, future studies will undoubtedly need to be conducted in a standardized manner to accurately evaluate resulting effects. Additionally, more assessments on the clearance rates, adverse effects, and the immunological components of the specific topical agents will aid in improving current treatment regimens for VP.

**AUTHORS’ CONTRIBUTIONS**

AB, DB, and MR equally conceived the design of the study, performed the database advanced search and evaluated abstracts. All authors designed figures, drafted, read and approved the final manuscript.

**STATEMENT OF COMPETING INTERESTS**

The authors declare that they have no competing interests.

**REFERENCES**

The Quadratus Plantae: A Review of Functional Theories Past and Present

Darla Thomas, BA, BS, and Ashley Varner, BS

Abstract

Introduction
Of the plantar intrinsic foot muscles, the quadratus plantae counts itself unique due to its structure and function. In recent years, advances in research methods and technology have brought the function of this muscle into question. The quadratus plantae is now believed to play an essential role not just in flexion of the toes, but in gait, posture and compartment syndrome secondary to a calcaneal fracture. Its role in pronation has also come into question with the emergence of electromyographic technology. This paper is a systematic review exploring old views and assessing new beliefs concerning the role and function of the quadratus plantae.

Study Design
Review of the Literature

Methods
A general literature search on “quadratus plantae”, “flexor accessorius” and “human foot anatomy” + “quadratus plantae” was conducted in PubMed, producing 28, 31 and 15 results respectively, along with four advanced literature searches. In addition, we also reviewed two anatomy books containing sections committed to the intrinsic plantar muscles, that specifically discussed the quadratus plantae. Articles based solely on the flexor accessorius longus and the intrinsic plantar foot muscles as a group were excluded.

Results
A total of 24 articles were selected from the online PubMed and Google Scholar searches (1892 to present). Section 9 of “Gray’s Anatomy, 40th edition” and Chapter 6 of “Clinically Oriented Anatomy, 5th edition” were also used as references.

Conclusion
Theories of quadratus plantae’s unique role in gait, posture, and compartment syndrome have been presented. Since the current literature is limited in its assessment of these various functions of the quadratus plantae, additional research is required to thoroughly examine these proposed mechanisms.

Key Words
quadratus plantae, gait, posture, pronation, flexor accessorius

Level of Evidence: 4
INTRODUCTION

The plantar intrinsic foot muscles are a specialized group of muscles in the sole of the foot. Although their general purpose is to provide structural support for the medial arch of the foot, their precise function individually remains unclear. Of these muscles, the quadratus plantae, also known as the flexor accessorius, counts itself unique based on structure and function, and the fact that it has no counterpart or homolog in the hand.

Considered part of the second layer of muscles on the plantar surface of the foot, the quadratus plantae does not really belong to any specific layer. It is located deep in the intermediate compartment, separated from the more superficial flexor digitorum brevis by a thin layer of fascia. It is innervated by the lateral plantar nerve, and receives blood from branches of both the lateral and medial plantar arteries. The quadratus plantae has been observed and documented in scientific articles and books dating as far back as 1892. In humans, this unique muscle has two points of origin consisting of a smaller lateral head arising from the lateral plantar surface of the calcaneus, and a larger medial head arising from the medial surface of the calcaneus. It is this larger medial head that is unique only to man.

Early analysis on the origin and evolution of the quadratus plantae seemed to generate much debate. One opinion was that the muscle developed along with the flexor hallucis longus, when observation of an early human embryo revealed a fusion of both muscles. Others disagreed with this, not being able to confirm this observation. Another opinion was that the quadratus plantae evolved from the original muscle mass that gave rise to the tibial and fibular flexors. Some went further on to say that its origin was associated more with the tibial flexors. In line with this same thinking, the quadratus plantae was believed to be associated with the tibialis posterior only. Unfortunately, there was not conclusive evidence to confirm any of these theories. The current and established teaching is that the lateral head descended developmentally from the flexor hallucis longus muscle and is believed to be the homologue of the quadratus plantae muscle present in other species of mammals. The emergence of the medial head is thought to be a new evolutionary development derived from the deep head of the flexor digitorum brevis muscle. The two heads come together, forming a bulky muscle body that inserts posteriolaterally to the tendons of the flexor digitorum longus. Although the above mentioned points of origin and insertion are seen in the majority of cases, it is also important to note that there is variability with all aspects of this muscle.

Over time, the individual function of the quadratus plantae has come into question. It was first postulated that the muscle aided the flexor digitorum longus in flexing toes 2-5; while straightening out the oblique pull of the flexor digitorum longus to bring the toes back in line with the axis of the foot. It was also believed that the quadratus plantae acted simultaneously with the fibularis longus, flexor hallucis longus, and flexor digitorum longus to stop inversion, thus stabilizing the subtalar joint during locomotion. However, improvements in research technology like electromyography and Magnetic Resonance Imaging (MRI) have called these findings into question. Therefore, it is the purpose of this paper to examine both previous and recent research on the function of the
quadratus plantae, in an effort to provide a better understanding of its role in the plantar foot.

METHODS

Both authors conducted an English language general online search in November 2013 of “quadratus plantae”, “flexor accessorius” and “human foot anatomy” + “quadratus plantae”. Four advanced searches related to variation, morphology and alternative function of the quadratus plantae were also executed. General searches yielded 28, 31 and 15 results respectively. Advanced searches in PubMed included Quadratus Plantae AND posture with 1 result, Quadratus Plantae AND gait with 1 result, Quadratus Plantae AND compartment syndrome with 7 results and Quadratus Plantae AND pronation with 0 results. A Google scholar general search of “quadratus plantae” yielded 4,020 results, many of which were also found in the PubMed searches. “Gray’s Anatomy, 40th edition” and “Clinically Oriented Anatomy, 5th edition” were books also used as references. Both contained sections dedicated to the intrinsic plantar muscles, providing background information and discussion of the quadratus plantae’s relationship to the other intrinsic plantar muscles. Articles based solely on the flexor accessorius longus and the intrinsic plantar foot muscles as a group were excluded.

RESULTS

It was found that the quadratus plantae’s role in assisting the flexor digitorum longus in flexion of digits 2 through 5. To support this theory, Duchenne stimulated both muscles independently, then together. When the flexor digitorum longus was stimulated alone, the distal phalanx of each toe exhibited an oblique pull during flexion; which was believed to cause medial rotation of the distal phalanges on each toe. When stimulated alone, the quadratus plantae only produced extremely weak flexion of the distal phalanx. When the quadratus plantae and flexor digitorum longus were stimulated together, there was straight flexion of the toe. In his investigations, Kaplan was unable to clinically and anatomically confirm any of Duchenne’s observations. Further anatomical analysis suggested that the insertion point of the quadratus plantae is too proximal to affect the pull of the flexor digitorum longus. Unfortunately, in his investigations, Kaplan was unable to clinically and anatomically confirm any of Duchenne’s observations. Further anatomical analysis suggested that the insertion point of the quadratus plantae is too proximal to affect the pull of the flexor digitorum longus. Additional evidence in support of Duchenne’s theory has also come to light recently. A case study of a 75-year-old male cadaver revealed an absence of deep and superficial flexors to the 4th toe on both feet. In their place was, on the right foot, a flexor muscle arising from the quadratus plantae, and on the left...

DISCUSSION

Initial Theories: Function of Quadratus Plantae

It was originally thought that the quadratus plantae aided the flexor digitorum longus in flexion of digits 2 through 5. To support this theory, Duchenne stimulated both muscles independently, then together. When the flexor digitorum longus was stimulated alone, the distal phalanx of each toe exhibited an oblique pull during flexion; which was believed to cause medial rotation of the distal phalanges on each toe. When stimulated alone, the quadratus plantae only produced extremely weak flexion of the distal phalanx. When the quadratus plantae and flexor digitorum longus were stimulated together, there was straight flexion of the toe. Based on his observations, Duchenne concluded that due to its posteriolateral attachment to the flexor digitorum longus, the quadratus plantae corrected this oblique pull, bringing the toes back in line with the axis of the foot. Additional support for this theory could also be seen in various pathologies including claw foot, which congenitally, is marked by a complete absence of the quadratus plantae. Kaplan further reinforced this theory by recognizing that during plantar flexion, the quadratus plantae aids in flexion of the toes when the flexor digitorum longus is maximally contracted. Unfortunately, in his investigations, Kaplan was unable to clinically and anatomically confirm any of Duchenne’s observations. Further anatomical analysis suggested that the insertion point of the quadratus plantae is too proximal to affect the pull of the flexor digitorum longus. Additional evidence in support of Duchenne’s theory has also come to light recently. A case study of a 75-year-old male cadaver revealed an absence of deep and superficial flexors to the 4th toe on both feet. In their place was, on the right foot, a flexor muscle arising from the quadratus plantae, and on the left...
foot, a flexor muscle arising from both the quadratus plantae and the flexor digitorum longus. The authors believe this discovery further strengthens the theory that the quadratus plantae is essentially an additional flexor head of the flexor digitorum longus.

It was also postulated that the action of the long flexor muscles on the subtalar joint was what caused supination of the foot during flexion in species who exhibited a large range of motion at this joint. In addition to aiding in flexion, it was also believed that the quadratus plantae, together with the fibularis longus, flexor hallucis longus and flexor digitorum longus, helped to suppress inversion/supination and stabilize the subtalar joint during the final push-off of the hallux in the last stage of the stance phase. Support for this theory was attributed to the absence of a quadratus plantae in species like rabbits, whose feet are in static pronation, and have no action of the long flexor muscles on the subtalar joint. Reduced muscle size was seen in species with feet normally supinated and with a reduced range of motion at the subtalar joint. However, this theory was eventually disproven with advanced anatomical studies using electromyography.

Current Theories: The various roles of Quadratus Plantae

Role in Pronation
Initially, it was believed that the quadratus plantae’s only role was as an accessory to the flexor digitorum longus due to the quadratus plantae’s insertion into its tendon. Later, it was surprisingly discovered that the hind limb of a bear (Ursa Americanus) and the foot of man, have some similarities. Because of these similarities, bear specimens were used in a study to examine the quadratus plantae. After dissection of the bear specimens, it was thought that the quadratus plantae acted not only as an adjuster of the toes medially deviated by the flexor digitorum longus, but also as a pronator of the foot with flexion of all the toes. More studies were done in species with free movement of the subtalar joint. It was found that the quadratus plantae helped prevent supination of the foot which is produced by flexor digitorum longus and flexor hallucis longus when they flex the toes. As previously discussed, Kaplan also concluded that the quadratus plantae was an active pronator of the forefoot working together with the long flexors of all the toes and the fibularis longus muscle.

In recent years the theory of the quadratus plantae as a pronator of the forefoot was tested using electromyographic technology. In his study, Reeser could not confirm this, as the quadratus plantae was not activated during eversion/pronation. This contradicted the previous research that suggested the quadratus plantae was active during pronation, thus making it a functional pronator. More research needs to be done to confirm or disprove both theories.

Role in Gait
As alluded to previously, the quadratus plantae has been implicated in playing a role in gait. In a study on the long accessory flexor muscle, it was found that the quadratus plantae provided a more direct pull on the flexor tendons to the toes as opposed to the more oblique pull imposed by the tendons from the leg. This direct pull allows the toe flexors to remain contracted while the extensor tendons also are contracted during the toe-off phase of gait. This unique pull allows for a more stable toe-off position during the toe-off phase of gait. The flexor hallucis longus and flexor digitorum longus play a vital role in toe-off and tip-toe movements. The flexor hallucis longus flexes the hallux as it delivers the final thrust of the toe-off phase of the gait cycle. The flexor hallucis longus has tendon slips that help distribute the load put on the hallux during toe-off to the second, third, and fourth toes. One of the main attachments of the quadratus plantae is to the tendinous slip of the flexor hallucis longus.
The flexor hallucis longus tendon slips increase the weight-bearing area in the forefoot to provide a more stable base and stronger propulsion during toe-off. During an anatomic study, the quadratus plantae of 50 embalmed adult cadavers were investigated. Their findings yielded three groups of quadratus plantae organization: 80% had two heads, 10% only had a medial head and 8% only had a lateral head. It was discovered that the medial head, which was found to be thicker than the lateral head, had a closer relationship with the tendinous slips of the flexor hallucis longus than did the lateral head. Thus one can infer that the quadratus plantae, and more specifically the medial head, is involved in the toe-off phase of the gait cycle through its close relationship and attachment to the tendinous slips of the flexor hallucis longus.

Role in Posture
In a surface electromyography study, it was found that the musculature located in the plantar region of the foot was important in supporting the medial longitudinal arch. This was indicated by the increase in navicular drop when plantar muscle activity was decreased by injecting lidocaine. Navicular drop was used as a measure of medial longitudinal arch and excessive pronation. In a study that explored the recruitment of plantar intrinsic foot muscles and posture, the researcher observed the activation of three intrinsic plantar foot muscles (quadratus plantae, flexor digitorum brevis, adductor hallucis) during three postural positions. The level of activity in the muscles was measured by an EMG signal collected on a force plate. These signals were then used to calculate the center of pressure (CoP). The CoP was additionally measured in both the medio-lateral and antero-posterior directions. These measurements were taken for each of the three postural positions: the relaxed sitting position, double leg stance and single leg stance. During the relaxed sitting (REL) position there was very little to no activation of any of the three muscles. During the double leg stance (DLS) position there was a slight increase in activity of all three muscles. During the single leg stance (SLS) all three muscles had the highest CoP mean. The high CoP for the single leg balance task indicated that a higher level of postural demand was needed to hold that postural position. Recruitment of the quadratus plantae was also correlated to medio-lateral sway during the single leg stance task, with increased recruitment during medial shifts of the CoP.

During single leg balance, it is known that foot posture and function have an important effect on ones ability to hold this position. Activation of the quadratus plantae and other intrinsic plantar muscles may be used to help stabilize the foot and therefore improve balance. The recruitment of the quadratus plantae and the other plantar intrinsic foot muscles is controlled by postural demands. As these demands increase so does the recruitment and activation of these intrinsic plantar muscles. The use of electromyography has helped to confirm this. Exploring the quadratus plantae’s role in posture, the Kelly study used electromyography to measure the activity of the quadratus plantae, abductor hallucis, and flexor digitorum brevis during 3 different postural positions. The single leg stance postural position had the highest activation of all three muscles while that position was being held.

Recently, ultrasound technology has been utilized to better visualize the quadratus plantae. Mickle’s study of the morphology of intrinsic muscles found ultrasound to be a reliable method, with limits of agreement between 8-28% to determine relative muscle size. Ultrasound is a readily available and inexpensive modality that can be used to identify atrophy or hypertrophy of the quadratus plantae individually. Based on these findings, it may give a potential etiology for postural problems.
**Role in Compartment Syndrome**

The quadratus plantae is considered to be a part of the central hindfoot compartment of the foot. Some suggest that the quadratus plantae should be further divided into a separate ‘calcaneal’ compartment.\(^{24}\) However, other studies believe that additional research should be done to confirm the validity of dividing the central hindfoot compartment into superficial and deep compartments.\(^{25}\) Regardless of which compartment it belongs to, there is evidence that the quadratus plantae does play a role in hindfoot compartment syndrome seen after a calcaneal fracture. In the Andermahr study on compartment syndrome, it was found that calcaneal fractures with a sustentacular fragment, blood vessels bled into the quadratus plantae compartment, causing a hindfoot compartment syndrome.\(^{26}\) The blood, coming from both intra and extraosseous vessels, causes an increase of pressure in the quadratus compartment. This leads to swelling in both the hind and midfoot, causing compression of both the medial and lateral plantar arteries and nerves as they pass through the quadratus compartment.\(^{26}\) Compression of the neurovascular bundles consequently leads to contracture of toe flexors (due to ischemia) laterally.\(^{26}\) An increase in pressure and edema has also been known to cause paraesthesia of the distal 2/3 of the plantar aspect of the foot.\(^{26}\) This study suggests that if the CT

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**Figure 1.** Past and present functional theories of the QP.
scan shows a sustentacular fragment and if a hindfoot compartment syndrome is suspected, then the quadratus plantae compartment should be opened and evaluated.

CONCLUSION

The quadratus plantae is truly unique among a group of highly specialized muscles. As originally theorized, the quadratus plantae participates in flexion of the toes, especially when the flexor digitorum is fully contracted. It was also initially postulated that the quadratus plantae helped to counteract medial rotation of the toes during flexion. However, Kaplan later disproved this theory. The quadratus plantae was thought to suppress supination of the foot and help stabilize the subtalar joint, but an electromyography study done by Reeser later brought this theory into question. It has only been recently that new information has come to light regarding its structure and function. Technological advances in electromyography and ultrasound have allowed researchers to study the intrinsic plantar muscles independently. In a recent surface study, electromyography was used to determine that the intrinsic plantar muscles are important in supporting the medial longitudinal arch, thus playing an important role in posture and balance. In addition to its role as an accessory muscle to the flexor digitorum longus, this new EMG study has also brought into question the quadratus plantae’s previously suggested role as an active pronator of the forefoot. Due to its location and close proximity to important neurovasculature in the plantar foot, if inflamed, it can cause a hindfoot compartment syndrome. Over time, the quadratus plantae has increased in size. In particular, the medial head has become bulkier. This change in the anatomical size of the quadratus plantae may have contributed to its newly postulated functions in gait, posture, and hindfoot compartment syndrome. A review of the literature only yielded a limited number of studies that explored these additional functions of the quadratus plantae. Therefore, more research needs to be done to confirm their validity.

Authors’ Contributions
DT conceived the research topic. DT and AV conceived the design of the study and drafted the manuscript. All authors read and approved the final manuscript

Statement of Competing Interests
The authors of the article, DT and AV, have no competing interests associated with this manuscript.

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The Efficacy of Subtalar Joint Arthroereisis In the Treatment of Pes Planovalgus in Adult and Pediatric Patients

J. Adrian Wright, AM, Elnaz Sabeti, BS, Juanita Rufran, BS, and Caitlin Miner, BS

Abstract

Introduction
The purpose of this study is to assess the effectiveness of subtalar joint arthroereisis as a surgical treatment option for adult and pediatric patients with pes planovalgus.

Study Design
Systematic Review of the Literature

Methods
The authors performed a search of the PubMed database using the MeSH word “arthroereisis”, which returned 99 articles. The Boolean operator “and” was also used to include the term “STJ”, thus narrowing the search to 67 articles. From the initial search the authors chose 9 articles, which met the inclusion and exclusion criteria for the study. Studies were included if they were written in English, involved the subtalar joint, and measured the outcomes of subtalar joint implants. Studies where excluded if they were cadaveric, focused on surgical techniques not patient outcomes, and published earlier than 2002.

Results
The authors found that in both the adult and pediatric patient populations, a notably large number of patients required removal of the subtalar joint implant following surgery.

Conclusion
From a review of the current literature, the authors found a considerable number of complications associated with the use of subtalar joint arthroereisis in the treatment of pes planovalgus. Cases requiring removal of the implant may be due to improper sizing as a result of discrepancies between radiologic assessment of the sinus tarsi and its actual size in vivo. Future studies should be conducted to assess sizing protocols in subtalar joint arthroereisis in relation to its effect on patient satisfaction outcomes postoperatively.

Key Words
Pes planovalgus, subtalar arthroereisis, pes planus

Level of Evidence: 4
INTRODUCTION

Uncovering the best treatment for symptomatic pes planovalgus is an area of great exploration that has yet to provide a definitive protocol. A patient with pathologic pes planovalgus deformity presents with a decrease in the medial longitudinal arch, a valgus hindfoot, and forefoot abduction.1 Pes planovalgus may be symptomatic or asymptomatic. According to one study, symptoms may depend on pain thresholds and tissue wear rather than deviations in 3D foot kinematics from those who experience no symptoms.2 Aside from the presence or absence of symptomatology in the physical or biomechanical exam, it may be prudent to assess the pathology radiographically.3,4 Studies have shown that certain key differences in various radiographic angles and osseous relationships may contribute to a more defined prognosis following surgical treatment for symptomatic pes planovalgus.5,20 The incidence of pes planovalgus is unknown in the pediatric population and arises in 20-25% of adults. Generalized ligamentous laxity is common in 25% of pes valgus cases and many times associated with gastrocnemius soleus contracture.1 It should be noted that the etiologies contributing to pes planovalgus are numerous, ranging from pronation, to limb length discrepancies and posterior tibial tendon dysfunction or PTTD.6,7 Some etiologies, such as PTTD, have been found to be controversial, with some literature suggesting that it is not an etiology unless disruption of the deltoid ligament is present, and others suggesting that the converse is true, strongly suggesting PTTD to be a result of pes valgus and not a cause.6,7 For the purpose of this study we focused on pes planovalgus second to PTTD and/or aberrant pronation. Although there exist many treatments to correct the condition of pes planovalgus, from conservative to surgical, there is no set gold standard due to the subjective nature of the pathology.8

The current standard of care based on numerous studies over decades suggests that the physician must start with the most conservative manner of therapy and escalate treatment tactics as each previous treatment attempt proves to be unsuccessful. Conservative therapy, such as orthotics, shoe modification, bracing, physical therapy and gait therapy are usually the first line of treatment and management of pes planovalgus.8 Recent studies have shown that the use of orthotics may improve the symptoms in the pediatric population, however, when conservative therapy fails, surgical treatment is warranted.7 Tendon transfer (tibialis anterior), osteotomy, arthrodesis, and subtalar arthroereisis are some of the most common surgical treatment options.8

Subtalar arthroereisis is a surgical procedure that involves the insertion of an implant into the sinus tarsi. Prevention of excessive subtalar joint pronation by limiting the motion of the talus makes subtalar arthroereisis particularly helpful in the management of pes planovalgus. The goal of this procedure is to preserve the subtalar joint and alleviate patients’ symptoms by reducing excessive talar displacement (limits plantarflexion, and adduction of the talus) and calcaneal eversion.10,11

The subtalar arthroereisis implant directly recovers the talocalcaneal and talonavicular subluxation reconstituting the medial longitudinal arch.12 There are various types of implants such as absorbable and non-absorbable that can be used. These implants may be used alone or in combination with other procedures.13 One study involving pediatric patients, showed that treating the equinus deformity through gastrocnemius recession and a resorbable arthroereisis plug yielded favorable clinical outcomes and symptom improvement.11,15,16

Post-operative care for subtalar arthroereisis is contingent upon the particular patient undergoing the surgery. For patients with one or more risk
factors of developing a deep vein thrombosis, it is advised that the patient undergo a thirty-day antithrombotic course with low molecular weight heparin. This regimen is, of course, for patients that have normal kidney function. Post-operative use of an assistive device, usually a walker, is employed for the first thirty-five days. At the end of this period, a walker or crutches are no longer needed, and weight bearing is gradually allowed. After fifty days, increasing mobility is encouraged, as long as pain and edema are no longer present. The final stage of rehabilitation involves antigravity training, after which the patient may return to everyday activities, including sports. Radiographic check-ups in certain intervals are usually performed to ensure correct implant positioning.

The use of subtalar joint arthroereisis is not for everyone. Contraindications to arthroereisis include active infection, advanced subtalar arthrosis, suprastructural deformities, neurotrophic foot types, and coalitions. The presence of an active infection could result in hematogenous osteomyelitis as a result of open exposure and disruption of bone during the arthroereisis procedure. Additionally, the use of any implant requires that the patient have good bone stock. Conditions such as arthritis, neurotrophic foot types, osteoporosis, and osteomalacia can severely disrupt the quality of bone and therefore increase the probability of poor osteointegration. Suprastructural deformities contribute a great deal of torsional strain at the site of the implant. This aberrant level of torsion leads to unsafe levels of transfer force as a result of cortical stress rising, which could cause a
Coalitions can severely impact the range of motion of a joint.

The arthroereisis procedure is not suitable for rigid foot types for similar reasons of suprastructural deformities. Additionally, an arthroereisis procedure requires an intact sinus tarsi for proper implantation. Individuals, especially with an osseous talocalcaneal coalition, may have a severe irregularity of the sinus tarsi compromising the use of any implant.

The goal of this study is to elaborate on the prognosis of subtalar joint arthroereisis in both pediatric and adult populations. The vast employment of this procedure in adult and pediatric patients with symptomatic pes planovalgus suggests that a thorough review of the outcomes of such procedures be assessed. Previous reviews of the efficacy of subtalar arthroereisis are limited or outdated, as many advancements in biomechanical implants have been made since the time of those studies. It is the hope of the authors of this paper to provide a thorough investigation on the relative outcomes of the subtalar joint arthroereisis. Such a review is targeted to supply podiatric surgeons with a survey of possible outcomes that should be considered when determining treatment plans for patients with symptomatic pes planovalgus after conservative measures have failed.

**METHODS**

Utilizing the MeSH advanced search building tool within the PubMed interface, an initial search of the literature was performed for “arthroereisis” yielding 99 articles. The Boolean operator “and” was employed to include the term “STJ” which effectively narrowed the search results to 67 articles. After individual analysis of each article, employing the inclusion and exclusion criteria, only 9 articles remained (Figure 1). The inclusion...
criteria for the study required that articles be written in English, were clinical studies involving the subtalar joint, and were studies that measured the outcomes of subtalar joint implants. A study was excluded if it was cadaveric, or was based on surgical approaches or techniques rather than outcomes of the procedure. Papers published prior to 2002 were excluded from the study.

RESULTS

Six of the articles from the literature search involved adult patients, whereas only two involved pediatric patients. One article compared both the pediatric and adult patients who received arthroereisis procedures.

Adult Patients

Of the six studies that were included in this review, all had at least one case requiring explantation surgery due to sinus tarsi pain. In a study by Needleman, 11 of the 28 patients that underwent subtalar joint arthroereisis required explantation.19 The remaining 17 patients in the study reported a favorable outcome. Outcomes were determined using the AOFAS Hindfoot Scale.19

Saxena et al assessed the use of bioabsorbable implants in lieu of traditional metal implants in 6 patients to find that only 1 implant required explantation.20 The authors of this paper suggest that the unfavorable outcome present in the patient requiring the explantation could be the result of sizing discrepancies. These sizing discrepancies arose from the implant

Figure 3. Columns on the left represent the total implants received in four studies on pediatric patients. Columns on the right represent those individuals requiring explantation. Both Baker and Jay studies had no patients requiring explantation.
In a study to assess the outcome of a subtalar arthroereisis procedure in patients with stage II posterior tibial tendon dysfunction, Viladot et al followed 21 patients to find that only two individuals required removal of the implant. The authors suggest that the suboptimal performance of the implant in these two individuals was the result of improper sizing. In both cases requiring explantation, the implant was too large. Of the remaining 19 patients in the study, 17 reported that they were “very satisfied” with the results. Utilizing the AOFAS scale to supply subjective and objective reporting of their findings, the authors reported that the mean improvement from preoperative to postoperative evaluation was 47.2 to 81.6. Radiographic assessments for efficacy of the procedure were performed using the Moreau-Costa-Bertani angle, yielding an overall reduction of 14.3° (Normal: 115° - 125°). Additionally Kite’s angle revealed a reduction of 8.7° (normal: 15-30). The authors found that 6 patients suffered discomfort over the sinus tarsi that did not resolve until 6 months post operation.

To explore possible risk factors for subtalar arthroereisis explantation, Cook et al investigated the outcomes of patients from 2002-2008. In their analysis, they found that of the 66 arthroereisis cases, 22 cases required explantation. Utilizing multivariate logistic regression, the authors determined a statistically significant increase in the risk of explantation in patients that had increased AP talar-first metatarsal angle (P=0.0012), a decreased AP talocalcaneal angle...
(P=0.0019), and an increased calcaneocuboid abduction angle (P=0.049).\textsuperscript{22}

In certain extreme cases, subtalar arthroereisis may result in explantation, and complicated revisional surgery. The work by Corpuz \textit{et al} discovered a talar neck fracture resulting from a subtalar arthroereisis.\textsuperscript{23} This severe complication was found to be the result of improper sizing and dislocation of the implant. Such a complication is not always mitigated by explantation. The authors reported complete intraoperative displacement of the fracture during attempted explantation.\textsuperscript{23}

The work by Baker \textit{et al} assessed not only non-absorbable implants, but absorbable implants as well to find that 19\% of absorbable implants and 21\% of nonabsorbable implants in adults are removed.\textsuperscript{15}

An assessment of the effects of subtalar arthroereisis in the pediatric patient through analysis of the current literature was also preformed. The following discussion outlines the findings.

\textit{Pediatric Patients}

Utilizing the AOFAS Ankle-Hindfoot Scale as a measure of clinical success and outcomes, Jay \textit{et al} assessed the efficacy of both bioabsorbable and nonbioabsorbable implants in the feet of 20 children.\textsuperscript{16} The authors found that the mean improvement was 21.3 points on the AOFAS scale, from an average score of 67.7 points preoperation to 89 points post operation. Additionally, they found that many times an equinus deformity is present with a flexible flatfoot deformity. Jay \textit{et al} suggest that gastrocnemius recession in addition to the arthroereisis procedure will yield better post-operative results.\textsuperscript{16}

Baker \textit{et al}, in his assessment of post-operative outcomes of subtalar arthroereisis in pediatric patients, found 100\% survivability of the nonabsorbable implants used.\textsuperscript{15} In contrast the authors found only 85\% survivability of the absorbable arthroereisis implants used.\textsuperscript{15} For a more thorough investigation of the outcomes of the absorbable implants, Baker \textit{et al} stratified the data into isolated and combined procedures, yielding 60\% survivability in the isolated procedure versus 90\% survivability in the combined procedure.\textsuperscript{15}

A cohort study involving 40 patients between the years of 1992 and 2002 who received subtalar arthroereisis procedures reported that 13 of the individuals receiving the implants required explantation.\textsuperscript{14} Of these 13 patients, 2 suffered from displaced implants, one of which required emergency early removal.\textsuperscript{14} The authors of the study found that 81\% of the remaining 27 patients were satisfied with the arthroereisis procedure.\textsuperscript{14}

A retrospective review of 39 pediatric patients by Scharer \textit{et al} revealed that of the 39 patients that received implants, 10 had complications that required an additional surgery.\textsuperscript{9} One of these 10 individuals required explantation with no replacement, the remaining 9 patients either had the sizes of the implants adjusted, or they had the implant repositioned.\textsuperscript{9}

\textbf{DISCUSSION}

From the five studies on adult patients we see a notable amount of individuals requiring explantation (figure 2). The authors in many of these studies attributed the need for explantation to be due to incorrect sizing of the implant. It has been discussed that the disparity between the size of the implant utilized and optimal implant size was the result of differences between radiographic assessment of the implant site and the actual size of the implant site. Additionally, one might notice that sinus tarsi pain was present in all patients for months after the procedure. From the studies
assessed, the time frame of sinus tarsi pain post operatively ranged from 3 to 6 months. Whereas some pain is the expected result of any surgery, it could be suggested, given the data in these studies, that the cases having prolonged periods of post-operative pain were the result of less than optimal implant sizing.

From the four studies addressing the outcome of subtalar arthroereisis procedures in pediatric patients, we see some similar trends to that of the adult populations, particularly in the studies by Koning et al and Scharer et al that required a significant number of explantations (Figure 3). In the study by Sharer et al, it should be noted that the authors classified only one case as explantation, even though 10 cases required that the initial implants be removed. The authors justified this classification by stating that the implants were replaced by implants that were less aggressive or more aggressively sized. The terms less aggressive or more aggressive were employed to describe the size of the implant that was selected for the arthroereisis procedure. This should not be confused with the positioning of the implant, which was adjusted in 2 of the 10 cases that required revisional surgery. For the purposes of this literature review, individuals requiring any form of revisional surgery where the initial implant was removed was classified as an explant procedure as an attempt to enforce the strict meaning of the medical term.

When comparing the stratified subsets of patients (pediatric versus adults) one can quickly see that both populations had a notably large number of individuals requiring explantation. These explantations were required due to the patient either not being able to tolerate the implant (sinus tarsi pain) or due to post-operative observance that the implant was either not sufficiently correcting the flexible flatfoot or over correcting the flatfoot. The latter causes could be the result of inserting an implant that was too large or too small. The sizing issues with the implants suggested in many of the studies could contribute to complications ranging from migration of the implant to a fracture at the surgical site.

**Limitations**

Certain limitations of this review were minimalized by only including clinical studies from living patients and not simulated cadaveric models. It should be noted, however, that although the number of patients presented in the study are substantial, they are not resolute, and arguably may not capture the true \( \mu \) of the represented population. Unfortunately, this limitation is a result of absence of such encompassing studies in the current literature. Additionally, the limited number of studies cross-referencing the absorbable implant efficacy in adult versus pediatric patients could contribute to a false treatment algorithm that eradicates the notion of absorbable implants in adults. It is suggested, however, that although these studies are few, they are quite compelling.

**CONCLUSION**

From the literature we can see a reasonable amount of complications that results from the use of the subtalar arthroereisis procedures for the treatment of pes planovalgus. These complications may be the result of poor sizing protocols in the initial procedure. Although at this time no large studies have been conducted to assess the relationship between suboptimal outcomes and sizing protocols for subtalar implants, it could be suggested that a correlation may exist between the two. Further research in the area of sizing protocols and the efficacy of subtalar arthroereisis could elucidate information as to the cause of such variable outcomes.
Authors’ Contributions
JR and ES performed initial literature reviews gathering evidence regarding the background of the paper. CM authored the abstract, ensured proper formatting, and adherence to publishing guidelines. JW, as the principal investigator, conceived the idea of the study, authoring the results, discussion, and conclusions. JR and JW developed the images used in the study. All authors reviewed and agreed upon the final manuscript.

Statement of Competing Interest
The authors of this paper declare no competing interests such as, but not limited, to organization affiliations or monetary compensation.

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Diabetic Adolescent Athletes: Prevalence and Treatment of Common Presenting Pathologies

Kiana Karbasi, B.Eng., BS, and Timothy Miller, BA

Abstract

Introduction
The purpose of this study was to thoroughly investigate common injuries associated with adolescent athletes affected with diabetes. It is highly recommended for youth with diabetes to become active in addition to their typical diet and insulin treatment regimen. Diabetes mellitus is prevalent among the youth, comprising 20-50% of new diagnoses annually. For the young diabetic athlete, it is imperative to know the potential complications involved, and the ways to prevent such injuries to ensure success in future athletic endeavors and, more importantly, overall well-being.

Study Design
Systematic Review of the Literature

Methods
All CLIN-EGUIDE: Medline, JAPMA and PubMed searches were performed limiting the criteria to the English language. A total of 79 articles were found for the various topics, of which a total of 11 articles were selected based on their relevance to diabetes, athletics, and adolescence.

Results
The authors found a wide variety of common foot and ankle pathologies in diabetic adolescent patients: plantar fascia thickening, Achilles tendon thickening, decreased bone mass, musculoskeletal injuries, delayed healing patterns, destruction of articular cartilage, ankle sprains, and exertional compartment syndrome. Etiologies associated with these various injuries include increased body mass index and increased serum glucose. Treatment for these injuries consists of both operative and non-operative methods, depending on the severity and nature of the injury.

Conclusion
This systematic review concludes that diabetic adolescent athletes are at an increased risk for certain injuries due to their aberrant glucose levels. The purpose of this paper is to provide clinicians with a reference for various treatment modalities directed towards the most common presenting pathologies in young diabetic athletes.

Key Words
Pes planovalgus, subtalar arthroereisis, pes planus

Level of Evidence: 4
INTRODUCTION

The diagnosis of Type 2 diabetes, in particular, has been shown to account for 20%-50% of new diagnoses in childhood pathologies.\textsuperscript{1, 2} It is highly recommended for youth with diabetes to become active in addition to their modified diet and insulin treatment regimen.\textsuperscript{3} Regular exercise of an accumulation of 30 minutes a day reduces the risk of developing type 2 diabetes by approximately 60%.\textsuperscript{4} School-age youth are advised to get at least an hour of moderate to vigorous exercise a day in order to benefit from the changes such as increased skeletal health and muscular strength.\textsuperscript{5}

Obese children are at greater risk of tendinopathy and focal osteopenia as a result of low bone mineral content.\textsuperscript{1, 6} Although it may seem counterintuitive, they are encouraged to participate in physical activities on a regular basis in hopes of preventing the development of diabetes.\textsuperscript{1, 3} The relative reduction in BMI second to an increase in overall physical activity drastically reduces the probability of early onset Type II DM.\textsuperscript{7}

Naturally, not all cases of Type II DM can be prevented, but even in such cases, preventive measures such as diet and exercise should be continued in an attempt to slow the progression of the disease by maintaining a controlled state.

Regardless of whether it is Type I (T1D) or Type II (T2D), numerous comorbidities may develop as a result of an uncontrolled state of serum glucose levels. It has been shown that patients with uncontrolled Type 1 (T1D) and Type 2 diabetes (T2D) will have a higher incidence of macrovascular and microvascular disease such as neuropathy and nephropathy.\textsuperscript{8} Should these individuals engage in regular exercise, even with uncontrolled serum glucose levels, these individuals have a reduced risk of macrovascular and microvascular compromise.\textsuperscript{8}

Exercise suggestions, however, should be made with caution. It should be noted that diabetic patients are more prone to musculoskeletal pathologies that may be exacerbated with exercise. Serious musculoskeletal injuries in diabetic patients related to convulsions linked to insulin-induced hypoglycemia have also been observed.\textsuperscript{1, 9} Factors contributing to these injuries include high BMI, peripheral neuropathy, and sensory blunting in the diabetic foot.\textsuperscript{1} Furthermore, patients with T1D have a higher incidence of tendinopathy, foot disorders, osteoporosis, fractures, cartilage injury and higher healing complications after trauma and surgery.\textsuperscript{10} Patients may not be compliant with clinical guidelines or may not have received them at all. Either may result in injury, most commonly involving the lower extremity. Sports related injuries to the knee and ankle make up 10-19% of all acute injuries in emergency departments, highlighting the importance of appropriate foot and ankle treatments and their pivotal role in the prevention of future sports related injuries.\textsuperscript{11} Given these types of complications, it may seem paradoxical to suggest activities that increase the risk of further pathology. However, current research states that the benefits far exceed the risks.\textsuperscript{7} Current studies also suggest that skeletal muscle loss may play just as important of a role in the progression of diabetes as malnutrition.\textsuperscript{12}

As previously presented above, there are many measures that can be implemented, from attempting to prevent diabetes to providing strict activity guidelines for patients already diagnosed with diabetes. It is also important to recognize and properly treat injuries when they present. The focus of this study is the last of these measures. It is crucial that clinicians be aware of the common presenting injuries in diabetic athletes, and the underlying mechanisms that predispose the individuals to those injuries. The goal of this paper is to provide the clinician a quick reference to effective current treatment management.
techniques for the most commonly presenting injuries.

METHODS

A search of the current literature utilizing: Medline, full text journals, and PubMed was performed. An initial search of the phrases: “diabetic adolescent athlete”, “Type II DM management in athletes”, and “Type I DM management in athletes” was performed. Utilizing the Boolean operator “and” to narrow search results, the initial yield was 79 articles.

The inclusion criteria required papers to be written in the English language, be non-cadaveric studies, and involve adolescent athletes with either Type I or Type II DM. The exclusion criteria were studies on geriatric populations and studies with confounding comorbidities or pharmaceutical therapies yielding adverse events (e.g. fluoroquinolones). After implementation of inclusion and exclusion criteria, only 11 studies were included in this review.

RESULTS

Review of the literature on common pathologies suggested 5 key conditions resulting in patients with DM. A brief overview of the studies and the works of the authors are summarized, highlighting mechanisms of injury and treatments consisting of both operative and non-operative methods, depending on the severity and nature of the injury.

DISCUSSION

Achilles tendon thickening

Type II diabetes in the youth is associated with a high BMI, which in conjunction with continued overuse, is associated with thickening of the plantar fascia and stiffening of the Achilles tendon. Mechanisms contributing to this thickening include enhancement of matrix metalloproteinase production and most importantly deposition of advanced glycation end-products (AGE) on the tendon.

Deposition of advanced glycation end-products (AGE) in diabetic patients is hyperglycemic-induced and a major contributing factor to microvascular damage. This is achieved by using AGE binding receptors on the surface of low turnover areas, such as cartilage, bone, and tendons, and activating pro-oxidant events using reactive oxygen species. Additionally, proinflammatory events caused by the body’s immune response contribute to AGE cross-linking of collagen fibers producing shortened and stiff dysfunctional tendon phenotype and thereby inadequate function.

Another cause of damage, matrix metalloproteinase production enhancement, is caused by activation of proinflammatory agents that lead to tenocyte apoptosis. This decrease in tenocyte numbers is accompanied by an increase in the density of collagen fibrils, causing tendon twisting, collagen fibril overlapping and thickening of the Achilles tendon and plantar fascia.

Moreover, in addition to tendon thickening, higher hemoglobin A1C levels and increased proteoglycan may cause pain and swelling resulting in tendinopathy of the Achilles tendon.

All mechanisms mentioned share the same endpoint of tendon structural deformity and
decreased ankle range of motion in diabetic patients. This reduced ankle joint range of motion restrains the forward progression of the tibia on a fixed foot during stance phase and causes excessive weight-bearing stress under the metatarsal heads. Such a mechanism serves as a profound contributor to fractures in diabetic patients.\textsuperscript{14}

Musculoskeletal injuries and chronic exertional compartment syndrome

Different types of musculoskeletal injuries present, depending on the type of diabetes. For instance, compared with healthy individuals, T1D patients have a higher incidence of musculoskeletal injuries and are more prone to chronic exertional compartment syndrome.\textsuperscript{1,15}

Factors contributing to the development of exertional compartment syndrome include microvasculature impairment and thickening of fascia surrounding the compartments.\textsuperscript{15,16} Inadequate enzymatic conversion of glucose to sorbitol, as well as changes in collagen metabolism, lead to impaired microvasculature blood flow, enhanced capillary permeability and tissue swelling.\textsuperscript{15,16,17}

Edmundsson et al further associate the cause of chronic exertional compartment syndrome in the diabetic population with thickening of the fascia surrounding the compartment.\textsuperscript{15} This fascial thickening also increases the risk of intermittent claudication.\textsuperscript{15}

T2D patients are more prone to decreased exercise capacity and increased healing complications.\textsuperscript{18} This is due to higher microvasculature compromise and reduced aerobic physical fitness of the individual, which can be measured by maximal oxygen consumption during incremental exercise (VO\textsubscript{2}).\textsuperscript{18}

According to Detmer et al, a fasciotomy may be a safe, economical, and effective treatment of chronic exertional compartment syndrome.\textsuperscript{19}

**Stress fractures**

As mentioned previously, reduced ankle range of motion, due to increased thickness of the Achilles tendon and plantar fascia, can lead to excessive stress under the metatarsal heads, increasing the incidence of fracture.\textsuperscript{14} In addition, lower bone mineral density has been associated with increased risk of fracture, predominantly in Type I diabetic patients.\textsuperscript{1} According to Wolf, the most common site of fractures in diabetic athletes appears at the second, third, and fifth metatarsals.\textsuperscript{21} Different surgical procedures may be utilized to address these stress fractures, or a more conservative option may be chosen, depending on the nature of the fracture.

**Cartilage injury and medial meniscal tears**

Cartilage in diabetic patients is softer and more permeable, leading to joint pathology and compromised structural integrity.\textsuperscript{23} According to Baker et al, medial meniscal tears have a high prevalence among athletic injuries. Baker et al reports the prevalence of medial meniscal tears in football and basketball to be 75% and 90%, respectively.\textsuperscript{24}

Meniscal tears need orthopedic attention, including surgical intervention, and are out of scope of the field of podiatry. Minor compromised cartilage can be treated with intra-articular injections of hyaluronan by orthopedic surgeons. These injections can restore the elastic and viscous properties of synovial fluid and allow for the reestablishment of cartilage shock-absorbing properties.\textsuperscript{14} This will allow for improved tissue elasticity and increased gliding over anatomical structures.\textsuperscript{14}
Ankle sprains- anterior talofibular ligament

Diabetic athletes are more prone to ankle sprain injuries due to delayed healing of previously injured tendons and insulin-induced hypoglycemia. This is seen more commonly in patients under intensive insulin therapy who may undergo insulin-induced hypoglycemia. This may increase the risk of hypoglycemic neuropathy of peripheral motor nerves and decrease proprioception while negatively impacting the patient’s balance, leading to higher incidences of ankle sprains. The most common site of ankle sprain is the anterior talofibular ligament, which can tear due to excessive foot inversion with plantarflexion. This tear will lead to chronic instability of the subtalar joint and may require surgical correction. In cases where surgical intervention is not warranted, RICE therapy (Rest, Ice, Compression, and Elevation) has proven to be effective.

3) Acupuncture: induces biophysical signals and allows for the activation of a healing response by targeting the nervous system.
4) Heat: increases the extensibility of tissues prior to stretch, resulting in decreased pain and increased blood flow to the area.
5) Electrical stimulation: increases cell metabolism and local blood flow while controlling pain and inhibiting spasticity.
6) Extracorporeal shock wave: improves blood supply, increases cell proliferation and disintegrates calcifications in the affected area.
7) Low intensity cold lasers: stimulates production of collagen and cellular metabolism.
8) Surgery: is reserved as the last option after conservative management. The excision of fibrotic adhesions and the removal of nodules and areas of degeneration help to restore vascularity.

General Treatment of Sports Related Injuries

Initial conservative management of injuries with anti-inflammatory drugs and corticosteroids has demonstrated good short-term results. Presenting side effects of these treatments may include local calcification and skin atrophy with depigmentation. According to Abate et. al, other treatment modalities of diabetes-related diseases include:

1) Rehabilitation: Physical rehabilitation improves joint motion and collagen synthesis, leading to better biomechanical effects.
2) Manual techniques: Manual techniques include friction massage, augmented soft tissue mobilization, myofascial release and active release techniques. These modalities break adhesions around joint structures, decreasing spasms and edema. This in turn leads to increased range of motion and the recovery of neuromuscular control.

CONCLUSION

Injuries are common when one is physically active. Sports injuries in adolescent athletes make up 10-20% of all acute injuries in emergency rooms. Such sports-related injuries involve more complications when they occur in diabetic athletes compared to others. Diagnosis of the most common injuries among diabetic adolescent athletes requires knowledge of the mechanism of injury consistent with the appropriate physical findings.

Special attention must be given to treatment of these injuries, and knowledge of the injury can help to accelerate the healing process. Knowing the most common injuries for diabetic adolescents is important in determining an appropriate activity guide to minimalize the risk of injury. The most common injuries are presented in this paper to provide the suggested causes, mechanisms, and treatment options for injuries in young diabetic athletes. Since proper foot care is a pivotal intervention for such patients, further research
must be done to elucidate any aberrant healing patterns. Such research would provide valuable information that could be emphasized to develop new forms of treatment. Furthermore, this may serve as a guide for clinicians to properly form preventative measures and potential treatment plans for their diabetic patients.

Authors’ Contributions
KK worked as the principal investigator for the study, constructing the central concepts. TM aided with revisions throughout the peer review process. Both authors have read and confirmed the final draft of the paper prior to publication.

Statement of Competing Interest
The authors of this paper declare no competing interests.

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Impact of Evolutionary Loss of Uricase Enzyme Efficacy in Human Gout Pathogenesis Based on a Computational Model

Sanghyuk Kim, BS, Nicholas Szwaba, MS, and Kiana Karbasi, B.Eng., BS

Abstract

Introduction
Gout is a medical condition where uric acid metabolites crystalize and cause recurrent attacks of acute inflammatory arthritis. With changes in diet and prolonged life span, gout has become a more common condition. In higher primates, including humans, gout seems to be more prevalent when compared to other mammals capable of purine metabolism. Construction of a model that focuses on the evolutionary loss of the uricase enzyme would allow for the understanding of changes that will have an effect on human purine metabolism and gout pathogenesis. Furthermore, such an analysis would reveal the level to which the loss of uricase enzyme efficacy contributes to the pathogenesis of gout.

Study Design
Original Research / Computational Model

Methods
The authors based their computational model of gout on the pathophysiology model of gout. The model was constructed utilizing studies of enzyme kinetics and basic chemical properties of the urate crystal. Based on physical characteristics of urate crystals and constants obtained from other works, a simple mathematical model was constructed in Matlab®, a computational analytic software.

Results
The computational model was able to correlate the chemical characteristics of urate to the pathological signs of gout. Based on the Michaelis-Menten properties of the uricase enzyme and studies of enzyme kinetics, the uricase kinetics profile was constructed. Analysis of the profile indicated the ineffectiveness of the uricase enzyme in the clearance of urate.

Conclusion
Gout has become a prevalent condition in current medical care. While an increased prevalence of gout could be the result of changes in diet and prolonged lifespan, many studies suggest a loss of function in the uricase enzyme. Our model suggests that although there is a loss in the efficacy of the uricase enzyme, that loss in minimal, and does not hold a pivotal role in the pathogenesis of gout.

Key Words
Uricase, Gout, Michaelis-Menten

Level of Evidence: 5
INTRODUCTION

Gout is a medical condition where uric acid metabolites crystalize and result in acute or chronic inflammatory arthritis, tophi, and urate nephropathy. The etiology of gout is currently thought to be the result of abnormally high levels of uric acid and consequent formation of gout crystals. In normal physiology, uric acid, the toxic metabolic product of purine metabolism, is converted into allantoin by uricase or urate oxidase. This enzymatic reaction may result in low serum uric acid levels. In the case of gout pathology, the uric acid concentration exceeds the local solubility limits, resulting in crystallization. Enzyme dysfunction and hyperuricemia have strong correlations with gout crystal formation.

In normal physiology, uricase, or urate oxidase enzyme, functions to convert toxic urate into less toxic and more easily excreted allantoin. Most mammals capable of such metabolism have the uricase enzyme for clearing uric acid. However, higher primates, including humans, may tend to exhibit an attenuated ability to convert urate. This phenomenon has been proposed as a direct result of evolutionary loss of uricase enzyme function.

This shift towards the loss of uricase efficacy would be better understood if one could understand the competitive advantage to such a shift. The current understanding is still limited, but there are different competing theories that focus on the evolutionary advantages of these changes in the uricase enzyme function. One theory suggests that uric acid contributes to more than 50% of the antioxidant capacity of blood. It is hypothesized that the loss of uricase expression, and resulting increase in uric acid level, have rendered an evolutionary benefit of increasing antioxidant capacity. This would suggest a possible increase in life expectancy as an effect of free radical sequestration. The second theory focuses on the ability of uric acid to maintain blood pressure in conditions of low salt ingestion. The last theory is based on the structural similarities between uric acid and certain neurotransmitters. The subsequent increase in uric acid level may have been resulting in quantitative and qualitative advancements in the intellectual capacity of hominids. Various competing theories suggest that the loss of uricase enzyme function has resulted in certain evolutionary benefits despite increased risk of gout.

The current pathogenesis mechanism of gout is based on two different mechanisms. One mechanism addresses the over-production of uric acid and the other addresses the under-excretion of uric acid. In this model both mechanisms are explored. The under-excretion mechanism is assessed by studying enzyme function in normal uric acid concentration. The over-production mechanism is studied via increasing the uric acid concentration. By incorporating both mechanisms, the mathematical model more accurately portrays the mechanisms observed in vivo.

This model approaches gout pathogenesis from the traditional physiochemical approach. By focusing on the uricase enzyme and its direct involvement in gout pathogenesis, the impact of evolutionary change can be assessed. The simplified model is based on enzyme kinetics data, urate chemical behavior, and physiological changes. The physiological reaction was modeled using the Michaelis-Menten equation for the uricase enzyme. Additional analyses were based on the chemical properties of urate for crystal formation, with the fundamental understanding of chemical kinetics by which crystal formation occurs (when solubility limit is reached).

In this study, we focused on the construction of the mathematical model to demonstrate the inefficiency of uricase due to the evolutionary loss. We hypothesize that even though current studies suggest a loss of uricase function to play a
role in the pathogenesis of gout, we feel that the role is minimal.

METHODS

The computational model construction started with assumptions. The first assumption is based on the current understanding of gout, a disease resulting from uricase enzyme dysfunction. Uricase is the enzyme involved in the actual chemical conversion of uric acid to allantoin. A one-step approach to analyzing the pathophysiology of gout can be employed for a systemic approach once the facets of the one-step approach have been defined. To further simplify the model, Michaelis-Menten theory is used to construct the kinetics model. Further approximation of the enzyme’s kinetic characteristics is based on the research by Zhao. The Km value of 65µmol/L is used in this model.

The kinetics study by Zhao is based on Bacillus fastidious uricase.

Calculation of Vmax

In order to theoretically construct an enzyme kinetics model, certain data need to be experimentally obtained or theoretically calculated based on existing kinetics studies. The Vmax value, or the maximum rate reaction, can imply the theoretical maximum rate of reaction or the amount of enzyme available in a simplified reaction model. The assumptions made for the Vmax calculation are based on the following enzyme kinetic characteristics/conditions:
1) chemical conversion of urate into allantoin, and
2) uricase enzyme binding and reacting with urate on a 1:1 basis.

Allantoin values were obtained from the study by Gruber. Two values from Gruber’s study were used, the amount of the allantoin formed, and the amount of the total uric acid involved. The discrepancies between Gruber’s study and this model are minimized by employing the same B. fastidious uricase enzyme. The Vmax value of 15.69735µmol/L is thus obtained and employed for this study.

Approximation of urate crystal formation

The approximation is based on the basic chemical principle that a precipitate forms if the solubility limit is reached or supersaturated. Gout crystal formation results when the uric acid concentration exceeds the local solubility limits. The theoretical chemical solubility limit is obtained based on the chemical characteristics of urate. However, a further assumption is made that any urate concentration above this solubility limit results in crystallization. When coupling both the assumptions, it can be conceived that the occurrence of gout increases with any concentration above this solubility limit.

The second assumption is based on the chemical reaction itself. This model assumes that 1:1 conversion of urate to allantoin occurs with high efficiency. A further assumption is made that any urate not converted into allantoin can be crystalized if the solubility limit is reached.

RESULTS

Normal physiology

From Figure 3, the normal Michaelis-Menten kinetics show a correlation with the normal physiological kinetics reaching limits very quickly. From this model, it is calculated that
415µmol/L is the serum concentration limit of possible crystallization occurrence. This shows that a high serum level of uric acid correlates with crystal formation and gout pathogenesis.

Enzyme dysfunction

Figure 4 shows the effect of enzyme dysfunction on Vmax. The kinetics of the enzyme are impacted, but the overall concentration profile does not show much change. The serum urate limit is calculated to be approximately 402µmol/L.

Figure 3. The normal Michaelis-Menten kinetics show a correlation with the normal physiological kinetics reaching limits very quickly.
Figure 5 shows the effect of uricase dysfunction on $K_m$. With limited binding and reaction, the kinetics model shows that the enzyme does not reach the physiological maximum. However, the concentration profile is affected to a lesser extent. The serum urate solubility limit is calculated to be 401.7$\mu$mol/L.

**DISCUSSION**

The simplified model correlates well with the chemical properties of urate. Even with the approximation of enzyme kinetics, the characteristics of reaching physiological maximum at lower concentrations was established. Additionally, the model reveals that serum concentration is not governed by the
uricase kinetics. This correlates with the limited efficiency of the uricase enzyme compared to other mammals.

The upper limit of the normal physiological level of serum uric acid is approximately 480µmol/L, well above the theoretical serum concentration limit. From this model it can be said that even within the normal serum level range, a higher concentration of uric acid may increase the risk of developing gout. Comparing the concentration profiles between the normal physiology case, Figure 3, and the enzyme dysfunctions cases, Figures 4 and 5, allows for a comparison of the impact of enzyme dysfunctions on gout. It can be seen that the enzyme function alone does not change uric acid conversion kinetics. Ultimately, a high uric acid level is the largest factor for the development of gout crystallization.

Based on this model, the uricase enzyme is very limited in its capability and shows insufficient conversion of urate into allantoin. Even at the “normal” physiological level, there is still risk of crystallization and developing gout. Furthermore, changes in uricase enzyme properties, such as Km. 

Figure 5. Shows the effect of uricase dysfunction on Km. With limited binding and reaction, the kinetics model shows that the enzyme does not reach the physiological maximum.
and Vmax, do not have large implications on uricase function or gout development. This suggests that compensations for the evolutionary loss of uricase enzyme efficacy may have occurred in other metabolic pathways. Thus, the uricase enzyme does not play a large role in gout pathogenesis.

CONCLUSION

Historically, gout has been referred to as “the disease of the kings” or “rich man’s disease.” Over the course of evolution, human culture has changed, specifically lifestyle and diet. These changes may be implicated in the development of gout. A physiochemical model was constructed using simple kinetics and chemical properties of the uricase enzyme. However, despite an appreciable difference in the efficacy of enzyme function, the model has shown that the uricase enzyme itself, does not play a pivotal role in the pathogenesis of gout. This would suggest that other enzymes involved in purine metabolism maybe more involved. Further studies of these other enzymes and their respective metabolic pathways may yield viable data to better understand the mechanism by which gout occurs.

It can be postulated that hyperuricemia, or a high urate level, can be attributed to both over-production and the inefficient clearance of uric acid. These two factors cause uric crystallization second to high concentration.

The simplified model, based on the chemical principles and physical properties of uricase, has shown that the current understanding of gout needs to be challenged. Therefore, the pathophysiology and pathogenesis of gout at the molecular level should be the focus of many future studies.

Authors’ Contribution
SK, acting as the principal investigator, formulated the computation model, designed the analysis of the model, and drafted the manuscript. NS participated in the designing of the analysis and drafted the manuscript. KK helped draft the manuscript and literature searches.

Statement of Competing Interests
The authors declare that they have no competing interests.

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The Influence of Academic Stress on Cortical Plasticity
Mohomad Sawah, BS, Mohammad Rimawi, BS
Eileen Chusid, PhD, Fortunato Battaglia, MD, PhD

A Podiatric Perspective to Common Injuries in Contact Sports
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Human Papillomavirus Types 2, 27, and 57 Identified in Plantar Verruca from HIV-positive and HIV-negative Subjects
Christy King, DPM, James Johnson, DPM,
Kene Ofili, DPM, Maylynn Tam, DPM,
Joel Palefsky, MD, Maria Da Costa, MS,
Yasha Mathur, BS, Peter Barbosa, PhD
The Influence of Academic Stress on Cortical Plasticity*

Mohomad Sawah, BS, Mohammad Rimawi, BS, Eileen Chusid, PhD, and Fortunato Battaglia, MD, PhD

Abstract

Introduction
Medical education is perceived as stressful. The purpose of this study was to explore the possible effect of academic examination stress on cortical long-term potentiation (LTP)-like plasticity in a group of university students.

Study Design
Cohort

Methods
The study included 9 healthy medical students (males: mean age 30.2 +/- 4.3 SE) and was conducted during a major exam period (stressed) and 5 weeks later after the exams (non-stressed). Facilitatory associative plasticity was induced by paired associative stimulation (PAS) in the human motor cortex (PAS-25 protocol). In addition, students were required to fill out the Perceived Stress Scale 10 (PSS) questionnaire.

Results
Sixty minutes after PAS-25 induction protocol, students showed lower amounts of potentiation during the exam period compared with after the exams (p=0.039). The average PSS score was significantly higher during the “stressed” period (P = 0.0024). LTP-like plasticity showed an inverse correlation with the perceived stress.

Conclusion
Academic stress appears to affect LTP-like plasticity in students. Deficit in attention and impairment of N-methyl-D-aspartate receptor-dependent neural plasticity associated with stress might underlie our findings. Larger scale studies are needed to address the interrelationship between LTP-like plasticity and academic performance.

Key Words
cortical plasticity, stress, cortical long-term potentiation

Level of Evidence: 4

*Journal entry formatted from original poster presentation.
INTRODUCTION

Medical education is perceived as stressful. The purpose of this study was to explore the possible effect of academic examination stress on cortical long-term potentiation (LTP)-like plasticity in a group of university students.

METHODS

Nine students were enrolled in the study (9 male, mean ages: 30.2 +/- 4.3 SE ). The subjects gave their informed consent. This study was approved by the Institutional Review Board of the New York College of Podiatric Medicine. Cortical plasticity and perceived stress were evaluated either during a major 4-week exam period that included 5 final exams (stressed) or after a non-stressful 4-week stretch that included a two-week break and two weeks of the following semester (non-stressed). The study took place in the afternoon between 2 and 5 PM. None of the students suffered from neuropsychiatric diseases nor had any positive family history. Students did not take any neuroactive drug. All the students were self-reported right-handers.

Figure 1. MEP amplitude (mV) in stressed and non-stressed students at baseline, T0, and T60 respectively.
RESULTS

**Paired Associative Stimulation**
M1 plasticity was tested by using the protocol of associative stimulation described by Stefan et al (1). Associative stimulation consisted of suprathreshold electrical stimulation of the right median nerve combined with a suprathreshold magnetic pulse applied over the left primary motor hand area 25 ms after peripheral nerve stimulation (PAS-25). 200 pairs of stimuli were given at a frequency of 0.25 Hz (Figure 1).

**Perceived Stress**
We used the 10-item Perceived Stress Scale (PSS) to assess perceived stress (2). This scale is a valid and reliable instrument to assess academic stress. The PSS measures the degree to which situations in one’s life are appraised as stressful. The items ask about feelings and thoughts during the last month. Subjects are asked how often they felt a certain way. Answers are given on a five-point Likert-type scale (1: never; 5: very often) anchored at 1 (never) to 5 (very often). The PSS results are shown in figure 2.

CONCLUSIONS

Medical academic stress has a detrimental effect on students’ cortical plasticity. Deficit in attention and impairment of N-methyl-D-aspartate receptor glutamate function might underlie our findings. Our results provide a new opportunity to objectively quantify the

Figure 2. Perceived stress scale results in Stressed and Non-stressed students.
negative effect of stress on brain functions and to use this neurophysiologic biomarker to design and evaluate psychotherapeutic and behavioral interventions.

REFERENCES

A Podiatric Perspective to Common Injuries in Contact Sports

Sameep Chandrani, MBS, and Timothy Miller, BA

Abstract

Introduction
The ankle and foot are susceptible to injury during athletic competition. Common injuries are to the ankle, the Lisfranc joint, and the hallux. The ankle joint is a mortise consisting of the tibia, fibula, and the talus. A lateral ankle sprain is the most common injury of this joint, consisting of a tear in the anterior talofibular ligament. The tarsometatarsal joint, commonly known as the Lisfranc joint, includes the five metatarsals, their articulations with the cuneiforms and the cuboid bone, and the associated ligaments. A Lisfranc injury describes a multitude of processes occurring at the joint, not just one specific event. The first metatarsophalangeal joint consists of the proximal phalanx of the first hallux and the first metatarsal. It contains a capsuloligamentous-sesamoid complex with collateral ligaments that is a frequent site of injury. Turf toe is an injury that is characterized with hyperextension of the first metatarsophalangeal joint with a sprain and possible rupture of the surrounding ligaments. Sand toe is a similar injury but occurs due to hyperflexion.

Study Design
Review of the Literature

Methods
All PubMed searches were performed limiting the criteria to the English language and free full text availability. First, a PubMed search was performed using the inclusionary term “Ankle Sprains”. 308 articles were found, nine were selected and read thoroughly, and four were finally selected based on their specificity towards lateral ankle sprains. Another PubMed search was performed using the term “Lisfranc Injuries”. Abstracts were reviewed of 91 articles, eight were selected and read thoroughly, and 5 were selected based on their specificity to injury in contact sports. A third search was performed with the term “Turf Toe”. 69 articles were found, and their abstracts reviewed. Three articles were selected based upon their specificity towards mechanisms of turf toe injuries. Finally, a search was done using the term “Sand Toe”. The search yielded 32 total articles, from which two were selected based on their relevance to athletics and mechanism of injury.

Results and Conclusions
This systematic review concludes that there are various mechanisms, symptoms and treatments for common foot and ankle injuries that occur in athletes and other active individuals. The purpose of this paper is to make clinicians aware of these components when treating patients with foot and ankle injuries so methods of prevention can be discussed or an effective treatment plan can be established to better achieve patient recovery and prevent future injury.

Key Words
Diabetes Mellitus, Common Sports Injuries, Contact Sports

Level of Evidence: 4
INTRODUCTION

It is common for athletes to present to physicians with a variety of lower extremity injuries while participating in contact sports. Contact sports are athletic activities in which the athlete is obligated to physically encounter their opponent, such as American Football, but contact sports don’t necessarily require physical contact between players as a component. An example of this is sand volleyball, in which it is common to see contact between individuals and also forceful contact between an individual and the ground. In a podiatric setting, athletes present with ankle and foot injuries. It is common for a practice to see a wide range of injuries dealing with these aspects of the lower extremity, but there are ones that present more frequently than others. The ability for the doctor of podiatric medicine to optimally manage the care of these individuals may be dependent upon the understanding of the mechanisms of injury and knowledge of the most effective treatments.

When considering the ankle joint mortise, the most common injury occurs as a result of trauma to the anterior talofibular ligament. In present day athletes, these lateral ankle injuries have been observed to occur from a forced inversion and plantarflexion of the rearfoot on the tibia. Since the anterior talofibular ligament is the weakest of the lateral collateral ligaments at the talocrural joint, these injuries are very common in active individuals and even athletes. Other structures may also be injured during a lateral ankle sprain such as: the peroneal tendons and the lateral joint capsule, to name a few. There are many ways to classify a lateral ankle sprain, based solely on the severity of damage to the ligaments. These sprains are graded on a scale from 1 - 3, one being the least severe to three being the most severe type of ankle sprain. It is with all this information, along with recognition of signs and symptoms, that initiation of a proper care plan can hasten the recovery process and help the athlete resume activities.

Further distally, common injuries among athletes are midfoot injuries. A common and debilitating midfoot injury is the Lisfranc injury. These occur as a result of trauma to the tarsometatarsal articulation of the midfoot. These injuries have been observed to occur in athletes when an axial force is driven down through the calcaneus while the foot is plantarflexed. The historical basis of this injury dates back to the French surgeon Jacques Lisfranc de St. Martin. Lisfranc reported midfoot injuries of soldiers who fell from their horses while their foot remained plantarflexed in the stirrup during the Napoleonic era.

Along with these, many athletes present with injuries to the first metatarsophalangeal joint (MTPJ). Two specific injuries occur here and are common among athletes in different sports. The first is called “turf toe.” As the name implies, this injury is common among athletes who participate on artificial surfaces, but can happen in a multitude of sports with different surfaces.

Deemed a hyperextension injury, it typically occurs when the toes are dorsiflexed and a force is applied to a raised heel, resulting in tearing of the surrounding ligaments. This injury is commonly seen in American football. The other common injury to occur at the same joint is known as “sand toe,” and typically occurs to athletes who participate in sports played on sand, particularly volleyball. This injury occurs due to hyperflexion of the first MTPJ, typical of a player diving for a ball and the sand gives way underneath the toes. This results in dorsal capsule rupture and injury to the extensor tendons of the muscles surrounding it.

The purpose of this study was to compare ankle and foot injuries to athletes in contact sports to see which specific injuries occurred most often. A secondary aim was to compare the methods of
treatment of the most common injuries to see which yielded the most effective outcomes.

METHODS

The database used to obtain literature sources on this topic was PubMed Central. A PubMed search was performed, limited to the English language and free full text availability, using the term “ankle sprains” with no inclusion or exclusion criteria. 308 articles were found, and abstracts were reviewed. From these, nine articles were picked and read thoroughly, and finally four were selected based on their specificity towards the lateral ankle sprain criteria.

Figure 1. Systematic literature search results.
This was repeated with the term “Lisfranc injuries” with no inclusion or exclusion criteria. Abstracts were reviewed of the 91 articles present. 8 articles were picked for review and five were selected based on details about injuries in contact sports. Another search was done with the term “turf toe,” where 69 articles were present. Upon further review, 3 were selected based on their relevance to the topic and their specificity of common mechanisms of turf toe injuries. Finally, a search was conducted using the term “sand toe.” From the 32 articles present, two were selected based on their relevance to athletics and the research of mechanisms of the injury (Figure 1).

RESULTS AND DISCUSSION

Lateral Ankle Sprains

Anatomy

On November 4th, Percy Harvin of the Minnesota Vikings suffered a lateral ankle sprain on his left foot that ended his season. A common injury suffered by athletes, the anatomy of the ankle joint is important to know. The ankle joint connects the leg (the tibia and the fibula) to the foot (talus). This joint, also known as the talocrural joint (TCJ), is essentially an ankle mortise with articulation between the distal portion of the tibia and fibula to the trochlear surface of the talus. The ankle joint functions together with the help of ligaments and tendons that encapsulate and protect it.

Ligaments in general connect one bone to another and are made up of dense parallel bundles of collagen fibers. Ligaments are in place to provide strength and alignment to the joint, but also to support the joints during excessive motion. The purpose of these ligaments is to resist this excessive motion using the collagen fibers to dissipate internal forces. “However, if the load surpasses the mechanical strength of the ligament and is applied at a fast velocity that exceeds the speed of a corrective muscle reflex, it may lead to microscopic failure of the collagen fibers or a complete rupture of the ligament”1. The main ligaments of the ankle are the medial ligaments of the talocrural joint (deltoid ligaments) and the lateral ligaments of the talocrural joint (lateral collateral ligaments). The deltoid ligament consists of the tibiocalcaneal, tibiocalcaneal, and the posterior tibiotalar (superficial part) superficial branches, and the anterior tibiotalar and the posterior tibiotalar (deep part) deep branches. Ligaments that support the ankle laterally include “the anterior talofibular (ATFL), calcaneofibular (CFL), and posterior talofibular (PTFL). The ATFL and the CFL are the primary stabilizers of the lateral side of the ankle,”2 and play an important role in lateral ankle sprains.

Mechanism

Lateral ankle sprains are common among young active individuals and athletes whose “center of gravity is shifted over the lateral border of the weight bearing leg, causing the ankle to roll inward at a high velocity.”1 Lateral ankle sprains occur during “excessive inversion and plantar flexion of the rear foot on the tibia in which the ATFL is most commonly torn.”2,3 The ATFL, being the weakest lateral collateral ligament, is the first to be injured during talar inversion at “approximately 30 – 45 degrees within the ankle mortise (Figure 2). Other structures that may be injured during a lateral ankle sprain may include the peroneal tendons, lateral joint capsule, and the proprioceptive nerve endings found within these soft tissue structures. There are many symptoms typically seen with lateral ankle sprain, such as “persistent ankle stiffness, swelling, and pain with delayed synovitis, tendinitis, and muscle weakness.”2
Ankle sprains are classified by the amount of damage that has occurred to the ligaments. "In a grade 1 sprain, there is stretching of the ligaments with little or no joint instability. A grade 1 ankle sprain usually entails microscopic tearing of the ATFL. Symptoms may include minimal swelling and point tenderness directly over the ATFL; however, there is no instability, and the patient can ambulate with little or no pain. Grade 2 sprains involve microscopic tearing of a larger cross-sectional portion of the ATFL, which occurs with some tearing of ligamentous fibers and moderate instability of the joint. Pain and swelling are moderate to severe and often immobilization is required for several days. With a grade 3 sprain, there is total rupture of the ligament with gross instability of the joint. Pain and swelling is so debilitating that weight bearing is impossible for up to several weeks."  

The cause and mechanism of injury can vary from patient to patient, as well as their healing and treatment time.

### Treatment

There are several ways to treat an ankle sprain, depending on the situation of the patient. Anatomically, the ligament goes through phases of healing, from an inflammatory phase that lasts a day to three days to a reparative phase of healing in which healthy cells replace damaged fibers and connective tissue. Finally the healing process ends at the remodeling phase. Here “the newly formed collagen fibers align themselves longitudinally, and cross-linkages form. By 3 weeks, as collagen maturation continues, the ligament may regain approximately 60% of its tensile strength. By 3 months, the ligament may regain its pre-injury strength.”  

Healing begins immediately by the body; however, implementing a non-surgical approach can accelerate treatment. As described by Fong et al, management could include various forms of braces, boards, and imagery such as ultrasounds and MRI’s. A semi-rigid ankle brace, an aircast ankle brace, allows for significant improvement in ankle joint function. This brace is “designed to fit against the medial and lateral malleoli of the ankle joint.” They also believe that an elastic support bandage could be used to “improve single-leg-stance balance and might decrease the likelihood of future sprains." Fong et al believe that training on a wobble board in which the patient practices balancing on a rectangular or square platform with a single plane-rounded fulcrum underneath can better one’s anteroposterior and mediolateral stability. Another method mentioned by Chinn and Hertel was with the help of a stationary bicycle, which can aid in dorsiflexion and plantar flexion motion in a controlled environment.”

The initial purpose of treatment is to be able to control the swelling and the pain in order to increase the strength of exercises to further better the range of motion at the ankle. In order to do so, dorsiflexion and plantarflexion are the main ankle motions that are targeted initially by physical therapists. Once that motion has strengthened and “ligaments heal, inversion and eversion strengthening should be added.” In order to do so, ankle weights, resistance bands, and even hydrotherapy are considered viable...
options to treat in all planes. Once range of motion and strength is regained, functional activities are included. Functional rehabilitation exercises should begin with simple, uniplaner exercises; walking and jogging in a straight line. Once the athlete can perform these without a pain or a limp, hops, jumps, skips and change of direction can start to be added.3

Treatment is determined in order to restore the patient’s complete range of motion and mechanical strength gradually and, nonsurgically, in order to protect the patients’ ligament from further injury.

Lisfranc’s Injury

Anatomy

On September 30, 2011, New York Jets wide receiver Santonio Holmes suffered what was described as an injury to the Lisfranc joint. The Lisfranc joint divides the midfoot from the forefoot. The bony elements of the 3 metatarsals articulating with the cuneiforms, along with the fourth and fifth metatarsals articulating with the cuboid, provide most of the overall stability.6 Ligaments are grouped according to anatomical placement, mainly dorsal, plantar, and interosseous. The strongest of these ligaments originates from the lateral side of the medial cuneiform and inserts on the medial side of the base of the second metatarsal. This ligament is known as Lisfranc’s ligament, an oblique interosseous ligament.6

Mechanism

A Lisfranc injury does not delineate a specific injury, but instead a spectrum of processes involving the tarsometatarsal joint complex. The Lisfranc joint promotes energy dissipation by allowing force to be transferred between the midfoot and the forefoot. Direct and indirect injuries can occur at this joint. Direct injuries occur in blunt force trauma to the foot and are clinically worse than indirect.7 The more common injury in athletics is the indirect injury. This is seen in football players and happens when one player falls onto the heel of another player while the foot is planted into the ground and in an equinus position.7 Approximately 4% of professional football players sustain injuries to the Lisfranc’s joint each year.8 These injuries also occur in gymnasts, soccer players and basketball players. These indirect injuries commonly involve failure of the weaker dorsometatarsal ligaments in tension with subsequent dorsal metatarsal dislocation.8 The Lisfranc joint provides a stable axis for rotation due to the limited mobility of the joint, and allows for plantar flexion and dorsiflexion of the forefoot. The axis about which extension and plantar flexion occur, called the horizontal axis, goes through the base of the second metatarsal.6 Thus, with the lack of dorsal support and the immobility of the second metatarsal, placing the foot in

Figure 3: Lisfranc’s Ligament Mechanism of Injury6
extreme plantar flexion with an axial load can provide sufficient stress to cause dorsal displacement of the second metatarsal base. Injuries can vary, from a simple injury that affects only a single joint to a complex injury that disrupts multiple different joints and includes multiple fractures (Figure 3). The severity of the injury depends upon the impact.

**Symptoms**

A key symptom indicative of a Lisfranc joint injury is bruising on the plantar surface of the foot. Bruising on the dorsal aspect is also common. Included with bruising is pain and swelling on the dorsal portion of the foot. Typically, the pain worsens with standing or walking, and may require crutches for mobilization. Lisfranc injuries lead to degenerative arthritis, loss of arch and chronic instability, and pain at the midfoot-forefoot articulations.

**Treatment**

If there are no fractures or dislocations in the joint and the ligaments are not completely torn, nonsurgical treatment may be all that is necessary for healing. A nonsurgical treatment plan includes wearing a non-weight-bearing cast for 6 weeks. This then progresses to weight-bearing in a removable cast boot or an orthotic. Surgery is recommended for all injuries with a fracture in the joints of the midfoot or with subluxation of the joints. There are two types of surgery recommended for this injury. The first is the internal fixation procedure where the bones are positioned correctly and held in place with K-wire fixations or temporary screw fixation using closed or open reduction techniques. If the injury is more severe and has damage that cannot be repaired, another procedure called fusion may be recommended as the initial surgical procedure.

Fusion attaches the injured bones together in order to form one piece of bone, and is recommended in cases where internal fixation will not work.

**Turf Toe**

**Anatomy**

On December 3, 2012 Carolina Panthers wide receiver Brandon LaFell suffered an injury that is commonly known as “turf toe.” Turf toe is an injury that is characterized with hyperextension of the first metatarsophalangeal joint with sprain and possible rupture of the plantar ligamentous complex. The capsuloligamentous-sesamoid complex contributes most of the stability observed in the MTP joint. This complex is made up of collateral ligaments, along with the plantar plate, flexor hallucis brevis, adductor hallucis, and abductor hallucis.
### Mechanism

This injury typically occurs in combination of dorsiflexed toes and the foot in an equinus position with the heel raised, forefoot planted on the ground, and an axial load applied to the posterior heel. Usually with a hyperextension injury, the plantar portion of the ligament complex tears while the plantar plate becomes detached distal to the sesamoid bones. Once the joint capsule is torn, unrestricted motion of the proximal phalanx results in severe compression of the articular surface of the metatarsal head. This produces the potential for fracture or dislocation. The injury is classified in a grading scale: Grade I is micro-tearing of the capsuloligamentous complex, Grade II is partial tearing of the same complex, and Grade III is complete tearing of the capsuloligamentous complex. The grading varies depending upon the severity of the injury, and clinical evaluation needs to be done in order to determine severity of injury.

### Symptoms

The risk factors for this injury are hard playing surfaces, lack of ankle dorsiflexion, pre-existing restriction of the first MPJ motion, and wearing flexible, lighter shoes. These patients present with swelling, ecchymosis, a misalignment of the structure of the hallux, weak plantarflexion strength, and pain on weight bearing and toe off.

### Treatment

Most cases of turf toe are treated conservatively. In the acute stages, treatment is centered on decreasing inflammation and promoting healing with rest, ice, compression, and elevation. Nonsteroidal anti-inflammatory drugs (NSAIDs) may aide in minimizing pain and inflammation.

In higher grade sprains, crutches and a short leg cast with a toe spica in slight plantarflexion or a walker boot may be prescribed for the first week or more.

### Sand Toe

#### Mechanism

One injury that is more commonly seen in sand sports such as volleyball occurs at the same joint as turf toe but occurs via a different mechanism. This injury, termed “sand toe,” is an injury that occurs during hyperflexion (Figure 5) of the first metatarsophalangeal joint. This hyperflexion occurs with sprain and possible rupture of the dorsal capsule, along with injury to the extensor tendons. This injury typically occurs when toes are in a plantarflexed position and momentum of body weight continues over the joint resulting in hyperflexion injury.

#### Symptoms and Treatment

These injuries clinically present with weak dorsiflexion strength, pain on weight bearing and
toe off, and swelling with ecchymosis. This injury is usually self-limiting and, unlike turf toe, is not plagued with long-term morbidity. The most common form of this injury is a capsular sprain with minor tearing, and is manageable with stabilization by taping. In addition, use of non-steroidal anti-inflammatories with rest, ice, compression, and elevation are recommended to expedite healing.

CONCLUSION

Injuries are common when one is physically active, particularly in contact sports. Diagnosis of the most common ankle, Lisfranc’s, and hallux injuries requires knowledge of the mechanism of injury consistent with the appropriate physical findings. Knowledge of the most effective treatments can help speed the healing process. Knowing the most common ankle and foot injuries is important before participating in athletics in order to properly avoid injury. There are many lower extremity injuries that can occur when dealing with sports. The most common are highlighted here in order to provide knowledge of the mechanism and treatment options of high-yield injuries. Further research needs to be done in order to provide an entire spectrum of lower extremity injuries while participating in contact sports.

Authors Contributions
The authors, SC and TM, equally contributed to the construction of this manuscript.

Statement of Competing Interests
The authors, S.C. and T.M., declare no competing interests in regards to this research topic and systematic review.

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Human Papillomavirus Types 2, 27, and 57 Identified in Plantar Verrucae from HIV-Positive and HIV-Negative Individuals

Christy King, DPM, James Johnston, DPM, Kene Ofili, DPM, Maylynn Tam, DPM, Joel Palefsky, MD
Maria Da Costa, MS, Yasha Mathur, BS, and Peter Barbosa, PhD

Abstract

Introduction
Although an increased prevalence of plantar verrucae has been associated with human immunodeficiency virus (HIV) infection, human papillomavirus (HPV) typing studies have not been published about this patient population. We sought to determine the prevalence of HPV types in plantar verrucae of HIV-positive (HIV+) and HIV-negative (HIV−) individuals.

Methods
Thirty-nine plantar verruca lesions in 17 individuals were examined. Nine participants were HIV+ and eight were HIV−. Detection of HPV was performed by polymerase chain reaction using two sets of primers: MY09=MY11. The type of HPV was determined by hybridization to 38 different HPV types. Clinical types of verrucae were correlated to the HPV strain identified in each lesion.

Results
Of the 39 plantar verruca samples, 38 typed to HPV-2, HPV-27, and HPV-57 strains in HIV+ and HIV− individuals. Specifically, a large proportion of the samples from HIV− individuals typed as HPV-27 (87.5%), and HPV-2 was the predominant type identified in HIV+ individuals (50%). No rare or atypical HPV types were found in either group. We identified HPV-2 and HPV-27 in 96% of verruca plantaris clinical type. Mosaic warts typed to HPV-27 and HPV-57, and 80% of punctate verrucae typed to HPV-57.

Conclusions
This study presents an increased prevalence of HPV-2, HPV-27, and HPV-57 in plantar verrucae in this study population and provides insight into the occurrence of these types in HIV+ and HIV− individuals.

Key Words
HIV, HPV, plantar verrucae

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INTRODUCTION

The human papillomavirus (HPV) is a circular double-stranded DNA virus. More than 150 different HPV strains have been characterized, of which approximately 90 have been completely sequenced. Human papillomavirus can be classified as mucosal or cutaneous according to the type of epithelium the virus infects. Plantar verrucae (plantar warts) are cutaneous manifestations of HPV on the sole of the foot. The benign hyperkeratotic lesions result from HPV infection of the epidermal keratinocytes in the stratum corneum and granulosum. Inoculation of the virus particles often follows trauma to the epithelium and rapidly proliferates the squamous cell layer to produce the classic appearance of a wart.1-3

One of the most common classification systems for the clinical manifestation of plantar verrucae includes three categories of clinical lesions: verrucae plantaris, mosaic warts, and punctate verrucae.4,5 Verruca plantaris, also known as myrmecia or deep plantar wart, is usually found deep in the epidermis. Lesions are also usually painful and found as a single wart. Characteristic of this type is the punctate bleeding caused by small blood vessels invading the lesion. The literature identifies this type of wart as being associated with HPV-1. The mosaic wart, reported as being associated with HPV-2, is composed of interconnected superficial warts, forming a mosaic pattern. The punctate verrucae are endophytic lesions usually smaller than verrucae plantaris and lack the characteristic bleeding observed in plantaris. This type of wart has been associated with HPV-4.4,5

Although HPV-1, HPV-2, and HPV-4 have traditionally been linked to the development of plantar verrucae, recent studies have highlighted the increased incidence of HPV-2, HPV-27, and HPV-57 in cutaneous lesions.6 These types are closely related to HPV strains that infect mucosal epithelia, but they more frequently cause cutaneous warts and may assume a mosaic or endophytic appearance.7

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome, can cause a progressively immunocompromised state. High prevalence rates of plantar verrucae have been documented in HIV-positive (HIVþ) individuals compared with HIV-negative (HIV–) individuals.8 Studies also suggest that HIVþ individuals with plantar verrucae present with more uncommon lesions typed to atypical viral strains, increased severity, and higher resistance to treatment.9 A study by Whitaker et al reported the unique occurrence of HPV-69 in an HIVþ individual with a recalcitrant wart.9 Similarly, a type commonly associated with the genital tract, HPV-66, was discovered in a large verrucous plaque on the foot of an HIVþ individual.10

Although few studies have determined the HPV type of mixed cutaneous warts, the prevalence of specific serotypes of plantar verrucae in HIVþ and HIV– individuals has been overlooked. The goal of this research study was to determine the prevalence of HPV types in plantar verrucae of HIVþ and HIV– individuals.

METHODS

Approval of this study protocol was obtained from Samuel Merritt University’s institutional review board (Oakland, California). A simple
questionnaire was distributed to 520 attendees at the Castro Street Fair in San Francisco, California, in October 2008. Demographic information collected from the participants included age, sex, race, and sexual orientation. In addition, information was collected on self-reported HIV status (positive, negative, not sure, decline to answer) and self-reported presence of plantar warts (yes, no, not sure). Individuals who responded “yes” or “not sure” to the question of presence of plantar warts were invited to have an on-site examination by the attending doctor of podiatric medicine to determine whether plantar verrucae were indeed present. An experienced doctor of podiatric medicine identified whether plantar verrucae were present clinically and classified the lesions into one of four categories: verrucae plantaris, mosaic warts, punctate verrucae, or indeterminate. Once the wart was identified, a scalpel with a disposable No. 15 blade was used to collect a sample by scraping the lesion. The cutaneous verruca samples were collected in 1.5-mL Eppendorf polypropylene microcentrifuge tubes containing 300 mL of specimen transport medium (Qiagen Inc, Valencia, California) and were stored on ice immediately after collection until they could be frozen at -20°C approximately 3 to 5 hours later.

After aspiration of the specimen transport medium, a DNA preparation was made from the specimen using the QIAamp DNA mini kit (Qiagen Inc, Venlo, Limburg Province, The Netherlands) per the manufacturer’s recommendation. Five microliters of this preparation was used in the HPV consensus polymerase chain reaction protocol. The polymerase chain reaction was performed using a modified pool of MY09/MY11 consensus HPV L1 primers and primers for amplification of the human b-globin as an indicator of specimen adequacy, as described previously.11 After 40 amplification cycles, specimens were probed with a biotin-labeled HPV L1 consensus probe mixture. A separate membrane was probed with a biotin-labeled probe to the human b-globin gene. Specimens were also typed by hybridizing to 38 different HPV types (6/11, 16, 18, 26/69, 30, 31, 32/42, 33, 34, 35, 39, 45, 51, 52, 53, 54, 56, 2/27/57, 58, 59, 61, 62, 66, 67, 68, 70, 71, 72, 73, 81, 82, 83, 84, 85, 86/87, 90/106, 97, 102/89) and two separate mixtures. Mix 1 contained types 7, 13, 40, 43, 44, 55, 74, and 91, and mix 2 contained types 3, 10, 28, 29, 77, 78, and 94. Samples positive for the 2/27/57 mix were reprobed for each HPV type individually. Specimens negative for b-globin gene amplification were excluded from the analysis. The results of the polymerase chain reaction were recorded on a scale from 0 to 5 based on the intensity of the signal on the dot blots, as described previously.12

RESULTS

Of the 520 participants who completed the survey questionnaire, 35 reported having plantar verrucae and were invited to undergo an on-site physical examination and to provide a sample of the lesion(s) by debridement. Twenty patients agreed to have a sample of their cutaneous lesion debrided for the study. Samples from 17 of the 20 patients successfully underwent the typing protocol.

Table 1 describes the demographic characteristics of the study population. Most of the patients were Anglo gay men aged 36 to 45 years. There were nine HIV– patients (52.9%) and eight HIV+ patients (47.1%).

In the 17 patients, 41 plantar verruca lesions were visually identified. Of the 41 lesions, three samples were removed from the data analysis: one was weakly HPV+ and did not type, one produced significant DNA amplification after polymerase chain reaction but no HPV was present, and one was b-globin negative and, therefore, failed
polymerase chain reaction DNA amplification. Thirty-eight samples were HPV typed in the study (Table 2). Twenty-six samples (68.4%) were verruca plantaris clinical type, five (13.2%) each were punctate verrucae or indeterminate, and two (5.2%) were mosaic wart type. Figure 1 illustrates a clinical picture of various lesions identified and typed in several of the participants.

Human papillomavirus type 27 was the most commonly identified HPV type in the entire study population, occurring 52.6% of the time, with HPV-2 following at 31.6%; HPV-57 was the least common, occurring 15.8% of the time (Table 3). For HIV+ individuals, HPV-2 was the most common (50%), and HPV-27 and HPV-57 occurred 27.3% and 22.7% of the time, respectively. In HIV– participants, HPV-27 was the most common, occurring 87.5% of the time. Both HPV-2 and HPV-57 were found only once (6.25%) each in the HIV– individuals.

Table 4 details the associations between HPV strains and clinical types of plantar verrucae. Of the 26 verrucae plantaris analyzed, approximately 42% and 54% typed to HPV-2 and HPV-27, respectively. Collectively, HPV-2 and HPV-27 composed approximately 96% of the total verrucae plantaris. The mosaic wart and punctate verruca lesions typed to HPV-27 and HPV-57. Most of the punctate verruca lesions (80%) typed to HPV-57.

DISCUSSION

This is the first study, to our knowledge, to focus on examining HPV serotypes of plantar verrucae lesions in HIV+ and HIV– individuals. Although the current literature primarily attributes plantar verrucae to HPV-1, HPV-2, and HPV-4, the present study demonstrates that types 2, 27, and 57 can be common in cutaneous warts found on the plantar foot region. This is similar to results from a recent study by Tomson et al, who found that 100% of the plantar verrucae typed to HPV-2, HPV-27, and HPV-57. The present findings indicate that HPV-2, HPV-27, and HPV-57 subtypes contribute to plantar verrucae in HIV+ and HIV– individuals. In fact, all 38 samples were typed to a member of the HPV-2/HPV-27/HPV-57 subset. Specifically,
HPV-2 was commonly found in HIV+ individuals (50%). On the other hand, HIV− individuals exhibited HPV-27 with an 87.5% prevalence rate. Overall, HPV-27 was the most common HPV type (52.6%), followed by HPV-2 (31.6%) and HPV-57 (15.8%).

Previous studies revealed that the HPV-2, HPV-27, and HPV-57 types are common causes of cutaneous warts. A study by Porro et al.\textsuperscript{16} investigated HPV types in HIV+ individuals and identified HPV-2 in 38%, HPV-57 in 31%, HPV-27 in 12%, HPV-6 in 12%, and HPV-7 in 6%. Although their study primarily focused on common warts located in the hands, the combined percentage of HPV-2/HPV-27/HPV-57 (81%) is comparable with the present study results. This alludes to the increased prevalence of HPV-2, HPV-27, and HPV-57 in many types of cutaneous warts in HIV+ and HIV− individuals.

The common contribution of HPV-2, HPV-27, and HPV-57 to the development of plantar verrucae and common warts may be attributed to their phylogenetic link.\textsuperscript{7} The three related viruses are classified under the super group of alpha-papillomaviruses. Although most of the group members infect mucosal surfaces, these three specific members primarily infect nongenital skin.\textsuperscript{3} These aberrant members are commonly associated with a longer duration of infection, fair response to treatment, and a history of atopic disease. Normally, they are seen in 10- to 30-year-old people.
patients with cutaneous lesions, with no preference for sex.6

The clinical manifestation of plantar verrucae has been classified into three subcategories: verrucae plantaris, mosaic warts, and punctate verrucae. Classically, these clinical classifications have been associated with HPV-1, HPV-2, and HPV-4, respectively.4,5 With approximately 96% of the total verrucae plantaris typed to HPV-2 and HPV-27, the results of this study again challenge the literature. Human papillomavirus type 2, traditionally linked to mosaic warts, was exclusively seen in verrucae plantaris. Moreover, 80% of punctate verrucae were seen in connection with HPV-57.

The prevalence of plantar verrucae is significantly higher in patients with HIV infection.8,17 Much of the research associated with HPV infection in HIV+ individuals has studied genital warts; however, plantar warts have been explored more recently. Increased prevalence, atypical types, and multiple lesions have been described in co-infection of HPV in HIV+ individuals.18,19

Studies have also reported rare types of HPV in plantar verrucae of HIV+ patients.9,10 Although no atypical HPV types were found in this study, HPV infection with two or more virus types in one individual was identified. Infection with more than one type of HPV is rare and not widely reported. Rubben et al6 suggest that co-infection in HPV-2–related variants is possible. In this study, a single HIV+ patient with 12 separate warts was found to have HPV-2 and HPV-27 in different plantar verrucae lesions. This finding suggests that more aggressive manifestations are observed in HIV+ patients.

This study has several limitations. Participants were recruited at a community fair and self-reported much of the data, so there may have been self-selection bias. Furthermore, the HIV status of the participants was based on their questionnaire responses and was not confirmed via HIV testing, which was not financially feasible. Confirmatory diagnosis of plantar verrucae clinical type requires histologic examination, and this was not conducted. Clinical type identification was based on evaluation by experienced doctors of podiatric medicine. Finally, HPV-1 and HPV-4 are reported as common causes of plantar verrucae, and these two types were not included in the testing of this study. Although all 38 tested samples typed to HPV-2, HPV-27, and HPV-57, one of the three samples eliminated from data analysis was weakly HPV positive. It is hypotheti-
cally possible that this one sample could have typed to HPV-1 or HPV-4.

The prevalence data acquired in this study and previous research may ultimately be used to provide the basis for personalized treatment options. Using an evidence-based therapy approach, aggressive types of plantar verrucae may be treated from the onset if found in a population that has a higher risk of unusual HPV infection types. The differences in the incidence of the HPV-2/HPV-27/HPV-57 subset for HIV+ and HIV– individuals may provide insight into why the expression of plantar verrucae differs clinically between the two groups. Additional evidence-based studies are needed to elucidate possible clinical correlations.

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