Podiatric Interventions and Phototherapy within the Management of Chronic Diabetic Foot Ulceration: A Review to Compare the Average Healing Time

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Abstract

Diabetic foot ulceration is a serious complication of Diabetes Mellitus and a most important risk factor for lower limb amputations. Diabetes is characterized by chronic hyperglycemia related to the resistance of target cells to the action of insulin; which leads to degenerative disorders caused by macroangiopathy, microangiopathy and neuropathy. These factors favor the occurrence of lower limb ulcers and so delay their healing. The slow healing rate of chronic diabetic foot ulceration has a negative impact on the patients' quality of life. Thus there is a need for the development of new treatment modalities to improve healing rate and outcome of diabetic ulcerations.

The management and treatment of chronic diabetic ulcerations can undergo extended periods due to the lack of response to treatment or the general nature of the ulcer. Current podiatric protocols for the management of chronic ulcers affecting the lower limb involves a dynamic approach which includes mechanical debridement of granulation and dead tissue, antibiotics to treat infections, alteration of footwear, mechanical off-loading using total contact casts and orthotic devices, as well as foot care education.

Phototherapy is an alternative treatment modality which is under investigation for the management of chronic diabetic foot ulceration. It has been found to significantly increase the healing rate of ulcers when used in combination with other conventional treatments. The continuous management, on-going surveillance and monitoring of chronic diabetic foot ulcers with various combination therapies which include phototherapy may increase a patients healing time as so improve a patients quality of life and physical activities.

The aim of this review is to compare the average healing time of diabetic foot ulcers when treated with standard podiatric treatment protocols or when treated in combination with phototherapy in terms of diabetic foot ulcer management.

Key words: diabetes, foot ulcers, wound healing, laser, phototherapy, offloading, wound debridement.

1. Introduction

Diabetes mellitus is a common metabolic condition that is increasing in prevalence worldwide. The estimates by the International Diabetes Federation, in 2009, suggested that the number of adults with diabetes in the world will expand by 54%, from 284.6 million in 2010 to 438.4 million in 2030. In Sub-Saharan Africa, the projected growth was 98% with the prevalence of type 2 diabetes rising quickly.[1] In 2003, a prevalence figure of 3.4% for 24 million South Africans between the ages of 20 and 79 was noted, however in 2015, there were 2.28 million (7.0%) adult diabetes cases noted in South Africa. [2] This drastic increase presents a substantial public health and socioeconomic burden to this country in the face of scarce resources.[3]

Type II diabetes is characterized by chronic hyperglycemia related to the resistance of target cells to the action of insulin; which leads to degenerative disorders caused by macroangiopathy, microangiopathy and neuropathy.[4,5] These factors favor the occurrence of the disease complications such as lower limb ulcers and delay their healing.[5,6] Diabetic foot ulcers (DFUs) are estimated to occur in 15% of all patients with diabetes and precede 84% of all diabetes-related lower-leg amputations. These ulcers are a leading cause of hospital admissions for people with diabetes in the developed world and are a major morbidity that is associated with diabetes, which often leads to pain, suffering, and an overall poor quality of life for a patient.[7]

1.1 Classification of DFUs

Diabetic foot ulcers can result from multiple factors and are thus classified according to the relative contribution of late diabetic complications of peripheral neuropathy and vascular diseases.[8] Most diabetic lower limb ulcers occur in the presence of peripheral neuropathy, foot deformity and trauma; and these are called neuropathic ulcers. Peripheral vascular disease, resulting into neuroischaemic ulcers and infection are believed to be the complicating factors that prevent or delay ulcer healing.[9] Literature suggests that the nature of chronic diabetic foot ulcerations disables the normal stages of healing, which in turn induces a state of pathological inflammation. This then results in the overall healing process becoming incomplete or delayed.[10]

Diabetic ulcers are also classified according to their severity or in grades using the universally accepted validated tools such as Wagner and University of Texas classifications. Wagner's classification grade 0– 5 divides ulcers from superficial or deep ulcer up to gangrene of the foot. The University of Texas classification stage 1-5 adds if there's presence of infection, ischaemia, or both infection and ischaemia together.[11,12] These classifications are important as we need to adequately describe the ulcer that we treat in order to review patients' outcome.[11]

1.2. General diabetic foot ulcer management

The management of diabetic foot often requires a holistic approach which involves a focused multidisciplinary team consisting of a wound nurse, a podiatrist, vascular surgeons, endocrinologists and other allied health care professionals.[6,9,13-16] However, the overall wound management of chronic DFUs can undergo extended periods without any healing response due to multiple complex pathophysiological mechanisms which are involved in patients suffering from diabetes. This can involves hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end-products.[10,17] Peripheral neuropathy can also contribute to the development and impaired healing of DFUs. Neuropeptides such as nerve growth factor, substance P and calcitonin gene-related peptide; and sensory nerves are needed to induce wound healing, however their low levels in diabetic patients have been associated with the development of DFUs.[10] Despite all these challenges, there is an increasing cause for optimism in the treatment of diabetic ulcers. This is due to the enhanced understanding and correction of these pathogenic factors, combined with stricter adherence to standards of care and with technological breakthroughs in biological agents, and this is giving new hope to the problem of impaired healing of diabetic ulcers.[18]

Key Message: Patients with diabetes mellitus develop foot problems, such as neuropathy, infections, ulcers and vascular diseases; which require an integrated multiple disciplinary approach to address all these problems. Failure to adequately treat and resolve the above mentioned problems can be due to the multiple complex pathophysiological mechanisms involved with diabetes a multisystem disease.

2. Podiatric diabetic foot ulcer management

A podiatrists approach to the treatment of diabetic foot ulcerations consists of an overall structure and function assessment of the lower limb by performing biomechanical evaluations, gait and plantar pressure analysis. It is for this reason that, podiatric management and involvement can prevent diabetic ulcer recurrence in patients, through the utilization of various offloading techniques and diabetic patient foot education.[15]

Podiatrists also provide patients with local wound care, which involves debridement of necrotic tissue and callus, cleansing with suitable solutions, wound dressings, topical or oral antibiotics when infection is present, and revascularization.[9,13,14,15,19] This is the general standard of wound management that is implemented in diabetic ulcer wound care clinics and it involves a multidisciplinary team, as alluded to earlier.

Key Message: Podiatrists are trained professionals to assess and implement treatment for diabetic lower limb and foot problems including diabetic foot ulcers. Podiatrists manage and treat diabetic foot through wound debridement, appropriate wound cleansing and dressings, offloading, infection control and education.

2.1 Offloading

Offloading is an essential podiatrist's tool that is used in the healing of diabetic foot ulceration. Particularly in the cases where a patient has a plantar neuropathic ulcer (Figure 1), or for secondary prevention, in patients with healed ulceration, but have foot deformity.[9,19] Different offloading techniques are commonly used to protect a diabetic foot from excessive pressures and other forms of trauma that sometimes lead to diabetic ulceration or even worse, amputation. These can be grouped into casting techniques, footwear related techniques, surgical offloading techniques and other.[20] Offloading techniques used by Podiatrists, in South Africa and overseas, include felt padding, prescription orthotics and insoles, removable cast walkers and total contact casting (Fig. 2 to 5).[9,14,15]

Key Message: Offloading can be defined as a treatment modality where practitioners try to protect or reduce excessive pressures that can lead to ulceration or even amputation in the diabetic foot. Different offloading techniques can be implemented with varying results/success with some techniques better than others.

2.2 Footwear and orthotic devices in prevention of diabetic foot ulceration.

Therapeutic footwear in combination with custom-made orthotics devices (Fig. 2) are considered the primary means of protecting the foot from excessive plantar pressures during walking, thus reducing the incidence of ulceration. In a study by Mueller et al. (2006) investigating the effect of total contact cast inserts (TCIs) and metatarsal pads (MPs) on metatarsal peak pressures and pressure time integrals. It was found that the TCI and the MP caused a substantial and additive reduction of pressures (29% to 47%) under the metatarsal heads of feet by increasing the contact area of weight bearing forces when compared to wearing shoes alone. In addition, it was reported that the MP reduced the pressure at the metatarsal heads of feet by off-loading the soft tissues and bone structures proximal to the metatarsal heads (Mueller et al, 2006).[21]

The findings from Mueller et al. (2006) are similar to a study done by Tong and Ng (2010). Tong and Ng (2010) investigated the amount of pressure reduction that occurred in feet when using different types of padding and four insole materials that are commonly used in podiatry. In this study it was found that all four commonly used materials; Slow Recovery Poron (SRP), Poron, Poron+Plastazote Firm (PPF) and Poron+Plastazote Soft (PPS); were able to reduce pressure across the whole foot with PPF achieving the most significant result of 28% pressure reduction. The subjects in this study were also tested with a semi-compressed felt metatarsal pad (Fig. 3) with an aperture on the first metatarsophalangeal joint of both feet. The peak pressure in this area showed significant reduction of 37% compared to a 29% decrease when PPF was used alone.[22] Overall both studies noted that the human foot generally has an increased pressure at the periphery of the aperture site, which if not corrected can cause harmful skin breakdown and in the insensate feet of diabetic patients, this can sometimes lead to severe ulceration. In addition, the pressure responses varied in both studies, suggesting that pressure reduction in terms of using foot wear and orthotic devices is highly dependent upon the condition of the patient's feet, and the patients' health status, as well as the difference of metatarsal pad material used which includes its size and shape.

Although there are indications that therapeutic footwear may be effective in secondary prevention of DFUs; [8] according to some literature; there are no experimental studies which report on the role of therapeutic footwear in primary ulcer prevention compared to normal footwear. This conclusion only came about because one randomized control trial found no effect of therapeutic footwear in secondary prevention of ulcers.[8, 20] However more literature suggests that various designs of therapeutic footwear such as rocker bottom outsole and half-shoes can effectively offload at risk foot regions thus preventing ulcer formation or recurrence. [8]

Key Message: Therapeutic footwear and custom-made orthoses is generally utilized by podiatrists to prevent the secondary occurrence of DFU.

2.3 Total contact casting

Over the years, total contact casting (TCC), has been known to be more effective in the treatment of non-infected diabetic plantar neuropathic ulcers when compared to other removable offloading devices. Studies by Sambrook et al (2015), noted that TCC has shown to reduce plantar pressure by 84 to 94%, increase healing rates and treatment time of plantar ulcers.[23]

However, TCC is difficult and time consuming treatment for podiatrists to apply and generally there is a low patient tolerance, with number of side effects associated with its application. Thus most clinicians prefer to not utilize this technique and rather prescribe various other offloading techniques that are far easier to apply such as felt padding, removable cast walkers (RCW), therapeutic footwear and orthotic devices.[24] Studies performed by Fife et al. (2010) using real-world data from a large wound care registry found that only 6% of DFU patients received TCC.[25] Years later in their reflective analysis Fife et al (2014) found that in over 25,000 patients with diabetes, only 3.7% of eligible ulcers received TCC.[26] Currently there is no data about the use of TCC for the management of DFU in South Africa.

Alternative approaches of non-removable offloading devices which are far more effective have been developed in recent years, which are a substitute for the classic Plaster of Paris total contact casting use. Armstrong and colleagues (2005) performed a study to evaluate the effectiveness of a RCW (Fig. 4) and an “instant” total contact cast (iTCC) (Fig. 5) in the healing of neuropathic diabetic foot ulcerations. [27] Patients with foot ulcers that were cast using iTCC reported more a significant ulcer healing rates of 82.6% than when compared to patients that received RCW which was only 51.9%, over a 12 week period. Similarly within a study conducted by Faglia et al. (2010) over a 90 day period whereby the efficacy of RCW and a non-removable fiberglass off-bearing cast (TCC) were compared in DFU healing, it was reported that 73.9% of patients in the TCC group and 72.7% in the RCW group achieved complete healing.[28] Overall these studies show that whether the offloading device is removable or non-removable, it can be utilized effectively to redistribute pressure on the plantar aspect of the foot, however results are dependent on the patients compliance to constantly wear removable devices and not take them off.

Key Message: Total contact casting has been shown to be effective in redistributing pressure in the plantar aspect of the foot and so either prevents ulcers from re-occurring or promotes healing of current DFU.

2.4 Wound debridement

In wound healing clinics various types of debridement techniques can be used by podiatrists to treat DFU such as; surgical and sharp debridement, mechanical debridement, autolytic and enzymatic debridement, and larvae debridement.[29] Debridement is the foremost important step towards achieving chronic diabetic wound healing, as it transforms chronic wounds into acute wounds.[31] Unlike acute wounds; chronic diabetic ulcers seldom follow the normal pattern of repair due to various physiological factors such as hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end-products, which delay wound healing. [7,30] In addition, there is also sometimes the accumulation of non-viable tissue (calluses) and slough with excess exudate, which also encourages bacterial colonization (biofilm), promoting the risk of infection and so prevents healing.[30,32]

Sharp debridement (scalpel debridement) helps to breakdown bacterial colonies, thus reducing the bacterial load of an ulcer even in the absence of overt infection and so promotes the release of growth factors to aid the healing process.[32] When combined with standard or advanced therapies that are currently used in ulcer treatment, the net rate of healing is increased.[32] Williams and colleagues (2005), evaluated the effect of sharp debridement on the progression of recalcitrant chronic venous leg ulcers, this study concluded that sharp debridement was effective in stimulating healing of ulcers. This study was conducted over a 12 month period and already at 4 weeks post-debridement some positive results were first observed; ulcers showed a 6 cm^2 reduction within the mean ulcer surface area (MSA) versus a 1 cm^2 reduction in controls groups. However, it was noted that the reduction in the MSA between the study groups over the entire period was not statistically significant. Nevertheless, wounds after debridement alone are capable of regressing in 57% of the days between visits because there is balance shift favoring the biofilm, even though the rate of healing immediately after debridement is more rapid.[32]

It has been suggested that frequent debridement of DFU and chronic venous leg ulcer, as part of wound treatment, may increase wound healing rates and closure of the ulcer.[33] If debridement is done in a sequential fashion, it will avoid re-establishment of microbial biofilm growth and tissue devitalization which is responsible for delayed non-healing ulcers.[7,32] Wilcox and colleagues (2013), investigated the frequency of debridement and time to heal for different types of ulcers which included DFU and chronic venous ulcers. This study noted that the median time to heal after weekly or more frequent debridement for DFU was 21 days compared to 64 days when debridement frequency was in a range of every 1-2 weeks and 76 days when debridement was once every 2 weeks or more.[34]

Furthermore, in a study performed by Ahmad and colleagues, which assessed the efficacy of radical debridement and skin grafting in treating DFU compared with other conservative wound treatments (such as use of dressings, negative pressure wound therapy and hyperbaric oxygen); the results showed a 100% skin graft take in 80% of the patients on day 4 after surgery. Debridement in this study was performed three times a week, every second day, and the amount of granulation tissue was assessed before skin grafting. The mean healing time and hospital stay was lower in the skin graft group compared to the control group (4.0 ± 1.5 weeks vs 10.0 ± 1.0 weeks).[31] These findings suggest that aggressive and repeated debridement definitely does increase ulcer healing rates of chronic wounds.

Both offloading and debridement methods are regularly practised by podiatrists to promote the healing process of diabetic lower limb ulcers. Additionally, selecting the right type of wound dressing is also important to aid the healing process, and this is also dependant on the characteristics of the individual ulcer that is receiving treatment.[9,13,14,19] Debridement practises offer an opportunity for additional antibiotic interventions, which may be applied topically and / or systemically, as it temporarily disrupts biofilm defence colonies forcing microbes to become more susceptible to these intervention treatments, as well as the hosts immunity defenses.[32]

A summary of this clinical studies are presented in Table 1.

Key Message: Mechanical or sharp debridement is one of the essential treatment procedures in podiatry; with which chronic inflammation can be converted to acute inflammation; to promote DFU healing.

3. Phototherapy

Phototherapy is a therapeutic modality that involves the application of laser light, at a particular wavelength and at low intensities, to tissue to stimulate various biological processes.[16,36] Low level laser therapy (LLLT) is widely used to accelerate tissue repair in surgery, dentistry, dermatology, somatology, pain management and ulcer healing.[35] Unlike high intensity medical lasers which are used to cut and coagulate tissues, LLLT involves the use of medical lasers that operate at low intensities, which instead of causing damage rather promote healing.[38]

3.1 LLLT in wound healing promotion

The exact mechanism of action of LLLT is not completely understood, however in some *in vitro* studies; it has been noted that LLLT supplies direct biostimulative light energy to body cells.[39] For LLLT to be effective, the light must be absorbed by the targeted tissue.[37,38] Photon energy is absorbed by photo-acceptors or chromophores within cells. The main photo-acceptors in cells are cytochrome c oxidase which are found inside cell mitochondria.[36] When the mitochondrion absorbs photons it is stimulated to produce more energy-rich adenosine triphosphate (ATP), which in turn temporally increases the cell membrane permeability to absorb calcium ions, enhancing cellular activity and repair.[36] In this way, when absorbed photons induce cellular changes, tissue repair and healing is accelerated.[38] Since chronic ulcers such as diabetic ulcers do not follow the normal pathway of healing, phototherapy has been shown as a promising form of treatment to promote the ulcer healing process.[16]

Studies utilizing LLLT have shown LLLT to positively stimulate diabetic ulcer fibroblasts which result in promoted wound healing through increased viability, proliferation, ATP, growth factors, cytokines and nitric oxide stimulations, as well as decreased cellular damage and pro-inflammatory cytokines expression.[16,39,40] According to literature LLLT transforms fibroblasts into myofibroblasts which are essential for the development of granulation tissue and so promotes wound contraction.[37,38]

In a double-blinded, randomised, placebo-controlled experimental trial, Minatel et al. (2009) treated the chronic diabetic leg ulcers of 23 patients that were unresponsive to other forms of treatment. Thirteen ulcers were treated with phototherapy (combined 660 and 890 nm) twice a week until healed, or for a maximum period of three months. The rest were sham irradiated (10 ulcers). In the group of ulcers that were irradiated, 58.3% resolved completely, and 75% of the ulcers achieved 90-100% healing by day 90.[5] In a clinical study by Mokmeli and colleagues which determined the effect of local and intravenous LLLT for the healing of 74 diabetic foot ulcers; the results showed that 62.2% of the patients ulcers completely healed, 12.2% of the patients ulcers healed by more than half, and only 8.1% of patients ulcers healed less than half. However, 12.2% of the patients did not complete their treatment (which only consisted of 5 sessions of LLLT). Excluding, the wounds that were found to be in stage 5, more than 80% of each categorized stage were found to have been almost completely healed (by more than 50%), within a 2 month duration.[41]

In their study Kajagar and colleagues, compared diabetic ulcer healing in 68 patients. These patients were randomized into a LLLT plus conventional care group which was compared with conventional care alone. On the basis of the ulcer size, the duration of exposure was calculated to deliver 2–4 J/cm2 at 60mW, 5 KHz, daily for 15 days. The ulcer floor and edges were irradiated. A significant percentage of ulcer reduction in the LLLT group compared with conventional care alone was noted: 40.24 ± 6.30 mm^2 in study group and 11.87 ± 4.28 mm^2 in control group ($p < 0.001$, $Z = 7.08$).[46]

According to literature, acute inflammation is a vital stage in healing and for chronic ulcers this must be induced by debridement in order for the healing to progress. Mechanical or sharp debridement is one of the essential treatment procedures in podiatry with which chronic inflammation can be converted to acute inflammation.[14,15] Once acute inflammation has been achieved it should then be followed by LLLT to stimulate the proliferation of endothelial cells and fibroblasts, accelerating the development of granulation tissue over which epidermal cells migrate and so enhance wound healing.[38]

Despite the fact that LLLT is not an established treatment modality for ulceration in South Africa, a number of studies, case reports and clinical trials with humans have shown good ulcer healing outcomes using LLLT. Beckmann and colleagues conducted a systemic review on relevant literature, on LLLT for the treatment of diabetic foot ulcerations in 2014 and the review showed that several clinical studies have been published between 1998 and 2011 which suggest that LLLT promotes wound healing of diabetic ulceration.[12]

A summary of these clinical trials is presented in Table 2.

Key Message: Once acute inflammation has been induced in DFU by mechanical or sharp debridement the healing process can be further promoted by LLLT which stimulates cellular proliferation and wound healing.

3.2 Phototherapy bactericidal effects and cellular repair which enhances wound healing

Different wavelengths are used for different applications in phototherapy as they have different depths of penetration into human tissue. Visible red, infra-red and near infra-red have been demonstrated to penetrate deep tissues and are absorbed by cytochrome c oxidase, when compared to violet and blue spectrum lasers. [37, 44] When blue laser light is absorbed by flavins (flavoproteins) and porphyrins that lack transition metal coordinating, these molecules have been shown to have bactericidal effects, through the production of reactive free radicals which destroy bacteria.[36-39]

A number of studies have found that, at different wavelengths, blue light laser is bactericidal to different infectious organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Propionibacterium acne* and *Pseudomonas aeruginosa.* [16] Enwemeka et al. (2009) found that blue light (470 nm) was able to kill MRSA *in vitro*.[42] Lipovsky et al (2008) suggested that high-intensity visible light in the range of 400-1000 nm is bactericidal to *S. aureus, P. aeruginosa* and *Escherichia coli,* to name a few.[43] Irradiation at a wavelength of 408 nm was suggested by Ankri and colleagues (2010), in treating infected wounds to clear an infection and then followed by irradiation at 730 nm to speed up the healing process.[44]

According to literature red lasers, as well as blue laser improve perfusion by release of nitric oxide (NO) from nitrosyl complexes with haemoglobin, enhanced epithelialization, and elevated keratin-10 mRNA level.[39] It has been discovered that the activity of cytochrome c oxidase is inhibited by NO and this was initially seen as an imperfection.[35] However blue light also facilitates the recovery of mitochondria inhibited by NO gas by release of NO from mitochondrial complexes, so an improved wound healing via the NO pathway induces endothelial cell migration by activating growth factors, resulting in an increase keratin expression.[39] This is important and shows that a combination of red light laser and blue light laser can be used to treat infection to promote and enhance the healing process of infected DFU, since infection plays a role in delaying wound healing process.

Key Message: Phototherapy can also enhance wound healing of DFU, since it exhibits bactericidal effects as well as stimulates cellular repair and growth

4. Conclusion

Diabetic foot ulceration still proves to be a difficult condition to manage and so generally has a negative impact on a patients' quality of life. Identifying a treatment modality to help resolve this complication remains a difficult task in clinical practice. However a number of clinical - trials suggest LLLT as an alternative, promising treatment modality that when combined with other conventional treatments has shown potential in assisting and improving the healing rate of chronic diabetic ulcerations. It is therefore essential to recognize that with the use of LLLT in podiatry and other wound clinics, the treatment or management of chronic diabetic lower limb ulcerations can be reduced to an average of 19 sessions to achieve a complete recovery, [44] when compared to 40 sessions which utilize conventional treatments alone.[5,45] This might lead to decreased hospital admissions for people with diabetic ulcers and the substantial public health and socioeconomic burden to our country. Further investigations are however still necessary to be able to obtain conclusive evidence of Low Level Laser in treating diabetic foot ulcers in South Africa.

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7. References

1. Mbanya JCN, Motala AA, Sobngwi E, Assah FK, Enoru ST. Diabetes in sub-Saharan Africa. Lancet 2010; 375: 2254–66.
2. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation. 2015.
3. Rheeder P. Type 2 diabetes: the emerging epidemic. South African Family Practice 2006; 48 (10): 20.
4. Edmonds ME. Metabolic Disorders. In Lorimer D, Frowen P, O'Donnell M, Burrow G. Neal's Disorders of the Foot, 8th ed. Europe: Churchill Livingstone. 2010; 246-249.
5. Minatel DG, Frade MAC, Franca SC & Enwemeka CS. Phototherapy Promotes Healing of Chronic Diabetic Leg Ulcers that Failed to Respond to Other Therapies. Laser Surg Med. 2009; 41: 433-441.
6. Clarke A. Avoiding Foot Complications in Diabetes. CME. 2010; 28(4):181-185.
7. Brem H & Tomic-Canic M.Cellular and molecular basis of wound healing in diabetes J. Clin. Invest. 2007; 117:1219–1222.
8. Cavanagh PR & Bus SA. Off-loading the diabetic foot for ulcer prevention and healing. J Vasc Surg 2010; 52:37S-43S.
9. Bergin SM, Wraight PR & Burr JM. Australian Diabetes Foot Network: Management of Diabetes-Related Foot Ulceration – A Clinical Update. Medical Journal of Australia. 2012; 197: 226-229.
10. Guo S & DiPietro LA. Factors Affecting Wound Healing. J Dent Res. 2010; 89(3): 219-229.
11. Jain AKC. A New Classification of Diabetic Foot Complications: A Simple And Effective Teaching Tool. The Journal of Diabetic Foot Complications, 2012; 4(1):1-5
12. Beckmann KH, Meyer-Hamme G & Schröder S. Low Level Laser Therapy for the Treatment of Diabetic Foot Ulcers: A Critical Survey. Evidence-Based Complementary and Alternative Medicine 2014; 2014: 626127

13. Chadwick P, Edmonds M, McCardle J & Armstrong D. International Best Practice Guidelines: Wound Management in Diabetic Foot Ulcers. Wound International. 2013; 4:1-27.
14. Clarke EAM & Tsubane M. The Role of a Podiatrist in Managing the Diabetic Foot Ulcer. Wound Healing Southern Africa. 2008; 1 (1): 40-42.
15. Kim PJ, Attinger CE & Evans KK. Role of a Podiatrist in Diabetic Limb Salvage. J Vasc Surg. 2012; 56: 1168-1172.
16. Houreld NN. Shedding light on a New Treatment for Diabetic Wound Healing: A Review of Phototherapy. The Scientific Journal. 2014; 2014:39841
17. Petrova N & Edmonds M. Emerging drugs for diabetic foot ulcer. Expert Opinion on Emerging Drugs. 2006; 11: 4, 709-724.
18. Falanga V. Wound healing and its impairment in the diabetic foot. Lancet (2005) 366(9498):1736-1743
19. Clayton W & Elasy TA. A Review of Pathophysiology, Classification and Treatment of Foot Ulcers in Diabetic Patients. Clinical Diabetes. 2009; 27(2): 52-58.
20. Bus SA, Valk GD, van Deursen RW, et al. The effectiveness of footwear and offloading interventions to prevent and heal foot ulcers and reduce plantar pressure in diabetes: a systematic review. Diabetes Metab Res Rev 2008; 24: S162–S180.
21. Mueller MJ, Lott DJ, Hastings MK, Commean PK, Smith KE & Pilgram TK. Efficacy and Mechanism of Orthotic Devices to Unload Metatarsal Heads in People with Diabetes and a History of Plantar Ulcers. Phys Ther. 2006; 86(6): 833-842.
22. Tong JWK & Ng EYK. Preliminary investigation on the reduction of plantar loading pressure with different insole materials (SRP – Slow Recovery Poron®, P – Poron®, PPF –Poron® + Plastazote, firm and PPS – Poron® + Plastazote, soft). The Foot. 2010; 20: 1–6.
23. Sambrook E, Delpierre T & Bowen G. Advancing the gold standard in offloading the diabetic foot: Product evaluation. Wounds UK. EWMA SPECIAL. 2015: 48-56
24. Raspovic A & Landorf KB. A survey of offloading practices for diabetes-related plantar neuropathic foot ulcers. Journal of Foot and Ankle Research. 2014, 7:35
25. Fife CE; Carter MJ, Walker D. Why is it so hard to do the right thing in wound care? Wound Rep Reg. 2010; 18: 154–8
26. Fife CE, Carter MJ, Walker D et al. Diabetic foot ulcer offloading: the gap between evidence and practice. Data from the US Wound Registry. Adv Skin Wound Care 2014; 27: 310–6
27. Armstrong DG, Wu S, Lavery LA & Boulton AJM. Evaluation of Removable and Irremovable Cast Walkers in the Healing of Diabetic Foot Wounds: A Randomized Controlled Trial. Diabetes Care. 2005; 28(3): 551-554.
28. Faglia E, Curci V et al. Effectiveness of Removable Walker Cast versus Non-removable Fiberglass Off-Bearing Cast in the Healing of Diabetic Plantar Foot Ulcer: A randomized controlled trial. Diabetes Care. 2010; 33(7): 1419-1423.
29. Chadwick P, McCardle J, Cundell J & Towson M. The Principle of Debridement: The Diabetic Foot. Developing Scope of Practice for Podiatrists in the UK. Foot in Diabetes UK 2014; 2014: 2-20.

30. Williams D, Enoch S, Miller D, Harris K, Price P & Harding KG. Effect of sharp debridement using curette on recalcitrant non-healing venous leg ulcers: A concurrently controlled, prospective cohort study. Wound Rep Reg. 2005; 13: 131-137.
31. Ahmad I, Akhtar S, Masoodi Z. Role of early radical debridement and skin cover in diabetic foot ulceration. J Wound Care. 2012; 21(9):442-4, 446-7.
32. Wolcott RD, Kennedy JP & Dowd SE. Regular debridement is the main tool for maintaining a healthy wound bed in most chronic. J Wound Care. 2009; 18 (2): 55-56.
33. Cardinal M, Eisenbud DE, Armstrong DG, et al. Serial surgical debridement: a retrospective study on clinical outcomes in chronic lower extremity wounds. Wound Repair Regen. 2009; 17(3):306-11.
34. Wilcox JR, Carter MJ, Covington S. Frequency of debridement and time to heal: a retrospective cohort study of 312 744 wounds. JAMA Dermatology. 2013; 149(9):1050-8.
35. Dinh TL & Veves A. Treatment of diabetic ulcers. Dermatologic Therapy, Vol. 19, 2006, 348–355
36. Nteleki B & Houreld NN. The Use of Phototherapy in the Treatment of Diabetic Ulcers. JEMDSA. 2012; 17:3, 128-132.
37. Hamblin MR & Demidova TN. Mechanism of Low Level Laser Light Therapy. Proc. of SPIE. 2006; 6140(614001): 1605-7422.
38. Dyson M. Low Level Laser Therapy.2014. [article] Available from: http://www.softlasers.com/low-level-laser-therapy-article.php.
39. Houreld NN & Abrahamse H. Low Intensity Laser Irradiation Stimulates Wound Healing in Diabetic Wounded Fibroblast Cells (WS1). Diabetes Technol Ther. 2010; 12(12): 971-978
40. Mokmeli S, Daemi M, Shirazi ZA, Shirazi FA & Hajizadeh M. Evaluating the Efficiency of Low Level Laser Therapy (LLLT) in Combination With Intravenous Laser Therapy (IVL) on Diabetic Foot Ulcer, Added to Conventional Therapy. Lasers Med Sci. 2010; 1: 8-13.
41. Enwemeka CS, Williams D, Hollosi S & Yens D. Blue light photo-destroys methicillin resistant Staphy-lococcus aureus (MRSA) in vitro. Photomed Laser Surg. 2009; 27(2): 221-6.
42. Lipovsky A, Nitzan Y & Lubart R. A possible mechanism for visible light-induced wound healing. Lasers Surg Med. 2008; 40(7):509-14.
43. Ankri R, Lubart R & Taitelbaum H. Estimation of the optimal wavelengths for laser induced wound healing. Lasers Surg Med. 2010; 42(8):760-764.
44. Kazemi-Khoo N. Successful treatment of diabetic foot ulcers with low-level laser therapy. The Foot. 2006; 16:184-187.
45. Cavanagh PR, Lipsky BA, Bradbury AW and Botek G. Treatment for diabetic foot ulcers. Lancet. 2005; 366: 1725–35.
46. Kajagar BM, Godhi A S, Pandit A and Khatri S. Efficacy of low level laser therapy on wound healing in patients with chronic diabetic foot ulcers—a randomised control trial. *Indian Journal of Surgery*. 2012; 74, (5): 359–363.