EOR | VOLUME 3 | MAY 2018
DOI: 10.1302/2058-5241.3.170073
www.efortopenreviews.org

EFORT open reviews

New trends in the orthopaedic management of diabetic foot

Önder İ. Kılıçoğlu[1]
Mehmet Demirel[1]
Şamil Aktaş[2]

- Although there are various types of therapeutic footwear currently used to treat diabetic foot ulcers (DFUs), recent literature has enforced the concept that total-contact casts are the benchmark.
- Besides conventional clinical tests and imaging modalities, advanced MRI techniques and high-sensitivity nuclear medicine modalities present several advantages for the investigation of diabetic foot problems.
- The currently accepted principles of DFU care are rigorous debridement followed by modern wound dressings to provide a moist wound environment. Recently, hyperbaric oxygen and negative pressure wound therapy have aroused increasing attention as an adjunctive treatment for patients with DFUs.
- For DFU, various surgical treatments are currently available, including resection arthroplasty, metatarsal osteotomies and metatarsal head resections.
- In the modern management of the Charcot foot, surgery in the acute phase remains controversial and under investigation. While conventional fixation techniques are frequently insufficient to keep alignment postoperatively, superconstruct techniques could provide a successful fixation.
- Retrograde intramedullary nailing has been a generally accepted method of achieving stability. The midfoot fusion bolt is a current treatment device that maintains the longitudinal columns of the foot. Also, Achilles tendon lengthening remains a popular method in the management of Charcot foot.

Keywords: diabetic foot; Charcot foot

Cite this article: *EFORT Open Rev* 2018;3
DOI: 10.1302/2058-5241.3.170073

Introduction

Diabetic foot problems include ulcers, infection and Charcot arthropathy, along with numerous underlying risk factors, including peripheral neuropathy, peripheral vascular disease, impaired immune function and delayed bone healing.[1] An appreciation of critical issues for diabetic foot management, such as aetiopathogenesis of ischaemia, principles of wound healing and immunology, has changed the traditional approach and led to new medical and surgical advances. The recent literature illustrates[2,3] that tissue engineering, biomedical and biotechnology applications, surgical corrective techniques and instruments for managing diabetic foot problems continue to evolve and become more sophisticated. Despite these significant improvements, the diabetic foot remains a major public health problem and one of the leading causes of hospitalization for diabetic patients.[4]

The current management of the diabetic foot includes various prevention and treatment options, some of which have been developed recently and others that have been used over the past few decades. This review aims to provide an up-to-date overview of the orthopaedic management of the diabetic foot.

Novel preventive approaches to diabetic foot ulcers (DFUs)

Prevention of ulcer recurrence is one of the most burning issues in diabetic foot management, given the dearth of diabetes-specific educational programmes in most countries, as well as the substantial recurrence, infection and amputation rates of DFUs.[5] Meticulous glycaemic control is the primary and only proven method to reduce or prevent all diabetes-related complications.[6] Home monitoring of daily foot temperatures has been proposed as an effective method for reducing the rate of ulcer recurrence.[7] As a novel method, higher resolution infrared thermal imaging may be beneficial for preventing the first ulcer or recurrent ones.[8]

Hyperspectral imaging is another new technique used to measure oxygen saturation in tissue and, therefore, to diagnose early microvascular disease in the diabetic foot.

It was proposed that this technology could determine ischaemic changes and inflammatory complications, with a sensitivity of 95% and specificity of 80%.[9] The skin perfusion pressure-testing system is a new portable device used in daily clinical practice to detect microvascular disease and estimate the healing potential of DFUs. It is considered that both hyperspectral imaging and skin perfusion pressure could be useful in early detection of peripheral arterial disease in people with diabetes.[10]

New diagnostic technologies and strategies for diabetic foot infections (DFIs)

The natural history of a DFU presents a highly discouraging course due to the complicated nature of the lesions. Hospital-based studies estimate that the mortality rates of patients with DFUs are twice as high as patients without.[11] More than half of diabetic ulcers are complicated by infection, and nearly 20% of DFIs require different forms of amputation.[5]

Today, when conventional clinical tests and imaging modalities such as radiography, ultrasonography and computed tomography (CT) fail to diagnose DFIs, advanced imaging techniques can be employed.[12] MRI is the most useful diagnostic imaging method for investigating DFIs.[12,13] However, in certain clinical conditions, particularly osteomyelitis and Charcot neuroarthropathy (CN), the use of MRI is limited because of the overlapping features of both conditions. Therefore, new functional MRI modalities, including dixon imaging, diffusion-weighted imaging and dynamic contrast-enhanced MRI, have been of interest in distinguishing the two entities. Nonetheless, these helpful techniques are not routinely used for diabetic foot assessment, and further studies are needed to verify their feasibility in discriminating between neuroarthropathy and osteomyelitis.[12,14]

Alternatively, high-sensitivity nuclear-medicine techniques have been recently used in diagnostic imaging of the diabetic foot. However, they suffer from either low specificity (bone scans) or poor ability to distinguish osteomyelitis from soft-tissue infection (leukocyte and anti-granulocyte scans).[15] More recently, positron emission tomography with 18 F-fluorodeoxyglucose (FDG-PET) and radiolabelled white blood cell (WBC) scintigraphy are still under investigation for DFIs, and a recent meta-analysis demonstrated that both techniques can offer high specificity to detect osteomyelitis in the diabetic foot.[16] Moreover, hybrid imaging techniques, such as single photon emission CT/CT (SPECT/CT), FDG-PET/CT and FDG-PET/MRI have been considered as potential tools to improve the specificity and accuracy of anatomical localization in the evaluation of diabetic foot osteomyelitis.[17-19]

Despite the above advanced techniques for deep-tissue imaging, clinical evaluation, including 'sausage' digits and probe-to-bone testing, the Infectious Disease Society of America infection grading criteria[20,21] maintain their importance as the most advantageous and suitable guidelines for the diagnosis of clinical infection in the diabetic foot.[22]

Current non-surgical treatment options for DFUs

The current principles of DFU care are the following:

1) infection management;
2) a rigorous off-loading regimen;
3) local care with several debridement and advanced wound healing methods together with a multidisciplinary approach to assess glycaemic status, cardiovascular risk, the potential for revascularization and surgical intervention.[15,22]

Off-loading treatment

The primary treatment of DFUs remains the restriction of weight-bearing to promote wound healing and avoid the recurrence of ulcers, hence preventing amputation. In current orthopaedic practice, even though widespread methods of off-loading are available such as total contact casts, removable cast walkers, therapeutic footwear, foot orthoses, custom shoes, custom braces, padding and strapping therapy,[23,24] recent studies have enforced the concept that total contact casts should be the benchmark and facilitate patient adherence to the off-loading regimen. Nonetheless, there is no consensus in the literature on the optimal off-loading strategy.[23,25,26]

Many studies have revealed that total contact casts and removable walkers can effectively off-load pressure.[27-29] In contrast, as reflected by multiple randomized controlled trials (RCT), total contact casting appears to ensure better improvement in both wound healing rates and time to healing when compared with removable devices.[29-32] Furthermore, a wide variety of therapeutic footwear is currently employed at the different foot regions to prevent these regions from the onset and recurrence of DFU, which is done by encouraging effective pressure off-loading.[28,33,34] Nevertheless, the efficacy and feasibility of these techniques are rarely studied in clinical practice; therefore, the robust evidence supporting their use is scarce in the current literature, and their efficacy needs further verification in prospective studies.[23,34]

New debridement methods and advanced wound-healing strategies

Despite the many modern alternative methods, sharp debridement using scalpel and scissors is still regarded as

the benchmark care for DFUs and plays a vital role in wound control by effectively removing relevant biofilm.[35] Recently, larval therapy is used for chronic, non-healing wounds, particularly in diabetic patients. The mechanism of therapy consists of debridement and disinfection of chronic wounds and wound healing promotion through maggot secretions and excretions against gram-positive and gram-negative bacteria.[36] Although there is no strong evidence for the practice,[37] larval therapy has been shown as a safe and efficacious adjunctive method for biosurgical debridement.[15,38] The Versajet Hydrosurgery System (Smith and Nephew, London, UK) is also a new development, which debrides the wound and removes the tissue by pumping a high-pressure jet-stream of sterile normal saline from a disposable handheld cutting/aspirating tool. A prospective randomized controlled clinical study showed that this system is a quick and effective method for debridement.[39] Furthermore, Clostridial collagenase is a novel enzymatic debridement method and that is reported as tolerable and clinically efficacious in achieving a viable wound bed. However, there is little evidence that suggests its application for DFUs.[40]

The current cornerstones of diabetic foot care are meticulous debridement followed by modern wound dressings to promote a moist wound environment.[2] With the breakthroughs in the field of biomaterial science and increased accessibility of biocompatible products more recently, advanced wound dressings have been developed and used as the modern treatment of choice for chronic wounds.[41] Their main attribute includes the ability to create and promote a moist wound environment.[11] The most commonly used wound dressings in current practice are basically categorized as hydrogels, hydrocolloids, alginates, semi-permeable, silver or biological dressings, and they are generally manufactured in three forms: gels, thin films or foam sheets.[2,11,42]

Most recently, a new generation of modern wound dressing has received increasing attention; these more advanced dressings can release therapeutic agents and healing enhancers such as drugs, growth factors (GFs), peptides, stem cells and other bioactive substances.[15,43] Recognition of the importance of an extracellular matrix for wound healing has convinced researchers to generate more advanced wound dressings including collagen and other extracellular matrix proteins, also called biological dressings, such as collagen, hyaluronic acid, chitosan, elastin and fibrin. Such dressings could decrease inflammatory cytokines and wound proteases while increasing GFs in the wound environment, therefore decreasing degradation of the present matrix and enhancing new collagen and granulation tissue formation.[41] An increasing variety of wound dressings have been developed and applied to enhance wound healing in DFUs, with favourable outcomes.[15,43] However, no clinical study has been conducted regarding which type of dressing would be best for diabetic patients with foot ulcerations.[15] Accordingly, RCTs have shown that no one dressing is superior to another.[2]

For patients with recalcitrant foot ulcers, advanced biological therapies including platelet-rich plasma, bioengineered cell-based therapies and recombinant growth factors (r-GF) may be of benefit in enhancing healing and quality of life. Nowadays, for DFU treatment, two cell-based therapies (allogeneic bilayered human skin equivalent and dermal skin substitute) and the recombinant platelet-derived GF (PDGF) constitute the benchmark of biological therapies considering the robust evidence that support their use.[41]

Among r-GF applications, PDGF is the most widely investigated and the only FDA-approved GF for DFUs, with promising results.[44,45] Furthermore, as a new therapy, the intralesional injection of recombinant human epidermal growth factor can prevent amputations in select complicated DFUs that are non-responsive to standard care.[46] Nonetheless, despite the current upward trend in the field of GFs, there is no compelling evidence to support the use of GFs in the management of DFUs.[2] One step beyond recombinant GFs, allogeneic bilayered human skin equivalent (Apligraf™) and dermal skin substitute (Dermagraft™) have been evolved and remain under investigation. These human skin equivalents include human fibroblast that produces GFs and different extracellular matrix elements.[2,15,41] Although these products are the benchmarks of biological therapies,[41] further RCTs are needed to evaluate the clinical efficacy and safety of such therapies.[15]

Hyperbaric oxygen therapy (HBOT)

The well-known benefits of HBOT involve a bactericidal effect through the oxygen free radicals and increased leukocyte activity.[15] In recent years, HBOT has aroused increasing attention as an adjunctive treatment for patients with DFUs. Nevertheless, the data on HBOT have shown contradictions with respect to the methodology and possible bias placed on its potential role in the management of DFUs. A number of studies reported satisfactory outcomes for HBOT.[47,48] However, the results of a meta-analysis obtained from pooled data of five trials with 312 patients indicated that there was no significant difference in terms of major amputation rate with HBOT.[49] Nonetheless, a current review strongly emphasized the role of HBOT in reducing the risk of amputation, particularly major amputation, for patients with DFUs compared with management without HBOT (13.63% *versus* 30.07%).[50] Furthermore, a more current meta-analysis in 2015 reported moderate evidence for HBOT as an adjunctive treatment for DFUs.[51]

Negative pressure wound therapy (NPWT)

NPWT, also called vacuum-assisted closure, has been cited as one of the most effective current strategies in reducing the risk of amputation and increasing healing rates for DFUs.[52-54] The reported properties of NPWT regarding the promotion of wound healing are reducing oedema, removing exudate and increasing perfusion, cell proliferation and granulation tissue.[54-56] A more recent meta-analysis of 11 RCTs further supported the use of NPWT in the management of patients with DFUs.[57] The addition of instillation to NPWT represents one of the latest trends and confers an extra ability to intermittently irrigate the wound bed and remove the fluid in addition to negative pressure.[58] A number of studies have suggested that this novel system presents potential advantages, which include removal of infection and non-viable material.[59,60] Nonetheless, the efficacy and effectiveness of this system for DFUs are still under investigation.[58]

Current surgical treatment options for DFUs

Traditionally, nonoperative treatments including off-loading techniques and local wound care are initiated to manage DFUs. However, when nonoperative treatments fail, various surgical treatments are used.[61]

First ray procedures – the first metatarsophalangeal joint (MTPJ) arthroplasty and the hallux interphalangeal joint (HIPJ) arthroplasty

Although no study has addressed the incidence of ulcers and their locations, the first ray of the foot (hallux and first metatarsal) is mostly predisposed to ulceration.[62] Determination of the underlying cause in patients with hallux ulcerations is a critical point in the decision-making regarding which treatment to use.[63] If the underlying cause is hallux rigidus characterized by the restriction of movement at the first MTPJ, this entity can be addressed by toe-preserving surgical interventions such as an arthroplasty of the HIPJ or the first MTPJ.[61,63]

Recently, the first MTPJ arthroplasty (resection arthroplasty) has been regarded as the preferred and effective surgical technique in the management of chronic plantar hallux ulcerations.[63,64] Likewise, in 2015, the evidence from a study by Tamir et al[62] showed that MTPJ resection arthroplasty can be considered to treat recalcitrant plantar hallux ulcers with treatable complications, even in the absence of a hallux rigidus.

Alternatively, the HIPJ arthroplasty can resolve recalcitrant hallux ulcerations and improve impaired foot pressure distribution, hence minimizing the amputation risk for lesser digits.[61,65] Although there is limited research investigating the efficacy of HIPJ arthroplasty,[61] our literature review revealed that both procedures are influential in preventing and reducing the hallux ulcerations and are still performed.

Lesser metatarsal procedures - metatarsal osteotomies and metatarsal head resection (MHR)

The plantar surface of the metatarsal head is among the most common locations for DFUs due to increased weight-bearing pressure. The main goal of the procedures for metatarsal head ulcers is to decrease the high local pressure under the affected metatarsal head. To achieve this goal, MHR or several metatarsal osteotomies can be performed. Several factors, such as age, vascular status, the presence of metabolic abnormalities, adherence to treatment, the presence of infectious processes and the quality of bone, should be considered in decision-making for the appropriate type of surgery (either osteotomy or joint resection).[66,67]

In the absence of osteomyelitis, a metatarsal osteotomy could serve as a viable treatment option. Various metatarsal osteotomies that use open or minimally-invasive technique have been described. Open osteotomies consist of the Weil osteotomy and a dorsal closing-wedge osteotomy with internal fixation using a plate and screws. Despite their effectiveness in off-loading the pressure on the ulcer, open procedures are associated with a higher rate of postoperative complications in terms of infection and wound dehiscence. In contrast, more recently, as a new technique, mini-invasive floating metatarsal osteotomy without internal fixation has been shown to offer adequate off-loading with a lower complication rate owing to the minimal soft-tissue damage.[66]

In the presence of osteomyelitis, MHR can be an option for the treatment of metatarsal head neuropathic ulcers.[68] Numerous studies have previously demonstrated high clinical efficacy and safety for MHR.[69,70] Recently, Motamedi and Ansari[67] have confirmed the clinical efficacy of MHR for DFUs based on lower complications, ulcer recurrence and hospitalizations and faster and better wound healing at the long-term follow-up compared with a medical treatment alone.

Charcot foot

Current concepts of diagnosis and treatment of Charcot foot

The Charcot foot is triggered by an extensive local inflammatory response that causes local osteoporosis, disabling deformity of the foot and ankle, and, eventually, even amputation.[71] The clinical onset of CN is characterized by a warm, swollen foot and ankle with erythema, and it is challenging to distinguish the acute CN from other clinical entities with a similar presentation such as osteomyelitis, cellulitis or deep-vein thrombosis. Although plain

radiography is the first line of imaging studies for patients with Charcot foot, its sensitivity and specificity in the early stages are low. Conversely, MRI is regarded as the most sensitive imaging method for detecting early changes in CN and, therefore, the modality of choice to differentiate between CN and infection.[71-73] Moreover, Chantelau and Grützner[74] have recently proposed a new MRI-based classification, with the rationale that the earliest, non-deforming, x-ray-negative inflammatory stage of the acute CN can be displayed using only MRI, and if not recognized in time and properly treated, this stage will result in significant arthropathy.

In contemporary orthopaedic practice, high-sensitivity nuclear medicine modalities present new opportunities to improve the diagnosis.[72] The technetium-99m methylene diphosphonate (Tc-MDP) scan confers high accuracy in identifying and localizing abnormal woven bone, but clinical conditions with high bone turnover, such as infection, surgery and trauma, may reduce the specificity rates. Although a four-phased bone scan with delayed image acquisition at 24 hours seems to be more specific for detecting abnormal bone, some clinical entities (i.e. tumours, degenerative changes and fractures) may lead to false-positive results.[71] With high accuracy levels, labeled white cell scans (In-WBC) are particularly helpful in detecting and following up on cases involving osteomyelitis. Accordingly, a combination of In-WBC and Tc-MDP has been shown to increase specificity and sensitivity for the diagnosis of deformity complicated by an ulcer in Charcot foot.[71,72] The role of FDG-PET and FDG-PET/CT in the diagnosis of acute CN remains a matter of ongoing investigation, with promising results.[75,76]

Surgical treatment

Primary treatment of the Charcot foot is widely recognized as nonsurgical and is frequently done using off-loading methods such as total contact casting and various bracing and therapeutic footwear as a vital part of CN's long-term management.[77] Nonetheless, some cases of Charcot foot ultimately require operation due to the resulting instability of the foot.

With the improvements in surgical corrective techniques and instruments, reconstructive procedures beyond the acute phase have recently gained popularity.[3] However, because of the increased likelihood of complications associated with poor bone quality, such as hardware failure, pseudarthrosis, delayed unions or nonunions, in addition to potential wound-site complications and infection, surgery in the acute phase of CN has been, and is still, a controversial subject. Moreover, in the modern management of CN, operative intervention at the acute phase is currently an under-researched issue. However, little evidence is available so far to recommend this new surgical concept.[3,78]

To obtain a successful arthrodesis in the Charcot foot, superconstruct techniques have been developed over the past decades.[79] The concept of a superconstruct consists of four factors: fusion beyond the injury zone, bone resection to permit reduction with limited tension on the soft-tissue envelope, the use of the strongest implants and device positioning that maximizes the mechanical function. Locking-plate, axial screw-fixation and plantar-plating technologies are well-defined examples of the superconstruct concept.[80]

In the literature, relatively little is understood regarding the role of surgical interventions in the CN, and no consensus exists regarding the appropriate timing or surgical method. The surgical techniques described in the literature include simple exostectomy, open reduction and internal fixation of neuropathic fractures, external fixation, arthrodesis, Achilles tendon lengthening and, eventually, amputation.[80]

Simple exostectomy of the midfoot

Symptomatic bony prominences are most likely to develop in patients with primary midfoot involvement, and simple exostectomy can be an effective procedure for plantar ulceration because it has less morbidity and quicker ulcer healing than a more invasive reconstructive procedure such as arthrodesis.[81] Furthermore, a recent systemic review indicated that a simple exostectomy has been performed with favourable results for midfoot Charcot deformities and their associated ulcerations.[82] To our knowledge, despite being an older procedure, simple exostectomy keeps its adjunctive role in preventing the onset or recurrence of ulceration in the current management of Charcot foot.

Reconstructive procedures of the midfoot

Miscellaneous internal and external fixation devices have been employed to correct midfoot deformities; however, surgeons have often been confronted with various complications, including nonunion, dehiscence and implant failure. The midfoot fusion bolt is a current treatment device that beams the longitudinal columns of the foot, and it was developed to offer resistance to both tensile and compressive forces.[83] In the past, the concept of 'beaming the longitudinal columns of the foot' was performed previously with cannulated screws, but cannulated screws are weak and cannot withstand extensive forces. On the other hand, the midfoot fusion bolt can confer more stability than other fixation methods in these challenging cases.[84]

A recent systematic review focusing on the current surgical interventions for CN of the midfoot referred to the intramedullary medial column bolt and multilevel external fixation as the most commonly used surgical interventions, highlighting that despite their widespread use, clinical indications to determine the use of these



Fig. 1 Radiographs show a severe case of hindfoot CN



Fig. 2 Radiographs display a successul treatment with pantalar arthrodesis using a retrograde intramedullary nail

techniques are not entirely independent from each other. Therefore, each procedure could be preferred when correcting osseous instability of the midfoot.[85]

Hindfoot and ankle procedures

Many authors have highlighted the salvage role of hindfoot arthrodesis in non-braceable, severe ankle and hindfoot deformities in patients with CN.[86-90] When the deformity involves only the subtalar joint or transverse tarsal joints, a triple arthrodesis can be performed. However, when the deformity affects the body of the talus and/or ankle, this generally requires a tibio-talocalcaneal or pantalar arthrodesis. Various methods, comprising intramedullary nailing,[86,88] crossed compression screws,[91] blade-plate[89] and external fixation,[92] have been employed for hindfoot arthrodesis. Nonetheless, with the increasing popularity and advantage of load-sharing, retrograde intramedullary nailing has been a universal method of yielding stability and generating a plantigrade, stable foot for CN.[86,88]

This study's senior author (OK) believes that hindfoot arthrodesis with a retrograde intramedullary nail for patients with diabetic CN is a useful technique in achieving fusion, limb salvage, a significant amelioration of quality of life and avoidance of postoperative complications, with preoperative modest glycaemic regulation and an ulcer-free foot approach (Figs 1 and 2).

Achilles tendon contracture has been attributed to the collapse of the midfoot in Charcot arthropathy, owing to lack of sufficient dorsiflexion of the foot.[93] The Achilles tendon lengthening is performed to reduce the loading at the midfoot and forefoot by altering its strength; therefore, much more dorsiflexion is available. Many surgical procedures have been performed with a combination of Achilles tendon lengthening or gastrocnemius muscle release.[94] The effectiveness of this procedure has been confirmed by several studies.[93] According to a systemic review, Achilles tendon lengthening remains a popular method in the management of Charcot foot.[95]

Medical treatment

Recent advances in the understanding of the pathophysiology of acute CN have opened new pharmaceutical perspectives. Several studies have investigated the role of bisphosphonate in the treatment of acute CN;[96,97]

however, there is currently no compelling evidence to support the use of bisphosphonate in the medical management of CN.[96] Additionally, it has recently been discovered that the osteoclastogenic cytokine receptor activator of nuclear factor-κβ ligand (RANKL) leads to increased osteoclastic activity in acute CN,[98] and a recent *in vitro* study demonstrated that the pro-inflammatory cytokine tumour necrosis factor alpha (TNF-α) regulates this osteoclastic resorption mediated by RANKL.[99] Accordingly, a better understanding of the role of osteoclasts and pro-inflammatory cytokines in the pathogenesis of acute CN has proposed the likely benefits of targeting inflammatory mediators, such as interleukin 1β blockers, RANKL inhibitors and TNF-α inhibitors.[82,97] Hopefully, these improvements will allow us to use these drugs for patients with CN.

Conclusions

In recent years, although commendable effort has been expended in the diagnosis and treatment of the diabetic foot, it remains a major public health problem. Therefore, primary prevention should be the main strategy for reducing the burden of the diabetic foot, and further diabetes-specific educational programmes are needed. Despite significant medical and surgical improvements, more research is required to define optimal treatment approaches for clinical practice. Hopefully, much more effort in the future will allow us to better understand the pathogenesis of the diabetic foot and more effectively employ newer technologies for patients with diabetic foot problems.

AUTHOR INFORMATION

[1]Department of Orthopaedics and Traumatology, İstanbul University, Istanbul Faculty of Medicine, Turkey.
[2]Department of Underwater and Hyperbaric Medicine, İstanbul University, Istanbul Faculty of Medicine, Turkey.

Correspondence should be sent to: O. Kılıçoğlu, Istanbul University, Istanbul Faculty of Medicine, Millet Cad. 118, Istanbul 34093, Turkey.
Email: onder.kilicoglu@gmail.com

ICMJE CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

LICENCE

© 2018 The author(s)
This article is distributed under the terms of the Creative Commons Attribution-Non Commercial 4.0 International (CC BY-NC 4.0) licence (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed.

REFERENCES

1. **van Netten JJ, Baba M, Lazzarini PA.** Epidemiology of diabetic foot disease and diabetes-related lower-extremity amputation in Australia: a systematic review protocol. *Syst Rev* 2017;6:101.

2. **Baltzis D, Eleftheriadou I, Veves A.** Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Adv Ther* 2014;31:817-836.

3. **Shen W, Wukich D.** Orthopaedic surgery and the diabetic Charcot foot. *Med Clin North Am* 2013;97:873-882.

4. **Centers for Disease Control and Prevention.** *National diabetes statistics report, 2017*. Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services; 2017. https://www.cdc.gov/diabetes/data/statistics/statistics-report.html

5. **Armstrong DG, Boulton AJM, Bus SA.** Diabetic Foot Ulcers and Their Recurrence. *N Engl J Med* 2017;376:2367-2375.

6. **Inzucchi SE, Bergenstal RM, Buse JB, et al.** Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2015;58:429-442.

7. **Lavery LA, La Fontaine J, Kim PJ.** Preventing the first or recurrent ulcers. *Med Clin North Am* 2013;97:807-820.

8. **van Netten JJ, van Baal JG, Liu C, van Der Heijden F, Bus SA.** *Infrared thermal imaging for automated detection of diabetic foot complications*. Los Angeles, CA: SAGE Publications Sage CA, 2013.

9. **Yudovsky D, Nouvong A, Schomacker K, Pilon L.** Assessing diabetic foot ulcer development risk with hyperspectral tissue oximetry. *J Biomed Optics* 2011;16:026009-09-8.

10. **Clokie M, Greenway AL, Harding K, et al.** New horizons in the understanding of the causes and management of diabetic foot disease: report from the 2017 Diabetes UK Annual Professional Conference Symposium. *Diabet Med* 2017;34:305-315.

11. **Andrews KL, Houdek MT, Kiemele LJ.** Wound management of chronic diabetic foot ulcers: from the basics to regenerative medicine. *Prosthet Orthot Int* 2015;39:29-39.

12. **Martín Noguerol T, Luna Alcalá A, Beltrán LS, et al.** Advanced MR imaging techniques for differentiation of neuropathic arthropathy and osteomyelitis in the diabetic foot. *Radiographics* 2017;37:1161-1180.

13. **Glaudemans AW, Uçkay I, Lipsky BA.** Challenges in diagnosing infection in the diabetic foot. *Diabet Med* 2015;32:748-759.

14. **Del Grande F, Subhawong T, Flammang A, Fayad LM.** Chemical shift imaging at 3 Tesla: effect of echo time on assessing bone marrow abnormalities. *Skeletal Radiol* 2014;43:1139-1147.

15. **Markakis K, Bowling FL, Boulton AJ.** The diabetic foot in 2015: an overview. *Diabetes Metab Res Rev* 2016;32(suppl 1):169-178.

16. **Lauri C, Tamminga M, Glaudemans AWJM, et al.** Detection of osteomyelitis in the diabetic foot by imaging techniques: a systematic review and meta-analysis comparing MRI, white blood cell scintigraphy, and FDG-PET. *Diabetes Care* 2017;40:1111-1120.

17. **Treglia G, Sadeghi R, Annunziata S, et al.** Diagnostic performance of Fluorine-18-Fluorodeoxyglucose positron emission tomography for the diagnosis of osteomyelitis related to diabetic foot: a systematic review and a meta-analysis. *Foot* 2013;23:140-148.

18. Kagna O, Srour S, Melamed E, Militianu D, Keidar Z. FDG PET/CT imaging in the diagnosis of osteomyelitis in the diabetic foot. *Eur J Nucl Med Mol Imaging* 2012;39:1545-1550.

19. Matthews R, Brunetti V, Martin B, Franceschi D. PET-MRI in diagnosing pedal osteomyelitis in diabetic patients. *J Nucl Med* 2015;56:307.

20. Lipsky BA, Aragón-Sánchez J, Diggle M, et al. IWGDF guidance on the diagnosis and management of foot infections in persons with diabetes. *Diabetes Metab Res Rev* 2016;32(suppl 1):45-74.

21. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections. *Clin Infect Dis* 2012;54:e132-e173.

22. Barwell ND, Devers MC, Kennon B, et al. Diabetic foot infection: antibiotic therapy and good practice recommendations. *Int J Clin Pract* 2017;71:e13006.

23. Elraiyah T, Prutsky G, Domecq JP, et al. A systematic review and meta-analysis of off-loading methods for diabetic foot ulcers. *J Vascular Surg* 2016;63:59S-68S. e2.

24. Mohammedi K, Potier L, François M, et al. The evaluation of off-loading using a new removable oRTHOsis in DIABetic foot (ORTHODIAB) randomized controlled trial: study design and rational. *J Foot Ankle Res* 2016;9:34.

25. Burns J, Begg L. Optimizing the offloading properties of the total contact cast for plantar foot ulceration. *Diabet Med* 2011;28:179-185.

26. Götz J, Lange M, Dullien S, et al. Off-loading strategies in diabetic foot syndrome-evaluation of different devices. *Int Orthop* 2017;41:239-246.

27. Nagel A, Rosenbaum D. Vacuum cushioned removable cast walkers reduce foot loading in patients with diabetes mellitus. *Gait Posture* 2009;30:11-15.

28. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *J Vasc Surg* 2010;52(suppl):37S-43S.

29. Morona JK, Buckley ES, Jones S, Reddin EA, Merlin TL. Comparison of the clinical effectiveness of different off-loading devices for the treatment of neuropathic foot ulcers in patients with diabetes: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2013;29:183-193.

30. Ha Van G, Siney H, Hartmann-Heurtier A, et al. Nonremovable, windowed, fiberglass cast boot in the treatment of diabetic plantar ulcers: efficacy, safety, and compliance. *Diabetes Care* 2003;26:2848-2852.

31. Caravaggi C, Faglia E, De Giglio R, et al. Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study. *Diabetes Care* 2000;23:1746-1751.

32. Armstrong DG, Nguyen HC, Lavery LA, et al. Off-loading the diabetic foot wound: a randomized clinical trial. *Diabetes Care* 2001;24:1019-1022.

33. Guldemond NA, Leffers P, Schaper NC, et al. The effects of insole configurations on forefoot plantar pressure and walking convenience in diabetic patients with neuropathic feet. *Clin Biomech (Bristol, Avon)* 2007;22:81-87.

34. Cavanagh PR, Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. *Plast Reconstr Surg* 2011;127(suppl 1):248S-256S.

35. Tecilazich F, Dinh TL, Veves A. Emerging drugs for the treatment of diabetic ulcers. *Expert Opin Emerg Drugs* 2013;18:207-217.

36. Cazander G, van Veen KE, Bouwman LH, Bernards AT, Jukema GN. The influence of maggot excretions on PAO1 biofilm formation on different biomaterials. *Clin Orthop Relat Res* 2009;467:536-545.

37. Armstrong DG, Salas P, Short B, et al. Maggot therapy in "lower-extremity hospice" wound care: fewer amputations and more antibiotic-free days. *J Am Podiatr Med Assoc* 2005;95:254-257.

38. Sun X, Chen J, Zhang J, et al. Maggot debridement therapy promotes diabetic foot wound healing by up-regulating endothelial cell activity. *J Diabetes Complications* 2016;30:318-322.

39. Caputo WJ, Beggs DJ, DeFede JL, Simm L, Dharma H. A prospective randomised controlled clinical trial comparing hydrosurgery debridement with conventional surgical debridement in lower extremity ulcers. *Int Wound J* 2008;5:288-294.

40. Tallis A, Motley TA, Wunderlich RP, et al. Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study. *Clin Ther* 2013;35:1805-1820.

41. Richmond NA, Vivas AC, Kirsner RS. Topical and biologic therapies for diabetic foot ulcers. *Med Clin North Am* 2013;97:883-898.

42. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: a review. *J Pharm Sci* 2008;97:2892-2923.

43. Moura LI, Dias AM, Carvalho E, de Sousa HC. Recent advances on the development of wound dressings for diabetic foot ulcer treatment-a review. *Acta Biomater* 2013;9:7093-7114.

44. Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care* 1998;21:822-827.

45. Niezgoda JA, Van Gils CC, Frykberg RG, Hodde JP, Group ODUS. Randomized clinical trial comparing OASIS Wound Matrix to Regranex Gel for diabetic ulcers. *Adv Skin Wound Care* 2005;18(5 Pt 1):258-266.

46. Aktaş Ş, Baktıroğlu S, Demir L, et al. Intralesional application of epidermal growth factor in limb-threatening ischemic diabetic foot ulcers. *Acta Orthop Traumatol Turc* 2016;50:277-283.

47. Löndahl M. Hyperbaric oxygen therapy as adjunctive treatment of diabetic foot ulcers. *Med Clin North Am* 2013;97:957-980.

48. Löndahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care* 2010;33:998-1003.

49. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2004;2:CD004123.

50. Liu R, Li L, Yang M, Boden G, Yang G. Systematic review of the effectiveness of hyperbaric oxygenation therapy in the management of chronic diabetic foot ulcers. *Mayo Clin Proc* 2013;88:166-175.

51. Huang ET, Mansouri J, Murad MH, et al. A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers. *Undersea Hyperb Med* 2015;42:205-247.

52. Armstrong DG, Lavery LA Consortium DFS, Diabetic Foot Study Consortium. Negative pressure wound therapy after partial diabetic foot amputation: a multicentre, randomised controlled trial. *Lancet* 2005;366:1704-1710.

53. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 2008;31:631-636.

54. Meloni M, Izzo V, Vainieri E, et al. Management of negative pressure wound therapy in the treatment of diabetic foot ulcers. *World J Orthop* 2015;6:387-393.

55. Game FL, Hinchliffe RJ, Apelqvist J, et al. A systematic review of interventions to enhance the healing of chronic ulcers of the foot in diabetes. *Diabetes Metab Res Rev* 2012;28(suppl 1):119-141.

56. Isaac AL, Armstrong DG. Negative pressure wound therapy and other new therapies for diabetic foot ulceration: the current state of play. *Med Clin North Am* 2013;97:899-909.

57. Liu S, He CZ, Cai YT, et al. Evaluation of negative-pressure wound therapy for patients with diabetic foot ulcers: systematic review and meta-analysis. *Ther Clin Risk Manag* 2017;13:533-544.

58. Garwood CS, Steinberg JS. What's new in wound treatment: a critical appraisal. *Diabetes Metab Res Rev* 2016;32(suppl 1):268-274.

59. Kim PJ, Attinger CE, Steinberg JS, et al. The impact of negative-pressure wound therapy with instillation compared with standard negative-pressure wound therapy: a retrospective, historical, cohort, controlled study. *Plast Reconstr Surg* 2014;133:709-716.

60. Lessing C, Slack P, Hong KZ, Kilpadi D, McNulty A. negative pressure wound therapy with controlled saline instillation (NPWTi): dressing properties and granulation response in vivo. *Wounds* 2011;23:309-319.

61. Lew E, Nicolosi N, McKee P. Evaluation of hallux interphalangeal joint arthroplasty compared with nonoperative treatment of recalcitrant hallux ulceration. *J Foot Ankle Surg* 2015;54:541-548.

62. Tamir E, Tamir J, Beer Y, Kosashvili Y, Finestone AS. Resection arthroplasty for resistant ulcers underlying the hallux in insensate diabetics. *Foot Ankle Int* 2015;36:969-975.

63. Armstrong DG, Lavery LA, Vazquez JR, et al. Clinical efficacy of the first metatarsophalangeal joint arthroplasty as a curative procedure for hallux interphalangeal joint wounds in patients with diabetes. *Diabetes Care* 2003;26:3284-3287.

64. Giurini JM. Surgical treatment of the ulcerated foot. In: Veves A, Giurini JM, LoGerfo FW, eds. *The diabetic foot*. Totawa, NJ: Humana Press, 2002:293-315.

65. Rosenblum B, Giurini J, Chrzan J, Habershaw G. Preventing loss of the great toe with the hallux interphalangeal joint arthroplasty. *J Foot Ankle Surg* 1994;33:557-560.

66. Tamir E, Finestone AS, Avisar E, Agar G. Mini-Invasive floating metatarsal osteotomy for resistant or recurrent neuropathic plantar metatarsal head ulcers. *J Orthop Surg* 2016;11:78.

67. Kalantar Motamedi A, Ansari M. Comparison of metatarsal head resection versus conservative care in treatment of neuropathic diabetic foot ulcers. *J Foot Ankle Surg* 2017;56:428-433.

68. Petrov O, Pfeifer M, Flood M, Chagares W, Daniele C. Recurrent plantar ulceration following pan metatarsal head resection. *J Foot Ankle Surg* 1996;35:573-577.

69. Patel VG, Wieman TJ. Effect of metatarsal head resection for diabetic foot ulcers on the dynamic plantar pressure distribution. *Am J Surg* 1994;167:297-301.

70. Griffiths GD, Wieman TJ. Metatarsal head resection for diabetic foot ulcers. *Arch Surg* 1990;125:832-835.

71. Ergen FB, Sanverdi SE, Oznur A. Charcot foot in diabetes and an update on imaging. *Diabet Foot Ankle* 2013;4:21884.

72. La Fontaine J, Lavery L, Jude E. Current concepts of Charcot foot in diabetic patients. *Foot* 2016;26:7-14.

73. Trieb K. The Charcot foot: pathophysiology, diagnosis and classification. *Bone Joint J* 2016;98-B:1155-1159.

74. Chantelau EA, Grützner G. Is the Eichenholtz classification still valid for the diabetic Charcot foot? *Swiss Med Wkly* 2014;144:w13948.

75. Pickwell KM, van Kroonenburgh MJ, Weijers RE, et al. F-18 FDG PET/CT scanning in Charcot disease: a brief report. *Clin Nucl Med* 2011;36:8-10.

76. Höpfner S, Krolak C, Kessler S, et al. Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. *Foot Ankle Int* 2004;25:890-895.

77. Ögüt T, Yontar NS. Surgical treatment options for the diabetic Charcot hindfoot and ankle deformity. *Clin Podiatr Med Surg* 2017;34:53-67.

78. Schade VL, Andersen CA. A literature-based guide to the conservative and surgical management of the acute Charcot foot and ankle. *Diabet Foot Ankle* 2015;6:26627.

79. Pinzur MS, Sammarco VJ, Wukich DK. Charcot foot: a surgical algorithm. *Instr Course Lect* 2012;61:423-438.

80. Lowery NJ, Woods JB, Armstrong DG, Wukich DK. Surgical management of Charcot neuroarthropathy of the foot and ankle: a systematic review. *Foot Ankle Int* 2012;33:113-121.

81. Brodsky JW, Rouse AM. Exostectomy for symptomatic bony prominences in diabetic charcot feet. *Clin Orthop Relat Res* 1993;296:21-26.

82. Wukich DK, Sung W. Charcot arthropathy of the foot and ankle: modern concepts and management review. *J Diabetes Complications* 2009;23:409-426.

83. Grant WP, Garcia-Lavin S, Sabo R. Beaming the columns for Charcot diabetic foot reconstruction: a retrospective analysis. *J Foot Ankle Surg* 2011;50:182-189.

84. Cullen BD, Weinraub GM, Van Gompel G. Early results with use of the midfoot fusion bolt in Charcot arthropathy. *J Foot Ankle Surg* 2013;52:235-238.

85. Shazadeh Safavi P, Jupiter DC, Panchbhavi V. A systematic review of current surgical interventions for Charcot neuroarthropathy of the midfoot. *J Foot Ankle Surg* 2017;56:1249-1252.

86. Pinzur MS, Kelikian A. Charcot ankle fusion with a retrograde locked intramedullary nail. *Foot Ankle Int* 1997;18:699-704.

87. Bennett GL, Cameron B, Njus G, Saunders M, Kay DB. Tibiotalocalcaneal arthrodesis: a biomechanical assessment of stability. *Foot Ankle Int* 2005;26:530-536.

88. Pinzur MS, Noonan T. Ankle arthrodesis with a retrograde femoral nail for Charcot ankle arthropathy. *Foot Ankle Int* 2005;26:545-549.

89. Alvarez RG, Barbour TM, Perkins TD. Tibiocalcaneal arthrodesis for nonbraceable neuropathic ankle deformity. *Foot Ankle Int* 1994;15:354-359.

90. Pelton K, Hofer JK, Thordarson DB. Tibiotalocalcaneal arthrodesis using a dynamically locked retrograde intramedullary nail. *Foot Ankle Int* 2006;27:759-763.

91. Papa JA, Myerson MS. Pantalar and tibiotalocalcaneal arthrodesis for post-traumatic osteoarthrosis of the ankle and hindfoot. *J Bone Joint Surg [Am]* 1992;74-A:1042-1049.

92. Russotti GM, Johnson KA, Cass JR. Tibiotalocalcaneal arthrodesis for arthritis and deformity of the hind part of the foot. *J Bone Joint Surg [Am]* 1988;70-A:1304-1307.

93. Mueller MJ, Sinacore DR, Hastings MK, et al. Impact of achilles tendon lengthening on functional limitations and perceived disability in people with a neuropathic plantar ulcer. *Diabetes Care* 2004;27:1559-1564.

94. Burns PR, Wukich DK. Surgical reconstruction of the Charcot rearfoot and ankle. *Clin Podiatr Med Surg* 2008;25:95-120, vii-viii.

95. Wukich DK, Raspovic KM, Hobizal KB, Sadoskas D. Surgical management of Charcot neuroarthropathy of the ankle and hindfoot in patients with diabetes. *Diabetes Metab Res Rev* 2016;32(suppl 1):292-296.

96. Richard J-L, Almasri M, Schuldiner S. Treatment of acute Charcot foot with bisphosphonates: a systematic review of the literature. *Diabetologia* 2012;55:1258-1264.

97. Mascarenhas JV, Jude EB. Pathogenesis and medical management of diabetic Charcot neuroarthropathy. *Med Clin North Am* 2013;97:857-872.

98. Pandolfi F, Pitocco D, Cianci R, Mancini L, Ghirlanda G. Increased osteoclastic activity in acute Charcot's osteoarthopathy: the role of receptor activator of nuclear factor-kappa B ligand. *Eur Rev Med Pharmacol Sci* 2010;14:69-70.

99. Petrova NL, Petrov PK, Edmonds ME, Shanahan CM. Inhibition of TNF-α reverses the pathological resorption pit profile of osteoclasts from patients with acute Charcot osteoarthropathy. *J Diabetes Res* 2015;10:1-10.