PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATION IN PATIENTS WITH TYPE II DIABETES MELLITUS AND SKIN TYPE III AND V

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Declaration

I, Nozipho Sithole declare that this research dissertation is my own work. It is submitted for the Degree of Master in Podiatry at the University of Johannesburg. It has not been submitted for any other degree at this or other university.

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Signature

On the 20th day of November 2019

Research Output

Outputs for this Degree included the following conference presentations and publications:

Conferences (Local and International)

- 14-16 August 2015 – Podiatry Association of South Africa (PASA) 10th Biennial Congress –**Poster Presentation**

Publications

- Sithole N. and Abrahamse H. (2017) Podiatric interventions and phototherapy in the management of chronic diabetic foot ulceration: a review to compare the average healing time. *SA Journal of Diabetes & Vascular Disease* 14: 4–10
- Sithole N and Abrahamse H. (2020) Phototherapy and Podiatric intervention for the management of chronic lower limb ulcerations in patients with Type II Diabetes Mellitus and Skin Type III and V. *Diabetes Technology and Therapeutics.* In Draft.

Dedication

I dedicate this work to my family: my late Grandmother Ragel Violet Sithole, my Mother, my brothers and my nieces.

Executive Summary

Diabetic foot ulcerations (DFUs) remain a severe complication of Diabetes Mellitus (DM) and the most critical risk factor for lower limb amputations. Their management involves a dynamic approach which includes wound debridement, antibiotics to treat infections, mechanical off-loading, as well as foot care education. 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 who have diabetes. Despite all the challenges faced with managing or treating DFUs, several clinical trials suggest Low-Level Laser Therapy (LLLT), more recently termed Photobiomodulation (PBM), as an alternative promising treatment modality. Photobiomodulation has shown potential in improving the healing rate of chronic diabetic ulcerations when combined with other conventional treatments. However, until this study, there have been no studies, in South Africa, that have investigated the effects of Blue laser therapy in the management of DFUs and whether skin tone has a positive or negative impact in these patients.

This study used a prospective experimental design with a single-blinded control. The aim was to investigate the effect of phototherapy (Blue light) in treating Type II diabetic ulcerations in different skin tones (Fitzpatrick skin Type III and Type V).

The study had a sample of 19 participants with 22 lower limb ulcers fitting the inclusion criteria. These ulcers were randomly divided into the control (n=9) and experimental groups (n=13) with Skin Type III and V. Participants in the experimental group received treatment with PBM, where wound bed and wound edges were irradiated locally with 625 nm and 850nm (1200 mW output) for ~ 1 minutes, delivered twice a week for 12 weeks. Photographic images were recorded every week for both the control and experimental group to analyse the healing progress. The experimental group participants completed a pain intensity questionnaire after each treatment, to analyse the adverse effects of PBM.

Of the 22 ulcers, 68.2% were on male participants, and this was the same percentage for the Fitzpatrick Skin Type V. At week one, 59.1% ulcers presented as Wagner's Grade 1 ulcer compared to 40.9% that presented as Grade 2 ulcers in both groups.

The mean duration of this ulcers was 8.04 months, with most ulcers between 1-5 months duration in both groups [63.6% (n=14)]. Significant changes, in ulcer parameters and areas, were observed in both groups, over the period of 12 weeks. In the control group, 25% of ulcers showed complete healing or wound closure [p = 0.043], compared to 58.3% of ulcers in the Photobiomodulation (PBM) group by week 12 [p = 0.028]. All healed ulcers in the PBM group were in the Fitzpatrick Skin Type V participants. This can be due to the concentration of melanin and thus chromophores in the epidermis of these participants and their properties of absorbing light. The action of low-level laser therapy is based and dependent on the absorption of the light by tissues, which will generate modifications in cell metabolism and promote tissue regeneration.

Results of the Pain Intensity Questionnaire indicated that during and after irradiation mild to moderate pain, heat, erythema, pricking, and tingling sensations were experienced in this group. However, at the end of treatment (12 weeks), only 10% of the participants reported mild to moderate heat, pricking, and tingling sensations. None of the participants reported pain at the end of this study.

In conclusion, PBM improved the healing rate of chronic diabetic foot ulcers when used in combination with podiatric interventions. The findings suggest that PBM might reduce the frequency and chances of lower limb amputation, without any adverse effects on the darker skin tones. It has been proven that irradiating with a 200 mW, 810 nm laser induce three to six times more heat in dark skin than in the other skin tone groups. However, in this study 625 nm and 850nm (1200 mW output) applied for ~ 60 seconds, did not induce any severe thermal effect in the darker skin tone participants. These effects are however a function of wavelength, power, and pulse duration. Time exposure is a crucial point because the duration of exposure depends on the penetration depth and the type of diseases treated (DFUs). The findings of this study can therefore be used as a guideline to practically use PBM for DFUs in darker skin.

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CHAPTER 1: BACKGROUND

1.1 Introduction

Chronic diabetic foot ulcers are one of the common ulcers seen in hospital wound clinics and podiatry clinics. In both settings, these ulcers still prove challenging to manage and show delayed response to standard wound treatments.

1.2 Background

Diabetic foot ulcerations are a severe complication of DM and the most critical risk factor for lower limb amputations. Diabetes is a chronic hyperglycemic condition related to the resistance of target cells to the action of insulin; leads to degenerative disorders caused by macroangiopathy, microangiopathy and neuropathy (Edmonds, 2010; Minatel et al., 2009). All of these factors favour the occurrence of lower limb ulcers and delay their healing (Clarke, 2010; Minatel et al, 2009). These ulcers are a significant cause of hospital admissions for people with diabetes in the developed world and constitute considerable morbidity associated with diabetes, often leading to pain, suffering, and overall poor quality of life for the patient (Brem & Tomic-Canic, 2007). It is therefore clear that there is a need and important to introduce new treatment modalities for DFUs to improve the healing rate and outcome of diabetic ulcerations.

Despite all these challenges, there is an increasing cause for optimism in the treatment of diabetic ulcers. More research is being conducted to enhance understanding and correction of pathogenic factors of these ulcers, and it is giving new hope to the problem of impaired healing of diabetic ulcers. However, this is still ongoing and very limited in South Africa. More research still needs to be executed to establish the best treatment modality taking in consideration the differences in skin tones.

In vitro studies conducted by the University of Johannesburg Laser Research Center (Houreld & Abrahamse, 2007 & 2010), suggest that PBM positively stimulate wounded diabetic ulcer fibroblasts resulting in increased viability, proliferation, Adenosine Triphosphate (ATP), growth factors, cytokines and nitric oxide as well as a decrease in cellular damage and proinflammatory cytokines; all of which are important in wound healing. In this way, PBM induces cellular changes which are believed to accelerate tissue repair and relieve pain in vivo. A

further suggestion is that blue light has bactericidal effects compared to red light alone. Therefore this could suggest that a combination of the red and blue light laser can be used to treat chronic infected ulcers. The previous in vitro study findings motivated and led to this research project. Thus, actual (in vivo) diabetic foot ulcers were irradiated by blue light (625nm and 850nm) to either dispute or support these suggestions/results.

1.3 Problem Statement

Since the early '90s, researchers have been investigating phototherapy or PBM as a treatment modality. It has been found to improve the healing rate for chronic ulcers abroad/overseas significantly.

Despite the published literature, phototherapy is still not an accepted and established treatment modality for chronic DFUs. There is also little knowledge and scientific research on the use of PBM, red or blue light, on diabetic foot ulcers affecting patients with type II diabetes in South Africa. Additionally, there is a lack of data both in South Africa and abroad on the effects of PBM on skin colour when treating ulcers.

1.4 Aim and Objectives

This study aimed to determine if chronic lower limb ulcers in patients with type II diabetes respond better to the combined treatment of podiatric intervention and phototherapy (625 nm and 850 nm / 1200 mW output).

The following objectives were identified in order to realise the aim of the study,

- To compare standard podiatric treatment alone with combined therapy of podiatric treatment and phototherapy,
- To determine the rate of healing of diabetic foot ulcers,
- To determine whether phototherapy is affected by skin tone/colour when treating ulcers,
- To assess if any pain is experienced by participants after treatment.

1.5 Possible benefits

The possible benefits of this study would be to identify a new treatment modality that would improve on current treatment strategies. Conventional Podiatric interventions have showed limited to significant success in treating diabetic ulcers. Photobiomodulation (PBM) has also shown significant effects that improve wound healing. After completion of this study, a combined therapeutic approach used by Podiatrists may be identified which would improve the outcomes of diabetic patients suffering from ulcers in their lower limbs.

In addition, much research has been done to determine the benefits of PBM on wounds worldwide. However, the participants of most of these studies have light skin in the Fitzpatrick scale of 1-3. This study may shed light on the effect of PBM on darker skin types and elucidate the possible need to change the laser parameters needed for more effective treatment. In the long term, the findings of this study may have an impact on the quality of life of patients with chronic diabetic foot ulceration. Moreover, the preliminary findings of this study might lead to more extensive clinical trials on the use of PBM in DFUs. Such clinical trials might allow for the subsequent acceptance of PBM as part of mainstream management of DFUs across all levels of care in South Africa.

CHAPTER 2: LITERATURE REVIEW

2.1 Diabetes mellitus (DM)

The prevalence of DM as a common metabolic disease is increasing worldwide. Approximately 50% of diabetes cases are undiagnosed, with the majority of these occurring in low-income and middle-income countries. In Africa, the proportion of undiagnosed diabetes is 69.2% (Pheiffer et al, 2018). The prevalence of Type II diabetes mellitus (T2DM) in Africa has increased over the past decades, with South Africa rated as moderate, and high in adults aged 20 – 79 years (Clarke, 2010; Dunbar, Hellenberg and Levitt, 2015). The International Diabetes Federation estimated that in 2017, 451 million adults worldwide had diabetes, with projections of 693 million cases by 2045 (IDF Diabetic Atlas, 2017).

In 2014, 22 million people with diabetes were living in Africa, and 2.713 million of them were South Africans (IDF Diabetic Atlas, 2014). In South Africa, the prevalence of diabetes mellitus is about 15.8% in the Indian population, 3.5% in the White population and 4.8% – 6% in the Black population (Seedat, 2006). In 2012, a study in Cape Town found a rising prevalence of diabetes of 7-11.7% in urban-dwelling, adult black South Africans between 1990 and 2008/2009 (Peer et al. 2012). The current prevalence of T2DM in SA is 5.5%, likely an underestimation, but predicted to rise in the future (IDF Diabetic Atlas, 2017).

The most severe and costly complication of DM worldwide is foot complications leading to ulceration preceding amputations (Clarke, 2010; Clayton & Elasy, 2009; Dunbar et al, 2015). Data on DFUs in South Africa remain very sparse. However, just as in other parts of the world, DFUs are associated with a high risk of amputation. Studies report that DM accounted for 60.2% of the non-traumatic lower extremity amputations in public hospitals in the Cape Town Metropole, South Africa (Clarke & Tsubane, 2008; Clarke, 2010; Dunbar et al, 2015).

2.2 The diabetic foot

Diabetic foot ulcers and amputations can reduce the patient's level of function and independence and as such, may place a burden on the individual, family, and health care system. Patients' may view amputations as an end to productive living and a start to long-term disability and loss of independence.

Diabetic foot is a classification used to describe the foot in a diabetic patient that is at risk of developing or already has ulceration. It is also associated with neuropathy and peripheral arterial disease of the lower limb in a patient with diabetes (Alexiadou & Doupis, 2012). Diabetic foot is said to be more prevalent in Type 2 diabetic patients than in Type 1 diabetic patients, as most people with Type 2 diabetes may live several years with the condition, not being aware of their condition before being diagnosed (IDF, 2017; WHO, 2017). There are three entities of the diabetic foot: the neuropathic foot, the neuroischaemic foot and ischaemic foot.

Neuropathic foot present with the loss of protective sensory mechanisms but have good circulation, whereas neuroischaemic foot present with absent foot pulses accompanied by neuropathy. Ischaemic foot present with no circulation but might have adequate sensation (Edmonds, 2010; Alexiadou & Doupis, 2012). Ischaemia, an inadequate blood supply to the feet, is the most destructive complications of diabetes. It predisposes a patient to ulcerations, as well as gangrene, which may result in lower limb amputations (Nteleki & Houreld, 2012). Whether single or in combination, these entities lead to alterations in foot shape, thus allowing increased pressure points and make the skin susceptible to damage from footwear with an increased potential for ulceration and delayed healing (Clarke, 2010).

The pathway to diabetic foot ulceration is complex and involves an interaction of many factors. Whereas none of the factors discussed in this literature review will alone result in ulceration, it is the interface and amalgamation of risk factors working together that leads to skin breakdown and subsequent DFUs as outlined in **Figure 1**.

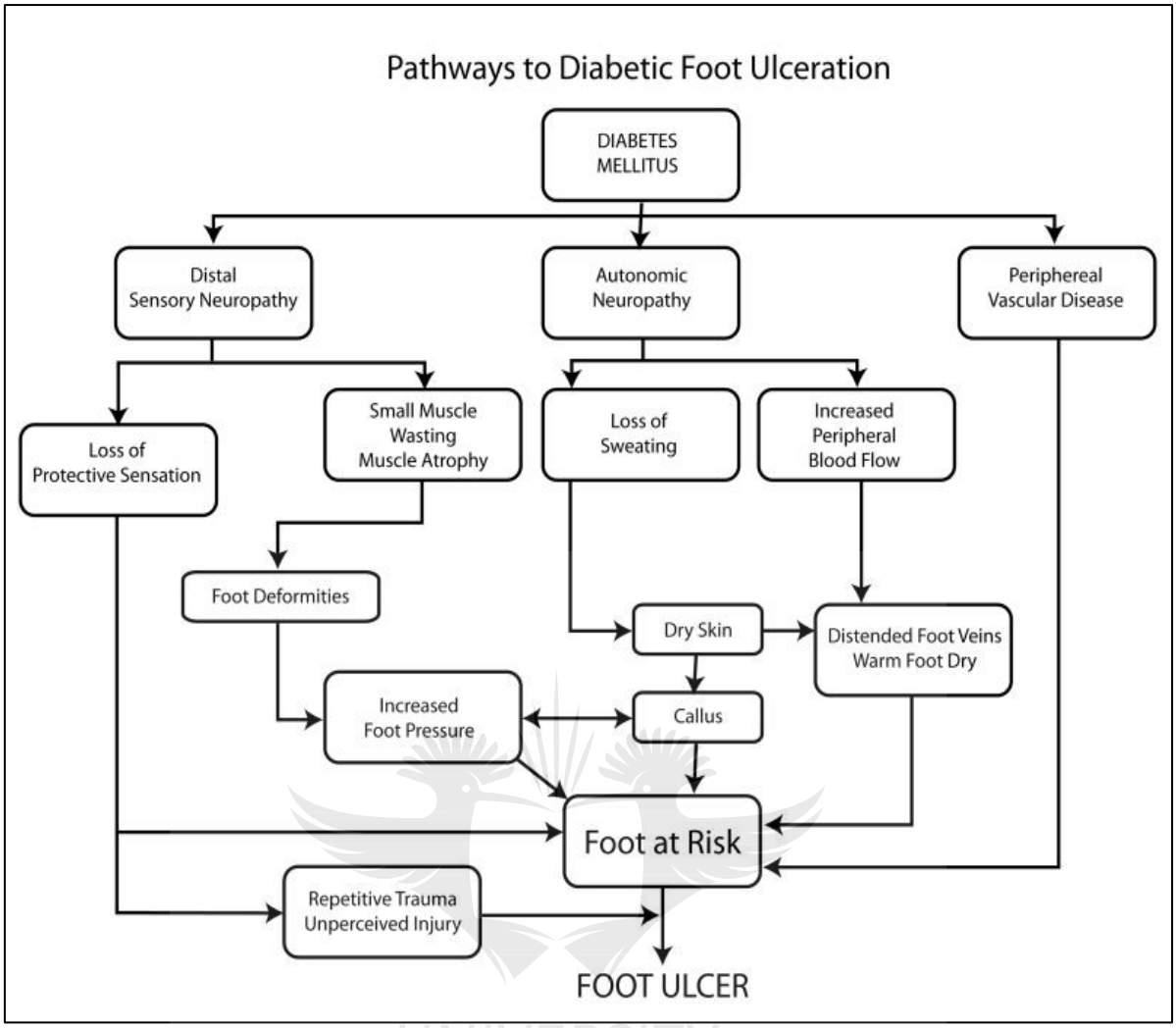

Figure 1. Physiological and Physical Pathways contributing to the development of diabetic foot ulceration (Boulton AJM, 2016).

2.3 Diabetic foot ulcers

Diabetes is the most common cause of foot ulcers. About 25% of patients with diabetes mellitus are likely to develop ulcers during their lifetime (Chadwick et al, 2013). Peripheral neuropathy is a significant contributor to diabetic foot ulceration and is frequently the most common microvascular complication of diabetes mellitus (Bergin et al., 2012; Chadwick et al., 2013; Edmonds, 2010; Nteleki & Houreld, 2012). Most diabetic lower limb ulcers occur in the presence of peripheral neuropathy, foot deformity and trauma. Peripheral vascular disease and infection are believed to be the complicating factors that prevent or delay ulcer healing (Bergin et al., 2012).

2.3.1 Classification of DFUs

Diabetic foot ulcers can result from multiple factors, and their classification is according to the relative contribution of late diabetic complications of peripheral

neuropathy and vascular diseases, similar to the diabetic foot classification above. They are also classified according to their severity or in grades using the universally accepted validated tools such as the Wagner and University of Texas classifications (Ho et al., 2012). Wagner's classification grades 0–V, divide ulcers from superficial or deep ulcers with or without the presence of osteomyelitis or gangrene (Wagner, 1981). The University of Texas classification (stages 1–5) further assess any presence of infection and ischaemia (Cavanagh et al., 2005; Ho et al., 2012).

These classification systems help provide prognosis on healing and aid in the formulation of management plans. However, patients and clinicians must understand that increasing stage, regardless of grade, is associated with increased risk of amputation and prolonged ulcer healing time (Ho et al., 2012). Additionally, deep ulcers of long duration have a prolonged healing time (Parisi et al., 2008). The reason for delayed healing is because the deep ulcers penetrate through the dermis, leading to more tissue damage, increased chances of necrosis, and osteomyelitis if neglected. The treatment in such cases is then more likely to be minor or major amputations (Musa & Ahmed, 2012). A study by Edo et al. (2013) support this reasoning. In his study, he found that 45.9% of their participants presented with Wagner grade IV and V ulcers, had an amputation rate of 52.5%.

2.3.2 Risk factors for Diabetic Foot Ulcers and Delayed Healing

DFUs can result from multiple factors; furthermore, these factors can also lead to impaired wound healing for diabetic patients. These factors can be either external factors or internal/intrinsic factors (Petrova & Edmonds, 2006). External factors include repeated trauma to the foot due to peripheral neuropathy, arterial insufficiency and foot deformities that result in abnormal pressure distribution (Petrova & Edmonds, 2006; Guo & DiPietro, 2010). Intrinsic factors include hypoxia, deficiency of growth factors, changes in extracellular matrix components with excess proteases, reduced fibroblast activity, cellular abnormalities, and deficiencies of angiogenesis, nitric oxide abnormalities (Petrova and Edmonds,2006).

Many other factors have been suggested, in literature, to contribute to the development of DFUs and their delayed healing. Factors such as poorly controlled hyperglycaemia, duration of diabetes, improper footwear, callus, history of previous ulcers/amputations, older age, impaired vision, chronic renal disease and poor nutrition have been demonstrated to play a role in the pathogenesis and progression of diabetic foot ulceration (Kavitha et al., 2014).

In a study by Shahi et al (2012), to determine the prevalence of and risk factors for foot ulceration in diabetic cases of North India, it was found that essential risk factors for DFUs included age >50 years, duration of diabetes: 4 to 8 years and > 8 years, rural location, oral hypoglycaemic treatment, insulin treatment, and tobacco use. Ahmad et al (2017) also found similar results in a study; in their study, they further identified that lack of awareness, male sex and barefoot walking as other major risk factors of developing of diabetic foot ulcers.

Edo et al. (2013) found that spontaneous blisters from ill-fitting footwear are one of the common risk factors of DFUs in a study to determine the risk factors, ulcer grade, and management outcome of patients with diabetic foot ulcers managed in a tropical tertiary hospital in Nigeria. Their study also found that poor diabetes control does not only play a role in delaying wound healing and providing an environment for infection to thrive, but mortality can result from diabetic ketoacidosis in the poorly controlled patients (Edo et al., 2013). Though this can be of short-term, health care practitioner must be familiar with its signs & symptoms and management. Deribe et al. (2014) reported similar results in a study conducted in Ethiopia. In addition to their findings, they reported that rural residence; the presence of co-morbidity such as obesity, duration of diabetes, mean arterial blood pressure and occupation (farmworkers) are factors associated with a diabetic foot ulcer.

The leading common risk factor of DFUs based on literature is peripheral neuropathy. Similarly, the main etiological factors associated with peripheral neuropathy are poor glycaemic control, visceral obesity, diabetes duration and height, with possible roles for hypertension, age, smoking, hypoinsulinemia, and dyslipidaemia (Ziegler, 2008). It is then evident that to prevent DFU development and delayed healing; treatment strategies must deal with peripheral neuropathy.

That approach will require identifying the underlying causative factor/s and treating or controlling them. Peripheral neuropathy in diabetic patients results from a complex interplay with multiple interactions between metabolic and vascular factors (Ziegler, 2008):

1. Increased flux through the polyol pathway that leads to the accumulation of sorbitol and fructose, myo-inositol depletion, and reduction in Na^+, K^+ - ATPase activity.
2. Nerve membrane structure and microvascular and hemorrheologic abnormalities as a result of disturbances in n-6 essential fatty acid and prostaglandin metabolism.
3. Endoneural microvascular deficits with subsequent ischemia and hypoxia, generation of reactive oxygen species (oxidative stress), activation of the redox-sensitive transcription factor NF-kB, and increased activity of protein kinase C (PKC).
4. Deficits in neurotrophism, leading to reduced expression and depletion of neurotrophic factors such as nerve growth factor (NGF), neurotrophin-3, and insulin-like growth factor and alterations in axonal transport.
5. Accumulation of non-enzymatic advanced glycation end products (AGEs) on the nerve and/or vessel proteins.
6. Immunological processes with autoantibodies to the vagal nerve, sympathetic ganglia, and adrenal medulla as well as inflammatory changes.

In the foot with the loss of the protective sensation (painless feet), motor dysfunction, and reduced sweat production due to autonomic involvement result in a markedly increased risk of callus and foot ulcers. Since this is a major contributory factor for diabetic foot ulcers and the lower limb amputation rates in diabetic patients, early detection by screening is of paramount importance (Ziegler, 2008). However, late presentation or delayed referral of these patients can result in this complication missed and thus worsening the outcome of DFU management (Edo et al., 2013).

Although literature have identified all these factors associated with DFUs and ways to manage them, the fact remains that there is a shortage of trained Diabetes care specialists and or Podiatrists in South African Primary Health Care sector. Moreover, most patients seek treatment from health care providers who have little or no training in managing diabetes and its complications such as diabetic foot ulcers.

2.3.3 Diabetic foot ulceration management

Management of diabetic foot requires a holistic approach which involves a focused interdisciplinary team that includes a wound nurse, a podiatrist and other allied health professionals (Bergin et al, 2012; Chadwick et al, 2013; Clarke & Tsubane, 2008; Clarke, 2010; Kim et al, 2012; Nteleki & Houreld, 2012; Houreld, 2014). This team is trained to implement and provide local wound care as the general standard of wound management in wound-care clinics. Local wound care involves debridement of necrotic tissue and callus, cleansing with suitable solutions, wound dressing, and prescription of topical or oral antibiotics when infection is present, revascularization and offloading (Bergin et al, 2012; Chadwick et al, 2013; Clarke & Tsubane, 2008; Clayton & Elasy, 2009; Kim et al, 2012).

However, this can last for extended periods without any healing response, due to the multiple complex pathophysiological mechanisms such as hypoxia, dysfunction in the fibroblasts and epidermal cells, impaired angiogenesis and neovascularisation, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end-products; seen in diabetic patients. These factors receive relatively little or no attention at all (Petrova & Edmonds, 2006; Guo & DiPietro, 2010). It is then evident that management for diabetic ulcers should focus on two main areas. These are external factors that cause diabetic foot ulcers and the internal factors that lead to impairment of wound healing. Such an approach indicates that there is a need to look beyond dressings and offloading but to focus more at the cellular level of the wound healing process.

Research has shown that understanding and correction of these pathogenic factors, combined with stricter adherence to standards of care and technological breakthroughs, is giving new hope to the problem of impaired healing of diabetic ulcers (Falanga, 2005). However, it might not always be possible because the multidisciplinary team is not always complete, and these technological breakthroughs are either not available or approved, especially in South Africa.

2.4 Podiatric management

Podiatrists approach diabetic ulcerations in a context of the overall structure and function of the lower limb. They perform local wound care and offloading with limb

function in mind, and therefore, continuous podiatric management can prevent ulcer recurrence through offloading strategies and diabetic foot education (Kim et al, 2012).

2.4.1 Wound debridement

Wound debridement is the removal of non-viable/unhealthy tissue that if not removed, it might promote infection and delay healing. There are different methods of debridement used in diabetic ulceration management, including sharp surgical debridement, non-surgical sharp debridement, autolytic and enzymatic debridement (Chadwick et al, 2014; Strohal et al, 2013). Wound debridement is an essential tool in the management of diabetic ulcerations as it allows a comprehensive examination of the ulcer bed and assessment of the actual ulcer size. It also has a potential to convert a chronic ulcer to an acute ulcer, aid in removing colonising bacteria in the ulcer and it also reduces local pressure on the ulcer (Chadwick et al, 2014; Strohal et al, 2013; Chadwick et al, 2013; Clayton & Elasy, 2009).

Some literature advises that the patient's vascular status must always be determined before sharp debridement as it could create a larger non-healing ulcer in vascular compromised patients (Brown, 2013; Bergin et al., 2012; Chadwick et al., 2014). Chronic neuropathic DFUs may accumulate callus and slough with excess exudate, which encourages the formation of biofilm (bacterial colonisation), promoting the risk of infection and thus delay healing (Williams et al., 2005; Wolcott et al., 2009). Sharp debridement helps to break down these bacterial colonies, thus reducing the bacterial load within an ulcer even in the absence of overt infection, and so promotes the release of growth factors to aid the healing process. Also, this offers an opportunity for additional antibiotic interventions, applied topically or systemically, to be useful as it temporarily disrupts biofilm defence colonies and forcing microbes to become more susceptible to these interventional treatments as well as the host's immune defence (Wolcott et al., 2009).

Literature suggests that frequent debridement of DFUs and chronic venous leg ulcers increase wound healing rates and closure of the ulcer when combined with other conventional and advanced therapies (Cardinal et al., 2009). Wilcox and

colleagues investigated the frequency of debridement and the time to heal for different types of ulcers, including DFUs and chronic venous ulcers (Wilcox et al., 2013). They found 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 the range of every one to two weeks, and 76 days when debridement was once every two weeks or more (Wilcox et al., 2013).

Another study by Ahmad and colleagues, which assessed the efficacy of radical debridement and skin grafting in treating DFUs, compared with other conservative wound treatments (such as the 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 four after surgery. In their study, wound debridement was done three times a week (Ahmad et al., 2012). Both studies support that frequent debridement of chronic DFUs, promote healing and speed up the healing process of these ulcers. In the current study, debridement was performed twice a week, as participants in both groups were seen twice a week for treatment.

2.4.2 Offloading

Offloading is also an essential tool in the healing of diabetic foot ulceration, particularly in the case of plantar neuropathic ulcer, or for secondary prevention in patients with healed ulceration but have a foot deformity (Bergin et al., 2012; Clayton & Elasy, 2009). The main goal of offloading is to redistribute pressures evenly around the ulceration sites and pressure points at risk of increased pressure bearing (Chadwick et al., 2013). Several offloading techniques are used by Podiatrists, in South Africa and overseas. These include felt padding, prescription orthotics and insoles, removable cast walkers and total contact casting (Bergin et al., 2012; Clarke & Tsubane, 2008; Kim et al, 2012).

The use of suitable or proper footwear combined with custom-made orthotic devices is considered the primary means of protecting the foot from excessive plantar pressure during walking, thus reducing the incidence of ulceration. A study by Mueller *et al.* (2006), which investigated the effect of total-contact cast inserts (TCIs) and metatarsal pads (MPs) on metatarsal peak pressures and pressure–time integrals support this approach. That study found that the TCI and MP

caused a substantial and additive reduction in pressure (29 to 47%) under the metatarsal heads on the feet by increasing the contact area of weight-bearing forces when compared to wearing shoes alone (Mueller *et al.,* 2006).

Tong and Ng (2010) investigated the amount of pressure reduction that occurred in feet when using different types of padding and four insole materials commonly used in podiatry. In their study, they found that all four commonly used materials, Slow Recovery Poron (SRP), Poron, Poron + Plastazote firm (PPF) and Poron + Plastazote soft (PPS) could reduce pressure across the whole foot. The PPF achieved the most significant result of 29% pressure reduction. Additionally, they combined PPF with a semi-compressed felt metatarsal pad with an aperture on the first metatarsophalangeal joint of both feet. The peak pressure in this area showed a significant reduction of 37% compared to a 29% decrease with PPF alone (Tong & Ng, 2010).

It is important to note that pressure responses vary in the two studies, suggesting that pressure reduction in terms of using footwear and orthotic devices is highly dependent upon the condition of the patient's feet and the material used. It is unclear how this factor is considered by podiatrists, nurses and other healthcare professionals when treating DFUs.

Over the years, total-contact casting (TCC) has been known to be more effective in the treatment of non-infected diabetic plantar neuropathic ulcers, compared to other removable off-loading devices mentioned above (Sambrook et al., 2015). However, TCC is a time-consuming and challenging treatment for podiatrists to apply, and generally, there is low patient tolerance, with several side effects associated with its application. Therefore most clinicians, including podiatrists, prefer not to use this technique and instead prescribe various other off-loading techniques that are far easier to apply (Raspovic and Landorf, 2014). These can be the other alternative non-removable devices or removable devices like instant total contact cast or removable cast walkers/moon boot (RCW) (Armstrong et al., 2005; Faglia et al., 2010).

Studies show that whether the off-loading device is removable or non-removable, it can be used effectively to redistribute pressure on the plantar aspect of the foot. However, results are dependent on the patient's compliance with wearing the

devices, especially the removable devices regularly. A comparative study on the efficacy RCW and a non-removable fibreglass off-bearing cast (TCC) by Faglia *et al.* (2010) in DFU healing over a 90-day period , found that 73.9% of patients in the TCC group and 72.7% in the RCW group achieved complete healing (Faglia et al., 2010).

Before Faglia *et al.*, Armstrong and colleagues in 2005 performed a study to evaluate the effectiveness of an RCW and an 'instant' total-contact cast (iTCC) over 12 weeks in neuropathic DFUs. They reported significant ulcer healing rates of 82.6% in the TTC group and 51.9% in RCW group. The advantage of using RCW is that it can be easily applied and removed. However, its ease of application is also its shortfall in that patient adherence to the walker is a significant factor in non-healing ulcers and frequent recurrence in those who do not continually wear their RCWs (Boghossian et al, 2017). To avoid this, all involved in the management of DFUs should employ a variety of skills. Training workshops on how to apply instant total contact cast for neuropathic DFUs could also be of benefit; as patients can benefit from the forced compliance of the iTCC while enjoying the more tolerable offloading capability of this device.

2.4.3 Wound dressing

Both offloading and debridement are considered very important to the healing process of diabetic lower limb ulcers. However, selecting the right wound dressing is also essential and the characteristics of specific dressing type can be beneficial; depending on characteristics of the individual ulcer (Bergin et al, 2012; Chadwick et al, 2013; Clarke & Tsubane, 2008; Clayton & Elasy, 2009). There are various wound dressings available for the management of diabetic foot ulcers including hydrogels, hydrocolloids, alginates, foam, silver-impregnated dressings, growth factors, and silicon impregnated atraumatic dressings, and more (Kavitha et al, 2014).

To promote wound healing, the wound dressing must comprise of these characteristics: it must be sterile, not contaminate the wound with foreign particles, maintain a moist wound healing environment, absorb excess exudate, non-adherent & non-toxic, protect the wound from microorganisms, allow

gaseous exchange and control wound odour, and provide thermal insulation and mechanical protection (BNF, 2010; Kavitha et al, 2014).

Most diabetic foot ulcers produce copious amount of exudate and the primary dressing, therefore, should be either foam-based or Hydrofiber, both which will absorb the exudate (Speak, 2014; Kavitha et al, 2014). Diabetic foot ulcers are often colonised with microorganisms (biofilm) first before they become infected (Cavanagh et al, 2005; Kavitha et al, 2014); therefore choosing an appropriate dressing to address and prevent infection is essential to achieve effective treatment of these ulcers. Silver impregnated dressings are believed to be antibacterial (Wall, 2010) and thus useful in the treatment of DFUs. However, some literature states that there is a need for more research to establish whether silver-containing dressings clear wound infection (Storm-Versloot et al., 2010).

Podiatrists are very well trained and well equipped to assess and implement these treatment modalities in the management of diabetic lower limb ulceration (Kim et al, 2012). However, these treatment modalities can go on for a long time with slow or no healing response of an ulcer, and this has a negative influence on a patient's quality of life. Thus, there is a need for new DFUs treatment modalities to be generated or introduced, such as phototherapy, to help improve the healing rate and outcomes of diabetic ulcerations.

2.5 Phototherapy

Phototherapy is a therapeutic modality that involves the use of laser light, at a specific wavelength at low intensities, stimulate biological processes in tissues (Nteleki & Houreld, 2012; Houreld, 2014). Low-level laser therapy (PBM) is widely used to accelerate tissue repair in surgery, dentistry, dermatology, somatology, pain management and ulcer healing (Hamblin & Demidova, 2006). Unlike the high-intensity medical lasers used to cut and coagulate tissues, PBM involves the use of medical lasers that operate at intensities too low to damage tissue or cause a rapid and significant increase in tissue temperature (Dyson, 2014).

2.5.1 Mechanism of action

Photobiomodulation is understood to supply direct biostimulative light energy to body cells; however; its full mechanism of action is not known (Beckmann et al, 2014). For PBM to be effective, the targeted tissue must absorb the light (Dyson,

2014; Hamblin & Demidova, 2006). Photo acceptors or chromophores within the cell absorb photon energy. The primary photo acceptors are thought to be the cytochrome c oxidase inside the mitochondrion, and the absorption of photons increases the amount of energy-rich adenosine triphosphate (ATP) produced by the mitochondria which also temporally increase cell membrane permeability to calcium ions, acting as a stimulus for cell activity (Nteleki & Houreld, 2012). In this way, when absorbed, the photons induce cellular changes, which accelerate tissue repair and relieve pain (Dyson, 2014). **Figure 2** illustrates the mechanism of action of PBM.

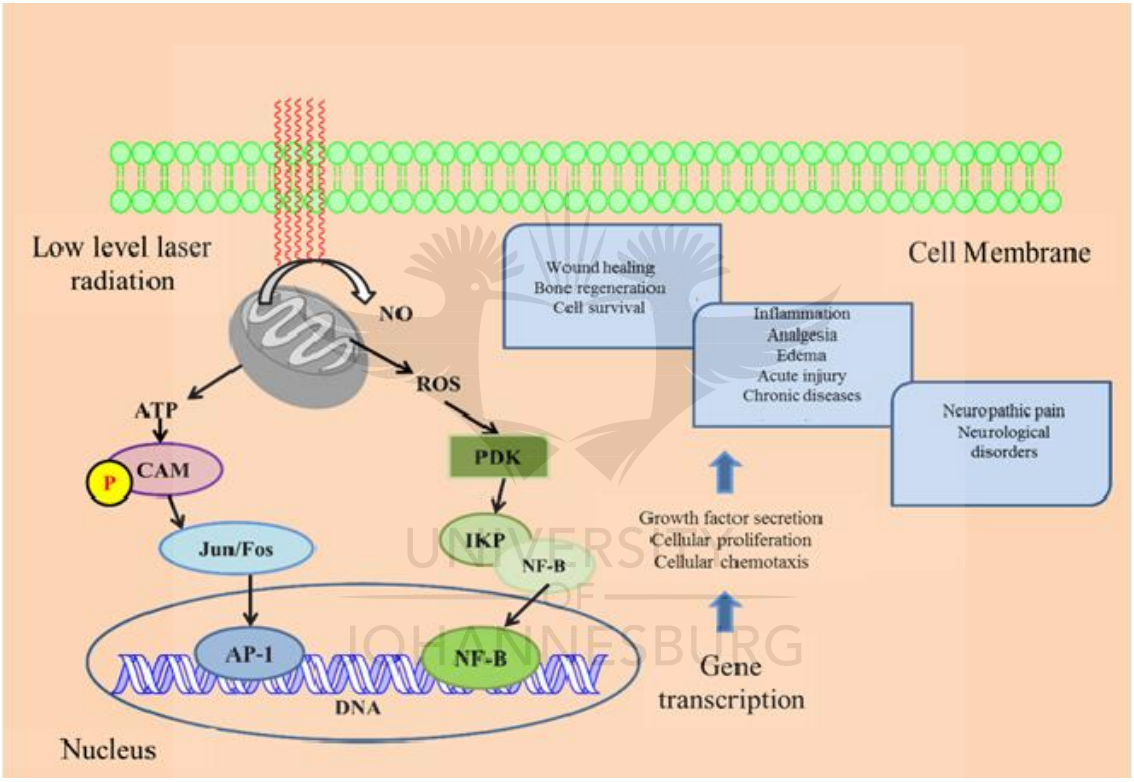

Figure 2. Mechanism of Action of PBM at cellular level. Light energy is absorbed by chromophores, which convert light energy into chemical energy that activates a cascade of cellular and molecular pathways contributing to wound healing (Amid et al, 2014)

2.6 Low-Level Laser Therapy accelerates wound healing in vitro studies.

According to literature, phototherapy stimulates mitochondrial oxidative metabolism in vitro, and increase cell and tissue repair in vivo (Nteleki & Houreld, 2012). In vitro experimentations with cultured human keratinocytes, mast cells, lymphocytes, endothelial cells and fibroblasts indicated potential effects of PBM in the treatment of chronic ulceration. Human skin fibroblasts are one of the targets in phototherapy as they are highly involved in initiating the healing process

by producing cytokines and undergoing proliferation, migration, deposition, and remodelling of extracellular matrix to form granulation tissue (Houreld & Abrahamse, 2010). **Figure 3** illustrates the effects of PBM on wound healing.

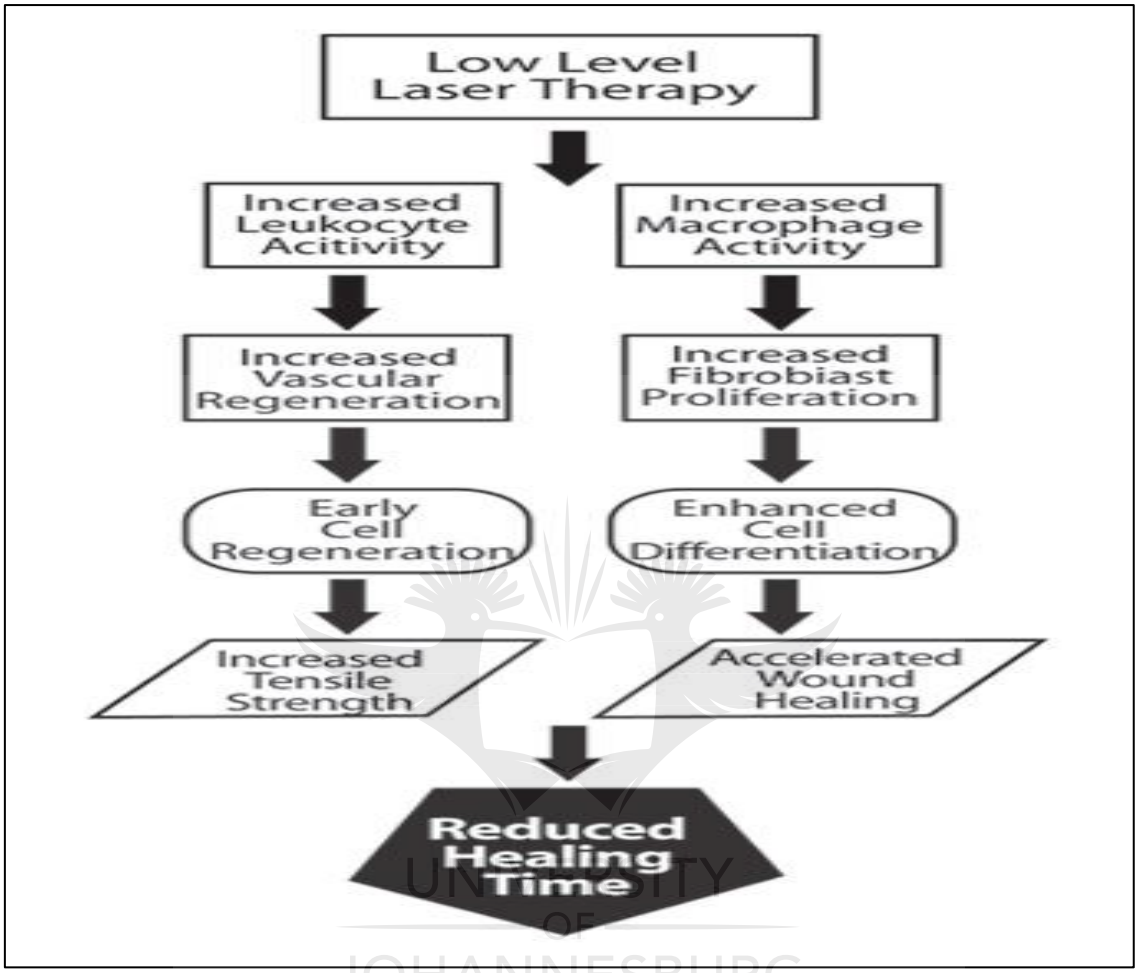

Figure 3. Photobiomodulation and its cellular cascade effects that promote accelerated wound healing (Martin R, 2011).

At the correct laser parameters, PBM has been shown to positively stimulate diabetic ulcer fibroblasts (Nteleki and Houreld, 2012) resulting in increased viability, proliferation, ATP, growth factors, cytokines and nitric oxide as well as a decrease in cellular damage and proinflammatory cytokines (Houreld & Abrahamse, 2010; Beckmann et al, 2014; Houreld, 2014). Studies done on wounds suggest that fibroblasts transform into myofibroblasts, which develop in the granulation tissue to produce wound contraction (Hamblin & Demidova, 2006; Dyson, 2014). A study by Minatel et al. (2009), found that the healing effect of combined 660 nm and 890 nm light resulted in rapid granulation and healing rate in a treatment group than in the placebo group; correlating the cellular effects produced by phototherapy.

Samaneh et al. (2015), review paper, reported that visible light at a wavelength of 630-780 nm could penetrate to a depth of 0.5-50 mm. This wavelength has shown great potential for wound healing. They also suggested that applying laser at doses between 4 J/cm^2 and 8 J/cm^2 are more effective (Samaneh et al, 2015). Houreld and Abrahamse (2007 & 2010) conducted a study to test the positive effects of low-intensity laser irradiation of different wavelengths on cellular migration, viability and proliferation in diabetic wounded and healthy human skin fibroblasts. Their findings showed that diabetic wounded cells irradiated at 1.064 nm had a lesser degree of migration, viability, and proliferation. Whereas cells irradiated at 632.8 nm had a higher degree of haptotaxis, migration and ATP luminescence compared to cells irradiated at 830 nm (Houreld and Abrahamse 2007 & 2010).

2.7 The Effect of PBM on infection

As previously stated, different wavelengths of light 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 compared to violet and blue spectrum lasers. Flavins (flavoproteins) and porphyrins lacking transition metal coordinating absorb blue laser (Nteleki & Houreld, 2012; Beckmann et al, 2014). Blue light absorption by these molecules has been shown to have bactericidal effects compared to red light. After absorption by these molecules, a photochemical reaction occurs and forms reactive free radicals that lead to bacterial destruction (Dyson, 2014; Hamblin & Demidova, 2006).

Several studies have found that, at different wavelengths, the blue light laser is bactericidal to different infectious organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Propionibacterium acne* and *Pseudomonas aeruginosa.* Enwemeka et al. found that blue light (470 nm) was able to kill MRSA in vitro. Lipovsky et al. suggested that high-intensity visible light in the range of 400-1000 nm was bactericidal to *S. aureus, P. aeruginosa* and *Escherichia coli,* to name a few. Ankri et al. suggested irradiation at a wavelength of 408 nm for treating infected wounds to clear the infection, followed by irradiation at 730 nm to speed up the healing process (cited in Houreld, 2014).

Red lasers as well as blue laser improve perfusion by the release of nitric oxide (NO) from nitrosyl complexes with haemoglobin, enhanced epithelialization, and elevated keratin-10 mRNA level (Beckmann et al, 2014). Studies have shown that NO inhibits the activity of cytochrome c oxidase, and this was initially seen off as an imperfection (Hamblin, 2006). However, there is evidence that blue light facilitates the recovery of mitochondria inhibited by NO gas. The release of NO from mitochondrial complexes leads to an improved wound healing via the NO pathway induced endothelial cell migration which activates growth factors resulting in an increase keratin expression (Beckmann et al, 2014). The ability of the blue laser to improve perfusion by the release of nitric oxide is significant and shows that a combination of red light laser and blue light laser can be used to treat infected ulcers. Thus, the current study used blue laser light to treat diabetic ulcer to promote both healing and apparent superficial infection.

2.8 Possible advantages of combining PBM and Podiatric intervention

Wound debridement in ulcers is a vital stage in the healing of chronic like DFUs as it returns the wound into acute inflammation (Halim et al, 2012). Mechanical or sharp debridement is one of the essential parts of wound treatment protocols in podiatry (Clarke & Tsubane, 2008; Kim et al, 2012). It helps facilitate the wound healing process by converting chronic inflammation to acute inflammation (Halim et al, 2012). Thus, phototherapy can be used immediately after debridement to stimulate proliferation of endothelial cells and fibroblasts, accelerating the development of granulation tissue over which epidermal cells migrate to achieve wound contraction (Dyson, 2014).

Sharp debridement temporarily, disrupts the biofilm defence colonies, forcing microbes to become more susceptible to interventional treatments (Wolcott et al., 2009). Ideally, following sharp debridement blue light laser must be used to irradiate DFUs as it bactericidal against different infectious organisms. The blue light laser is active and can eradicate microbes such as methicillin-resistant *Staphylococcus aureus* (MRSA), *S aureus, Escherichia coli, Propionibacterium acne* and *Pseudomonas aeruginosa,* which is critical in the treatment and clearing of infection. In turn, this can speed up the healing process of ulcers (Houreld, 2014).

Since peripheral neuropathy is the major contributor to DFUs and is known to results from a complex interplay with multiple interactions between metabolic and vascular factors seen in diabetic patients (Ziegler, 2008); perhaps PBM can assist in controlling or reversing it. According to literature, PBM promotes nerve regeneration by stimulating the production of nitric oxide that relaxes endothelial cells, which form the lining of blood vessels and thus, improves blood flow. It also stimulates mitochondrial ATP production, accelerates antioxidant mechanisms, and improve cell function; resulting in all of these processes serving to repair damaged nerve endings (Robinson et al., 2017). Further studies and investigations are ongoing in this area to validate the efficacy of this intervention.

In addition, most DFUs occur in the presence of peripheral neuropathy, foot deformity and trauma, due to uneven distribution of pressure in a diabetic foot (Bergin et al., 2012). To redistribute pressures evenly, around the ulceration sites and other risk pressure points to a broader contact area is achieved by offloading techniques (Chadwick et al., 2013). It is then somehow clear that combining PBM with podiatric interventions might further improve and accelerate wound healing as both these interventions play a role in controlling or eliminating both the internal and external risk factors of DFUs. Therefore, the current study aimed to determine and establish if combining these two interventions can accelerate wound healing in Type II Diabetic patient with Fitzpatrick Skin Type III and V.

2.9 Fitzpatrick skin types

South Africa has diverse ethnic groups with different skin colours and might have more sunlight compared to other regions of the world. In 1975, Fitzpatrick developed a skin typing system based on the history of an individual's tendency to get burns or tan from ultraviolet radiation (UVR). There are six classifications from this system: skin type I, II, III also known as white-skinned. Skin type IV is for light brown, type V for dark brown skin and type IV for black skin. Fitzpatrick classification of skin type has been used to estimate the risk of skin cancer and cutaneous malignant melanoma (Ravnbak, 2010). Melanin and other molecules absorb ultraviolet radiation which can cause structural cell damage. Its effects are, however, wavelength-dependent, just like laser irradiation.

Melanin is the skin pigmentation produced from melanocytes in the epidermis, and it plays a role in photo-protection of the skin. The UV radiation may have some beneficial effects on humans, but most evidence suggests that it is toxic to human skin and health. The acute adverse effects of UV radiation are erythema, keratitis and immunosuppression (Ravnbak, 2010). According to literature investigating the effects of phototherapy in wound management, PBM is an adverse effect free treatment modality in the management of ulcers. However, the uses of phototherapy in dermatology clinic have proven to have unwanted side effects, especially in dark skin toned patients.

Most of these effects relate to melanin's vast absorption spectrum of light (250-1200 nm). Visible ultraviolet and infrared light can target melanin. In darker skin types (type IV to VI), epidermal melanin competes as significant chromophores and laser light intended for deep tissue might not reach them; reducing its efficacy. Unwanted thermal injuries such as blistering, transient or permanent dyspigmentation, textural change and scarring can occur due to the conversion of the absorbed light within the pigmented epidermis to heat (Battle & Hobbs, 2003; Battle & Soden, 2009). However, this might not be obvious in people of skin type II or III in their natural untanned state (Battle & Soden, 2009). The current study investigated the effects of skin tone/colour with the application of PBM in DFU treatment.

2.10 Conclusion

Literature suggests that PBM is one of the treatment modalities that, when combined with other conventional treatments, has shown potential in assisting and improving the healing rate of chronic diabetic ulcerations. Therefore, this study aimed to determine if chronic lower limb ulcers in patients with Type II Diabetes respond better to the combined treatment of podiatric intervention and phototherapy and whether there are any adverse effects when treating these ulcers in patients with skin type III and V.

CHAPTER 3: METHODOLOGY AND RESEARCH DESIGN

3.1 Research design

To realize the aim and objectives of the study, the researcher chose a prospective experimental single-blinded controlled design for this study (Appendix A).

A prospective study is a study that watches for outcomes, such as the development of a disease (in the context of the current study the efficacy of PBM in DFUs healing rate), during the study period and relates this to other factors such as suspected risks (Elmes, Kantowitz & Roediger III, 2011; Jhangiani, Chiang & Price, 2015). The study was also an experimental design study. An experimental design is a study designed accurately to answer the question of whether there is a causal relationship between two variables. This design was suitable since experiments have high internal validity because of the way they are conducted with the manipulation of the independent variable and the control of extraneous variables, which provides strong support for causal conclusions (Jhangiani, Chiang & Price, 2015).

3.2 Materials and methods

3.2.1 Setting

The setting for this study was the University of Johannesburg Podiatry clinic and Helen Joseph Hospital: Podiatry Department and Surgical Outpatient Department. These settings were suitable for examination and management of diabetic ulcerations under appropriate sterility as diabetic ulcers are highly prone to secondary complication such as infection.

3.2.2 Sample and population

In this study, the population were all Type II Diabetic patients presenting with a diabetic lower limb ulcer at UJ Podiatry clinic and Helen Joseph Hospital.

3.2.3 Study sample and sampling methods

The researcher used non-probability purposive sampling techniques to select participants in this study. Purposive sampling is a judgmental and deliberate selection of study participants for inclusion in the study (Grove, Burns & Gray, 2013). The sample was the 19 diabetic patients who volunteered to participate in the study, who had 22 lower limb ulcers among them.

3.2.4 Inclusion criteria

- Type II diabetes with neuropathic or mixed ulcers
- Lower extremity ulcer
- A stable or worsening ulcer which has been present for a minimum of four weeks
- Fitzpatrick skin type III and V
- Willingness to participate in and commitment to the study
- Signed consent to participate in the study.

3.2.5 Exclusion criteria

- Evidence of acute cellulitis, osteomyelitis or gangrene anywhere in the affected extremity
- Presence of one or more conditions (a renal, hepatic, hematologic, neurologic or immune disease) not related to diabetes
- Presence of malignant disease (other than basal cell carcinoma) not in remission for more than five years
- Use of oral or parenteral corticosteroids, immunosuppressive or cytotoxic agents
- Known infection with HIV or the presence of AIDS
- Use of other investigational drugs or devices within 30 days of recruitment into the study
- Other leg ulcers, such as ulcers due to decubiti or vasculitis

The researcher randomly divided the participants who met the prerequisite inclusion criteria of the study into four groups:

- Group 1 was the control group of Fitzpatrick skin type III, receiving placebo irradiation and standard podiatry treatment for diabetic ulcers.
- Group 2 Fitzpatrick skin type III received irradiation of the ulcer and standard podiatry treatment for diabetic ulcers.
- Group 3 was the control group for Fitzpatrick skin type V, receiving placebo irradiation and standard podiatry treatment for diabetic ulcers.
- Group 4 Fitzpatrick skin type V received irradiation of the ulcer and standard podiatry treatment for diabetic ulcers.

3.3 Ethical consideration

To ensure patients' rights to equality, justice, human dignity/life and protection against harm, the researcher observed ethics throughout this study. Ethics are a set of moral principles that are widely accepted, which guide the researcher in observing ethical and moral rules. Research participants were therefore, treated with respect and dignity during the collection of data. The researcher protected the rights of respondents in this study and took every precaution to prevent any violation of their ethical rights. The following ethical principles guided this study: permission to conduct research, informed consent, anonymity and privacy, confidentiality as well as autonomy.

3.3.1 Permission to conduct the study.

The University of Johannesburg's Faculty of Health Sciences Higher Degrees and Research Ethics Committee (Appendix A and Appendix B) approved the study and issued an ethical clearance. Upon receipt of ethical clearance, the podiatry clinic manager and Helen Joseph Hospital Ethics Committee (Appendix C) were approached to request access to diabetic patients.

3.3.2 Informed consent

Informed consent means that participants should understand that they are taking part in research and what it requires of them. Thus, it is an agreement by a prospective subject to participate voluntarily in a study after he or she has assimilated essential information about the study (Grove, Burns & Gray, 2013). In this study, the researcher provided details on the PBM intervention to all potential participants.

Potential participants were alerted of their right to choose either to volunteer for the study or not as well as their right to withdraw at any point during the study without prejudice. Potential participants were at liberty to discuss their participation in this study with their treating clinicians. Diabetic patients presenting with diabetic foot ulcers were approached to solicit their participation in the study. The researcher read an information letter (Annexure D) outlining the aim, objectives as well as risks and benefits of the study to all potential participants. The researcher also dealt with any specific question that potential participants

raised. Patients who elected to participate signed a consent form (Annexure E) to indicate their informed consent before any data collection.

3.3.3 Right to Confidentiality

Confidentiality in a participant's information is the management of private data in research in such a way that only the researcher knows the subjects' identities and can link them with their responses (Grove, Burns & Gray, 2013). Only the researcher and research had access to the data collected as part of this study. The researcher kept all hard data in a lockable cabinet and soft data in a password-protected file. The Department of Podiatry will keep data collected in this study, for three years. Furthermore, the researcher will ensure participant confidentiality in all subsequent publication of the current study findings in peer-reviewed journals.

3.3.4 Anonymity and privacy

Anonymity and privacy is freedom to determine the time, extent, and general circumstances under, which private information to share with or withhold from others (Grove, Burns & Gray, 2013). In this study, the researcher did not collect any patient identifying data as part of data collection. Thus, safeguarding participant anonymity and privacy (Pera & van Tonder, 2011).

3.3.5 Right to self-determination or autonomy

Autonomy is when a person is capable of controlling his or her self-destiny and have the freedom to conduct his or her life without force or control (Pera & van Tonder, 2011). Thus, participants in this freely choose whether to participate or not without any external control, force or exploitation as well as had an option to withdraw from the research at any time during data collection.

As the study involved a clinical intervention, the researcher emphasised to each participant their right to withdraw without any changes to their usual treatment. Additionally, the researcher informed each participant that there had been no risks reported with PBM in wound management, as it is a non-invasive therapy. Moreover, potential participants were informed that any adverse effects occurring during this study would be dealt with efficiently, and after completion of the study, participants will continue receiving their long term treatments.

3.4 Study procedure

After signing the informed consent, each participant had to complete the study questionnaire (Appendix F). The questionnaire explicitly designed for this study was to ensure that the participants met all the prerequisites inclusion criteria of the study. The researcher evaluated the vascular status and sensation of each participant as part of patient assessment. The Wagner ulcer grading system was used to assess, measure and graded each ulcer as follow:

- Grade 1: Superficial diabetic ulcer
- Grade 2: Deep ulcer; involving the tendon, ligament, joint capsule or fascia
- Grade 3: Deep ulcer with abscess or osteomyelitis
- Grade 4: Gangrene affecting the portion of the forefoot
- Grade 5: Extensive gangrene of the foot

This study included only participants with Grade 1 and Grade 2 ulcers of at least four weeks' duration.

3.4.1 Podiatric treatments

All participants received their routine general podiatric treatment for diabetic ulcers, which included wound debridement (sharp debridement), cleansing with saline and dressing with a silver dressing (Biatain Silicone Ag). Antibiotics and offloading devices were prescribed when needed. The common offloading devices prescribed were moon-boots and custom-made simple insoles, depending on the site of the ulcer and deformity present. Diabetic foot care education also formed part of these participants' management.

The researcher took baseline images for each presenting ulcer before treatment, and then again at each treatment session. A camera (Nikon D7000, 18-55mm lens) set at a fixed height of ~ 80 cm using a tripod and at a distance of 30 cm from the ulcer to ensure standard photography. Participants were treated twice a week until the ulcer was healed or for a maximum of 12 weeks.

3.4.2 Phototherapy

All participants in the study (PBM) group wore the required safety goggles, which filtered out the laser light. Participants were treated with the

Photizo®Physio/Home642 unit (Photon Therapy Systems (Pty) Ltd, Kosmosdal, Samrand, South Africa) with a 1200 mW cluster probe twice a week before wound dressing was completed (**Figure 4**). The cluster probe has eleven (625nm and 850nm) LEDs emitting blue light (at 1200 mW output) for ~60 seconds. The instrument is pre-programmed and to treat ulcers, the “Wounds” protocol was chosen. The probe was covered with clear, sterile plastic to prevent cross-contamination. The covered probe was lightly pressed onto the ulcer (contact mode) and sequentially one spot at a time was treated until the entire ulcer was treated. This delivered a total energy of 3 J/cm^2 per spot (15 cm^2) with a penetration depth of ~ 12 mm (60% dose absorbed in superficial tissue and 40% penetrates further.

Figure 4. Photizo®Physio/Home642 unit.

Post irradiation, ulcers were dressed according to the standard podiatric treatment. This depended on the wound and the stage of healing (e.g. moist / dry wound, infection/no infection.). Participants were treated twice a week until the ulcer healed for a maximum of 12 weeks. Although no pain from irradiation was

expected, participants were requested to complete a pain questionnaire (Appendix G) on a weekly basis.

3.5 Data analysis

The researcher measured the size of the ulcer and area of granulation tissue using Image J® software. The following quantitative data were analysed using SPSS version 25. Basic comparative statistical analysis was undertaken to determine the healing rate in different skin Types III and V. The results are presented in tables, bar charts, line graphs and ulcer images in the next chapter.

CHAPTER 4: RESULTS

4.1 Introduction

The initial target sample was 50 ulcers (25 in PBM and 25 in Control). However, the researcher could not reach this number due to the high participant attrition rate. This study used new intervention in the treatment of DFUs.

Despite the lower than expected number of ulcers treated using the PBM method, the findings of the study are significant. As alluded in the methodology section, this study was an experimental design study. The purpose of an experimental design is to demonstrate that two variables are statistically related and to show that in such a way that supports the conclusion that the independent variable (PBM irradiation) caused the observed difference in the dependent variable (DFUs).

The findings of the study showed marked improvement and statistically significant ulcer healing (*p-value* control 0.043 vs *p-value* PBM 0.028). Therefore, though limited in the number of participants, this study provides preliminary results on the effectiveness of PBM in vivo.

4.2 Demographics

The demographics in this study include the following: gender, ulcer classification, ulcer duration, and duration of DM, comorbidities/risk factors and the skin tone of each participant. The study sample comprised of 19 participants, 12 males and 7 females, with 22 lower limb ulcers. Out of all the 22 ulcers, 15 ulcers (68.2%) were from male participants, and seven ulcers (31.8%) were from females. **Table 1** shows the distribution of ulcers in the different genders.

Table 1. Ulcer-Gender distribution of participants in this study.

Group		Gender	
		Male	Female
Control	Count	6	3
	%	66.7%	33.3%
PBM	Count	9	4
	%	69.2%	30.8%
Total	Count	15	7
	%	68.2%	31.8%

The ulcers were randomly divided into Control group (n=9) and PBM group (n=13). **Table 2** shows, the classification of ulcers, according to Wagner's classification, and it shows that 59.1% were Grade 1 ulcers vs 40.9% Grade 2 ulcers in both groups.

Table 2 Diabetic foot ulcer Classification/grade.

Group	Grade 1	Grade 2	Total
Control	7 (77.8%)	2 (22.2%)	9 (100%)
PBM	6 (46.2%)	7 (53.8%)	13 (100%)
Total	13 (59.1%)	9 (40.9%)	22 (100%)

A majority of ulcers duration was between 1-5 months in both the Control and PBM group, respectively (**Figure 5)**. The mean duration of ulcers was 8.05 months, with a minimum duration of one month and maximum duration of 24 months.

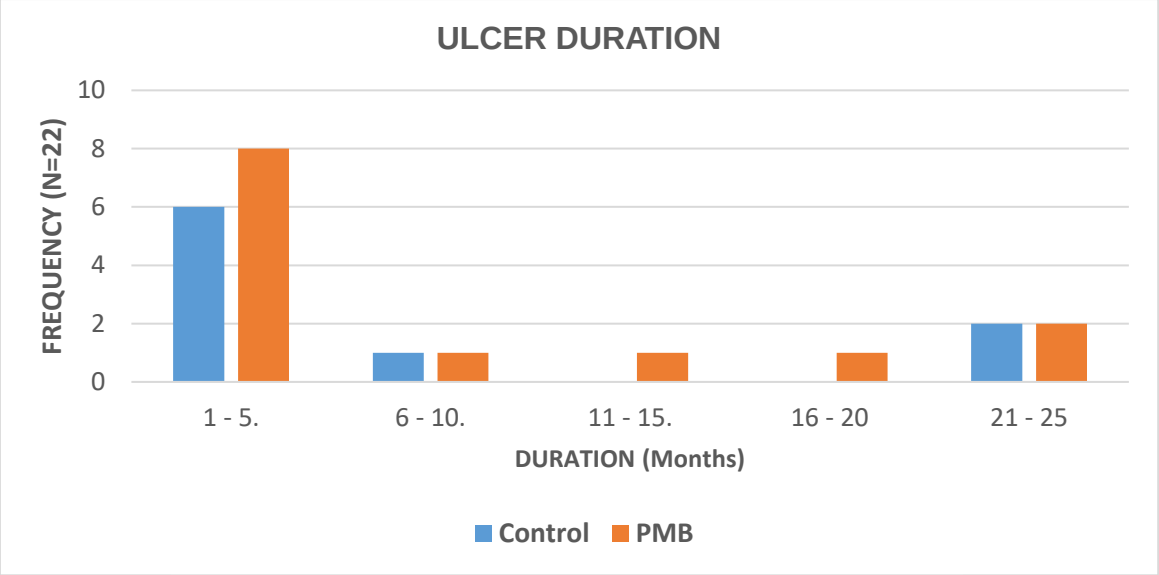

Figure 5. Ulcer duration in Control and PBM groups indicating majority of ulcers duration ranged between 1-5 months.

The mean age for the two groups was 54.36, with a minimum age of 44 and a maximum of 74 years. **Table 3** presents the descriptive statistics of age distribution in the two different groups.

Table 3. Age Distribution of the study groups.

Group	Statistic		
Control	Mean		**57.00**
	95% Confidence Interval for Mean	Lower Bound	**50.42**
		Upper Bound	**63.58**
	5% Trimmed Mean		**56.78**
	Median		**56.00**
	Variance		**73.250**
	Std. Deviation		**8.559**
	Minimum		**44**
	Maximum		**74**
PBM	Mean		**52.54**
	95% Confidence Interval for Mean	Lower Bound	**48.92**
		Upper Bound	**56.16**
	5% Trimmed Mean		**52.49**
	Median		**52.00**
	Variance		**35.936**
	Std. Deviation		**5.995**
	Minimum		**44**
	Maximum		**62**

The study groups were divided according to their skin tone (Fitzpatrick Skin Type III and V) and the results are presented in **Table 4**.

Table 4 Fitzpatrick Skin Type III and V Distribution.

Group		Skin Type		Total
		III	V	
Control	Count	3	6	9
	%	33.3%	66.7%	100.0%
PBM	Count	4	9	13
	%	30.8%	69.2%	100.0%
Total	Count	7	15	22
	%	31.8%	68.2%	100.0%

The results in **Figures 6** shows the duration of Diabetes Mellitus (DM) for both groups. The mean duration of DM was 11.6 years with a minimum of two years and a maximum of 27 years.

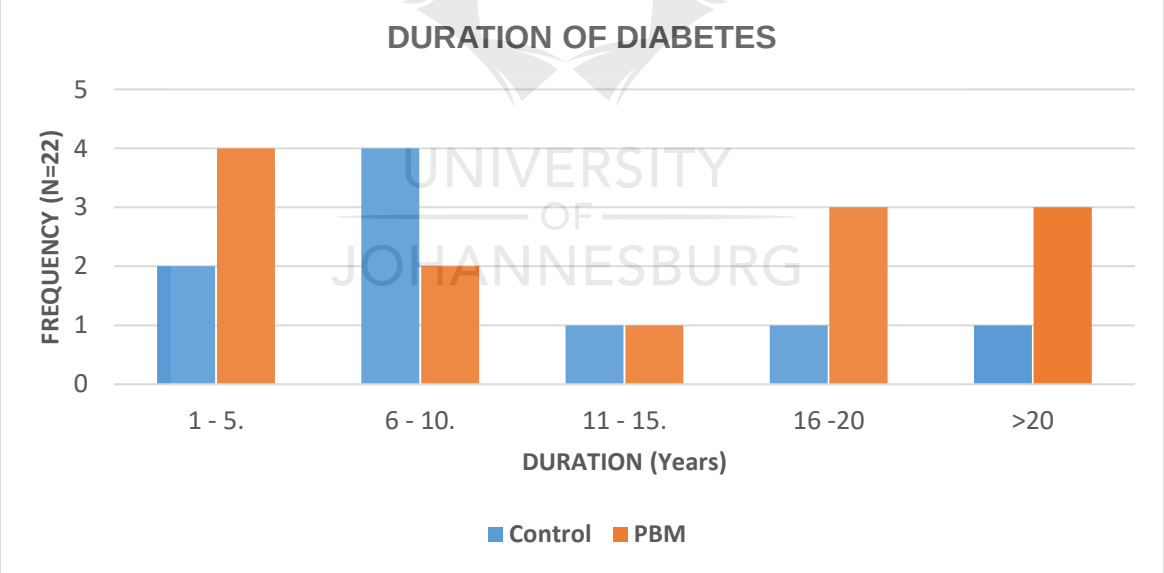

Figure 6. Duration of Diabetes distribution indicates a majority of the participants' DM duration, in the PBM group (n=9), ranged between six years and >20 years.

The results in **Table 5** show the summary of the other risk factors (co-morbidities) that have an impact on wound healing. Out of 22 ulcers, 81,8% were on participants diagnosed with Hypertension and 45.5 % had DM >10-year duration in both groups, respectively.

Table 5 Risk Factors for Diabetic Ulcers.

Group		Risk factors					Total
		Male sex	DM duration >10 yrs.	Peripheral Neuropathy	Hypertension	Smoking	
Control	Count	6	3	4	9	5	9
	%	66.7	33.3	44.4	100	55.6%	100%
PBM	Count	9	7	9	9	7	13
	%	69.2%	53.8%	69.2%	69.2%	53.8%	100%
Total	Count	15	10	13	18	12	22
	%	68.2%	45.5%	59.1%	81.8%	54.5%	100%

4.3 Ulcer healing rate

Overall ulcer healing rate results showed complete healing in 25% (n=2) in the Control group compared to 58.3% (n=7) in the PBM group (**Figure 7**).

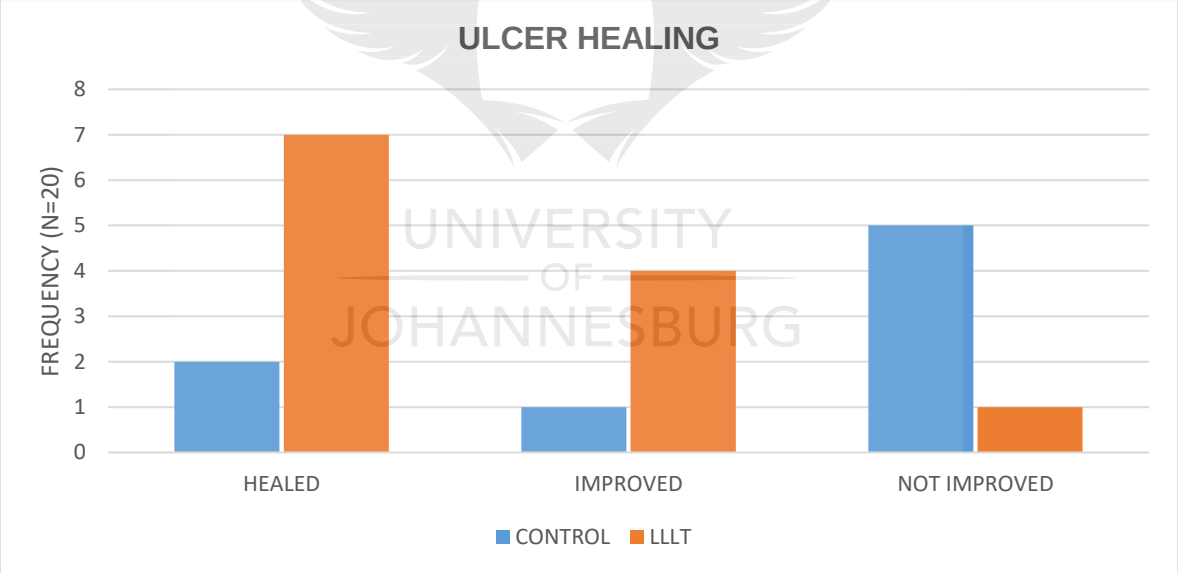

Figure 7. Overall Control versus PBM healing indicates 25% (n=2) of ulcers in the control group were healed completely compared to 58.3% (n=7) in the PBM group. A majority of ulcers (n=5) in the control group remained a same Grade (Not improved) at the end of this study compared to the PBM group (n=1).

The results in **Table 6** show how the ulcers severity (Grade) in both groups changed at the end of the study. These results show that 42.9% of Grade 2 ulcers and 80% of Grade 1 ulcers were completely healed in the PBM group.

Table 6 Ulcer severity (grade) before and after treatment in both groups.

Group				Grade after			Total
				Healed ulcer area	Grade 1	Grade 2	
Control	Grade before	Grade 1	Count	2	4	0	6
			%	33.3%	66.7%	0.0%	100.0%
		Grade 2	Count	0	1	1	2
			%	0.0%	50.0%	50.0%	100.0%
	Total		Count	2	5	1	8
			%	25.0%	62.5%	12.5%	100.0%
PBM	Grade before	Grade 1	Count	4	1	0	5
			%	80.0%	20.0%	0.0%	100.0%
		Grade 2	Count	3	4	0	7
			%	42.9%	57.1%	0.0%	100.0%
	Total		Count	7	5	0	12
			%	58.3%	41.7%	0.0%	100.0%

Both groups showed significant changes in the ulcer perimeters and areas over the study period (**Figures 8 and 9**).

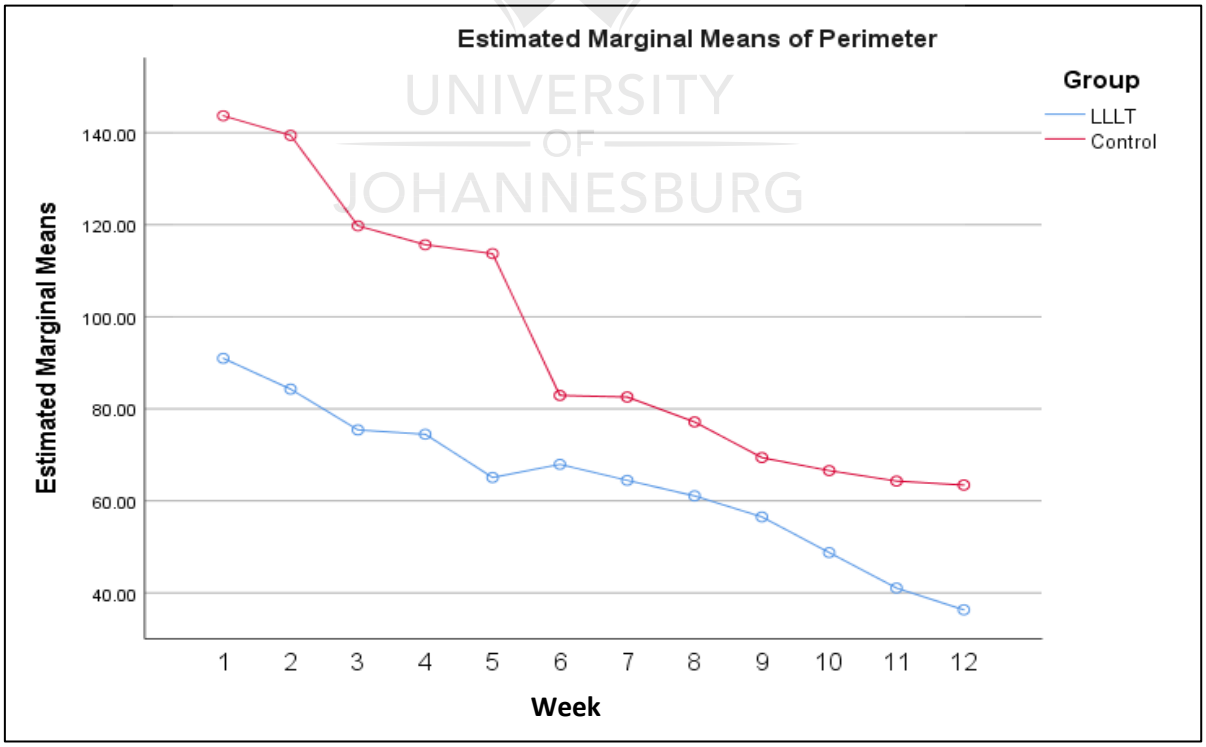

Figure 8 Means of Perimeters for the 12 weeks of treatment indicate significant changes for both groups respectively. The marginal means of parameters of the

control group were higher (>140 mm) than that of the PBM (<100 mm), but these were significantly reduced overtime.

The findings showed statistically significant reduction (p=0.011 Control group vs p=0.003 PBM group) in ulcer perimeters between week 1 and week 4 (**Table 8**).

Table 7 Statistical significant changes in Ulcer Perimeters.

Group		Week1 Perimeter – Week4 Perimeter	Week1 Perimeter – Week8 Perimeter	Week1 Perimeter - Week12 Perimeter	Week4 Perimeter – Week8 Perimeter	Week4 Perimeter – Week12 Perimeter	Week8 Perimeter – Week12 Perimeter
Control	Z	-2.547[b]	-2.201[b]	-2.023[b]	-2.201[b]	-2.023[b]	-2.023[b]
	Asymp. Sig. (2-tailed)	0.011	0.028	0.043	0.028	0.043	0.043
PBM	Z	-2.981[b]	-2.701[b]	-2.201[b]	-2.803[b]	-2.201[b]	-2.201[b]
	Asymp. Sig. (2-tailed)	0.003	0.007	0.028	0.005	0.028	0.028
a. Wilcoxon Signed Ranks Test							
b. Based on positive ranks.							

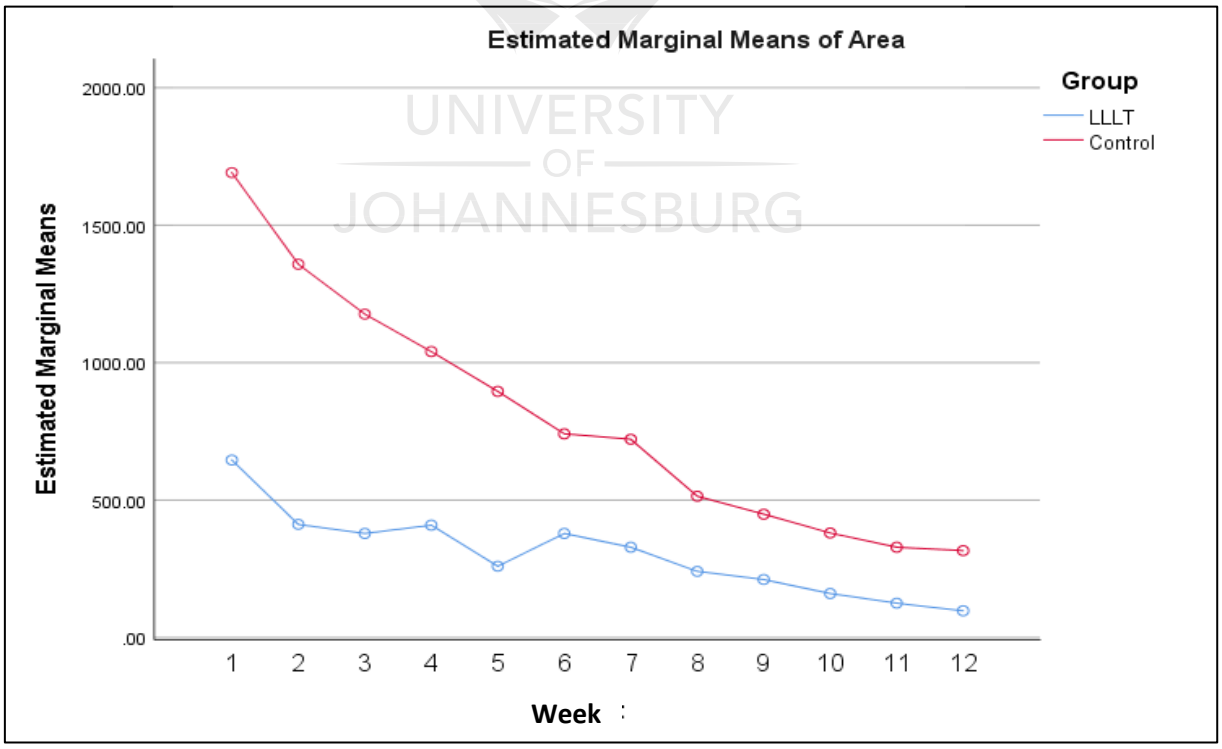

Figure 9. Means of Area for the 12 weeks of treatment indicate significant changes for both groups respectively. The marginal means of parameters of the

control group were higher (>1500 mm^2) than that of the PBM (>500 mm), but these were significantly reduced overtime.

The results show statistically significant reduction (p=0.04 Control group vs p=0.03 PBM group) in ulcer areas at week 12 (**Table 8**).

Table 8 Statistical significant changes in Ulcer Area.

Group		Week1 Area – Week4 Area	Week1 Area - Week8 Area	Week1 Area - Week12 Area	Week4 Area – Week8 Area	Week4 Area – Week12 Area	Week8 Area – Week12 Area
Control	Z	-2.547[b]	-2.201[b]	-2.023[b]	-2.201[b]	-2.023[b]	-2.023[b]
	Asymp. Sig. (2-tailed)	0.011	0.028	0.043	0.028	0.043	0.043
PBM	Z	-3.059[b]	-2.803[b]	-2.201[b]	-2.803[b]	-2.201[b]	-2.201[b]
	Asymp. Sig. (2-tailed)	0.002	0.005	0.028	0.005	0.028	0.028
a. Wilcoxon Signed Ranks Test							
b. Based on positive ranks.							

The results in **Figure 10** show healing in all the other risk factors that may have an impact on wound healing in both groups. The results show that a majority of healed ulcers (n=7) are from the PBM group.

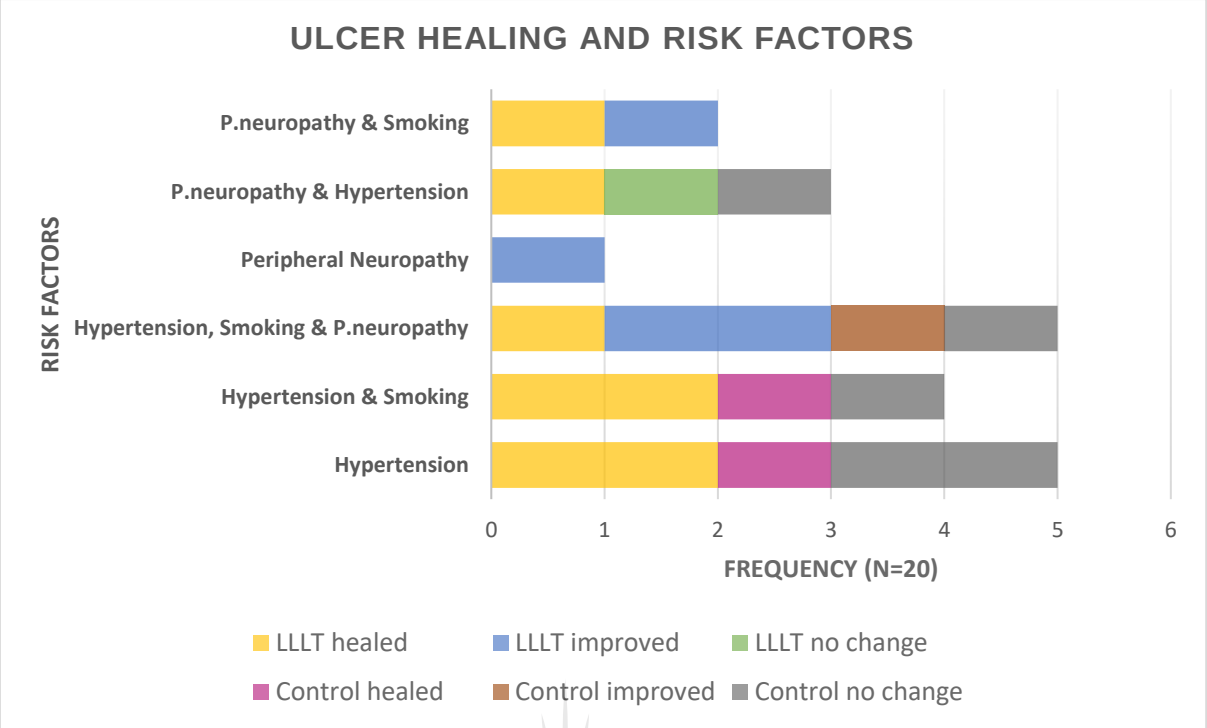

Figure 10. Ulcer healing in different risk factors indicates majority of ulcers that healed (n=7) and improved (n=4) were from the PBM group compared to the control group healed (n=2) and improved ulcers (n=1). The mean number of healed ulcers was 3.33 for both groups respectively.

The results were further analysed to reflect findings on healing in male gender and duration of DM. **Tables 9** present the findings of ulcer healing of ulcers that were on male participants.

Table 9. Ulcer healing in the Male gender.

Group				Grade after			Total
				Healed ulcer area	Grade 1	Grade 2	
Control	Grade before	Grade 1	Count	1	3	0	4
			%	33.3%	66.7%	0.0%	100.0%
		Grade 2	Count	0	1	1	2
			%	0.0%	50.0%	50.0%	100.0%
PBM	Grade before	Grade 1	Count	4	1	0	5
			%	80%	20.0%	0.0%	100.0%
		Grade 2	Count	1	3	0	4
			%	25.0%	75.0%	0.0%	100.0%
	Total		Count	6	8	1	15
			%	40.0%	53.33%	6.67%	100.0%

The findings in **Table 10** shows ulcer healing in the participants living with DM for >10 years.

Table 10. Ulcer healing and Duration of DM (>10year).

Group				Grade after			Total
				Healed ulcer area	Grade 1	Grade 2	
Control	Grade before	Grade 1	Count	1	1	0	2
			%	33.3%	66.7%	0.0%	100.0%
		Grade 2	Count	0	1	0	1
			%	0.0%	100.0%	0.0%	100.0%
PBM	Grade before	Grade 1	Count	4	1	0	5
			%	80%	20.0%	0.0%	100.0%
		Grade 2	Count	2	0	0	2
			%	25.0%	75.0%	0.0%	100.0%
	Total		Count	7	3	0	10
			%	70.0%	30.0%	0.0%	100.0%

4.4 The Control group results

Initially, there were nine ulcers in this group; however, at week seven, one control participant left the study. Only eight ulcers stayed in this study for 12 weeks or until healed. The following pictures and line graphs present the results from Control participant 1 to 9 to show ulcer-healing progress.

4.4.1 Control 1

A 52-year-old Indian male participant with a Grade 1 ulcer on the plantar aspect of his right. Ulcer of five months duration, a smoker and a person with diabetes for five years. The ulcer healed within six weeks (**Figure 11.1** and **11.2**).

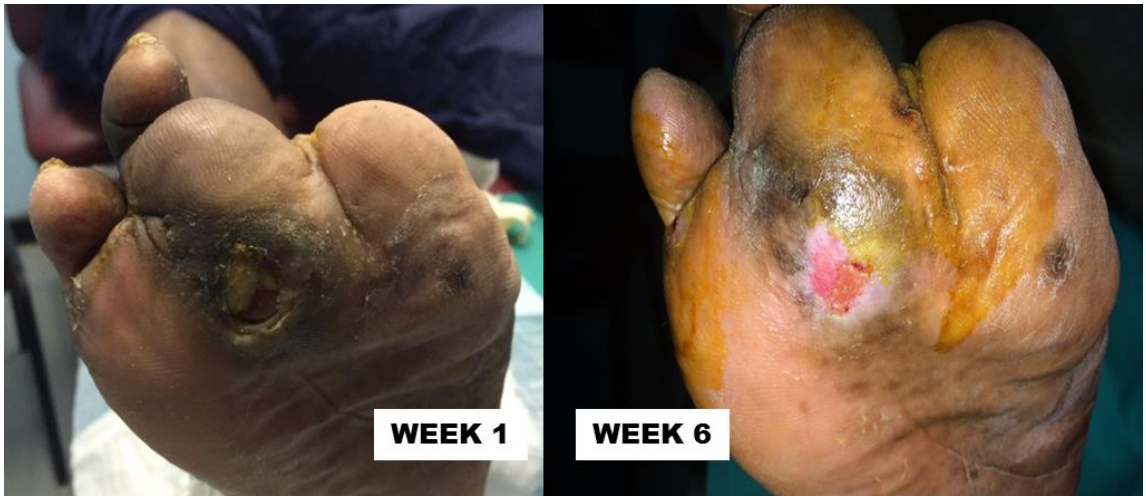

Figure 11.1. Control 1 ulcer: shows the ulcer before podiatric intervention (Week 1) and after healing (Week 6).

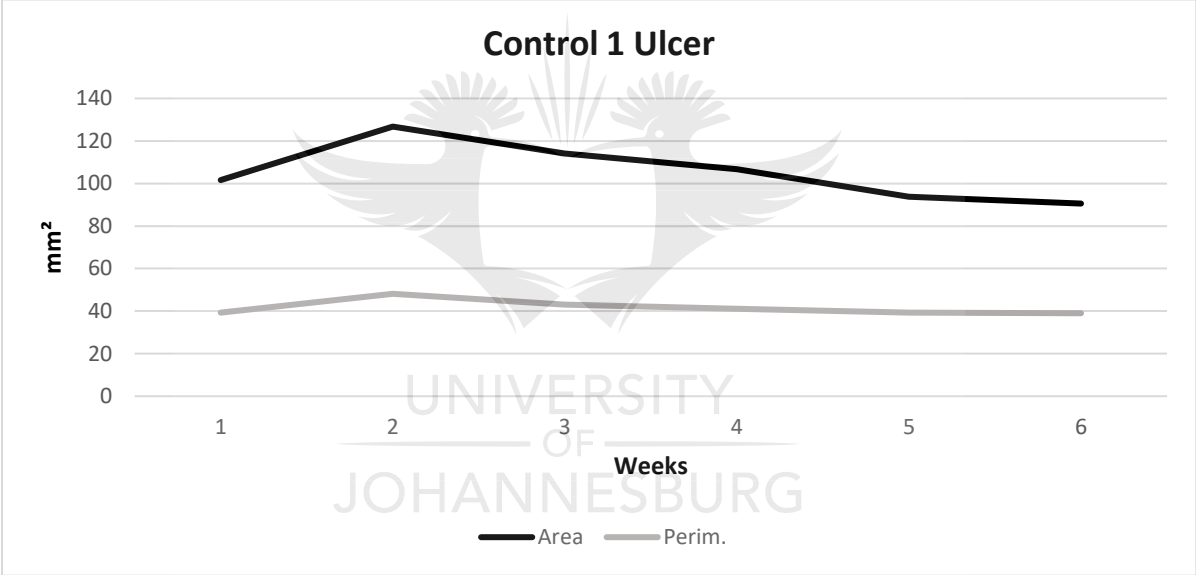

Figure 11.2. Control 1 ulcer progress graph shows the ulcer area and parameter decreased by ~ 11% and < 1% in six weeks. These measured the site where the healed ulcer is/was.

4.4.2 Control 2

A 59-year-old Caucasian male participant with a Grade 2 ulcer on the lateral plantar aspect of his left foot (amputation site). Ulcer duration: 2 months. Was also a smoker and living with diabetes for 17 years.

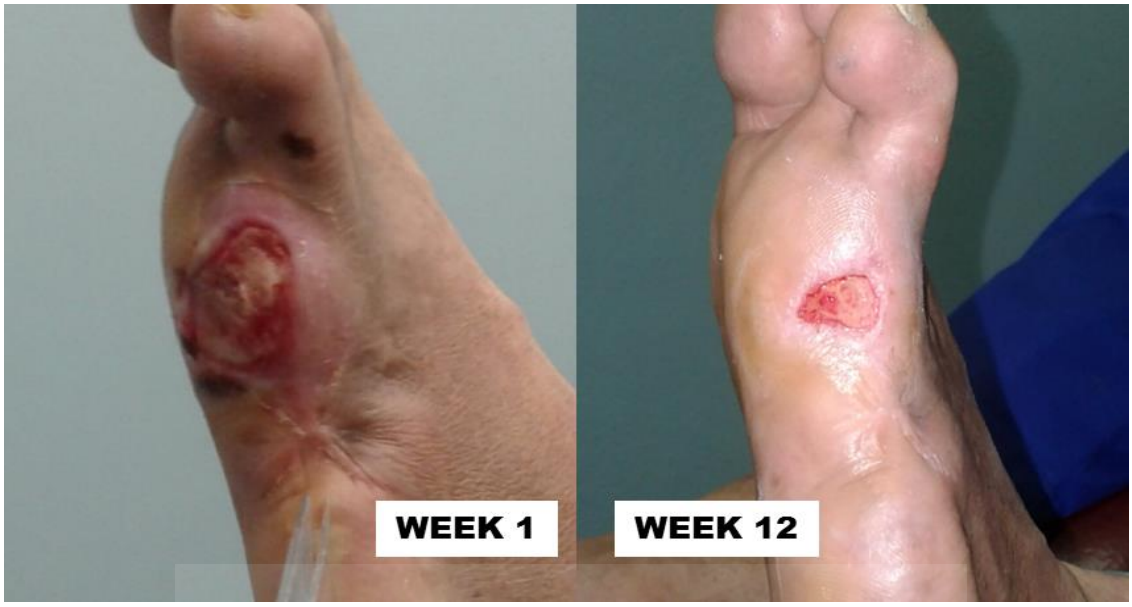

Figure 12.1. Control 2 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 12).

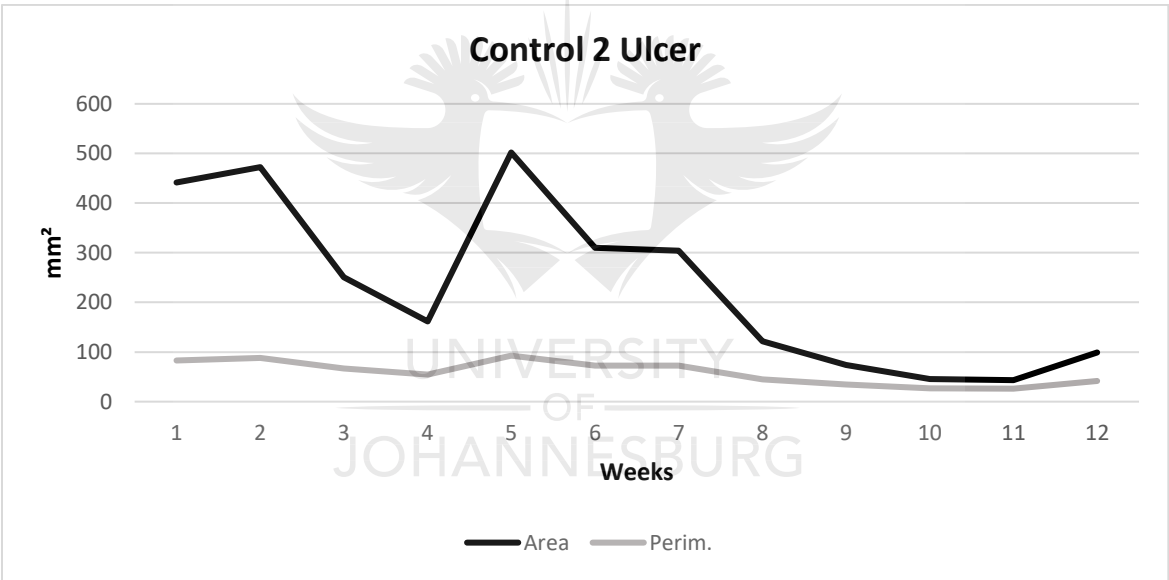

Figure 12.2. Control 2 ulcer progress graph shows the ulcer area increased between week 4 and week 5. Also shows how it decreased between week 7 and week 11.

4.4.3 Control 3

A 52-year-old Black African female participant with a Grade 1 ulcer on the lateral aspect of her leg. Ulcer of four months duration and a diabetic and hypertensive for two years.

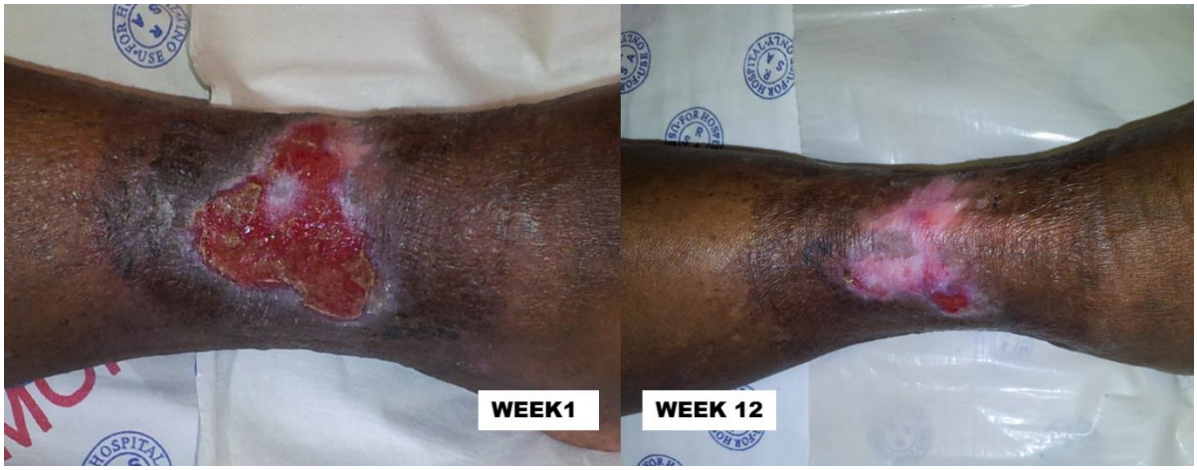

Figure 13.1 Control 3 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 12).

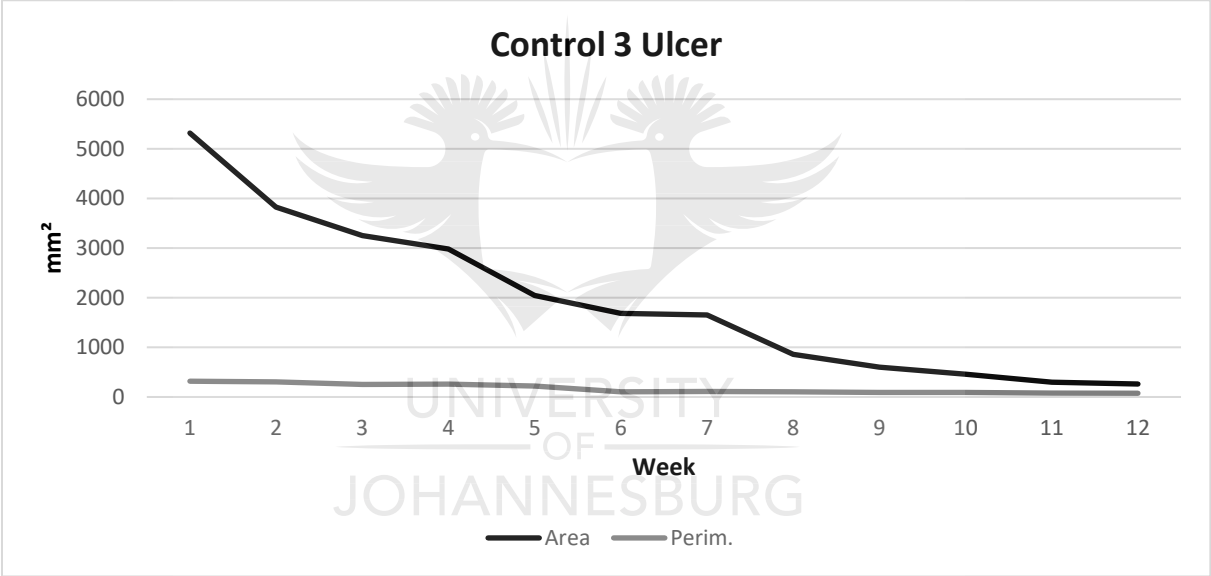

Figure 13.2 Control 3 ulcer progress graph shows ulcer healing in 12 weeks. The graph shows decreased by 98.6% by week 12.

4.4.4 Control 4

A 56-year-old Caucasian female participant with a Grade 1 ulcer on the plantar-medial aspect of her left hallux. Ulcer of 2 months duration and had diabetes for 15 years.

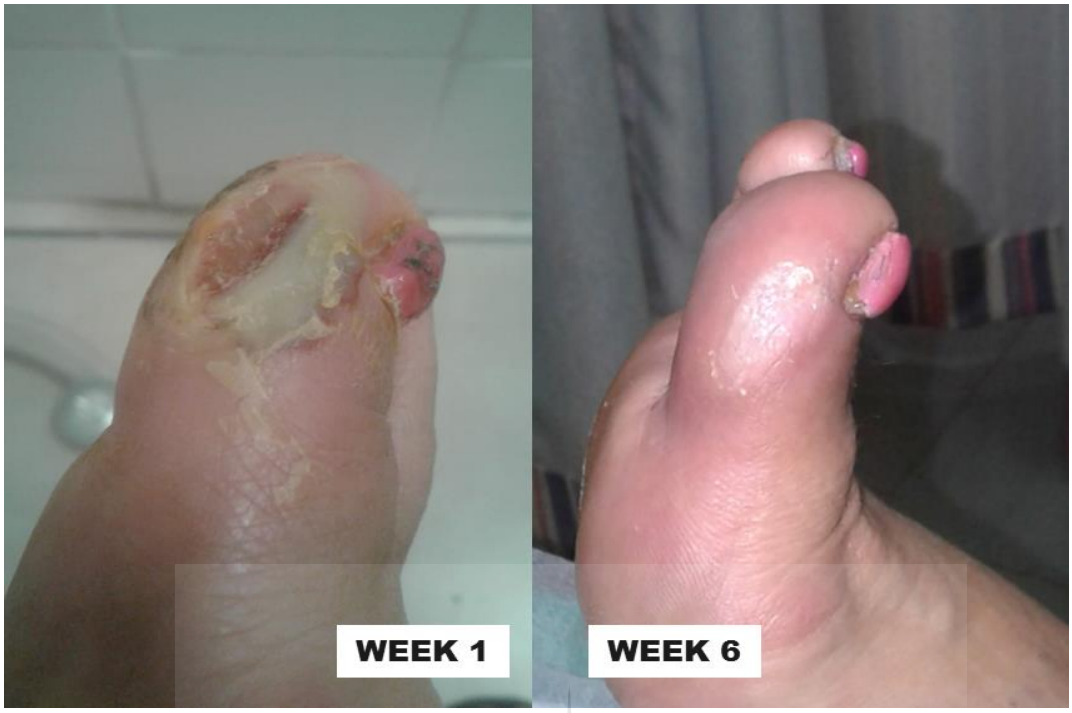

Figure 14.1. Control 4 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 6)

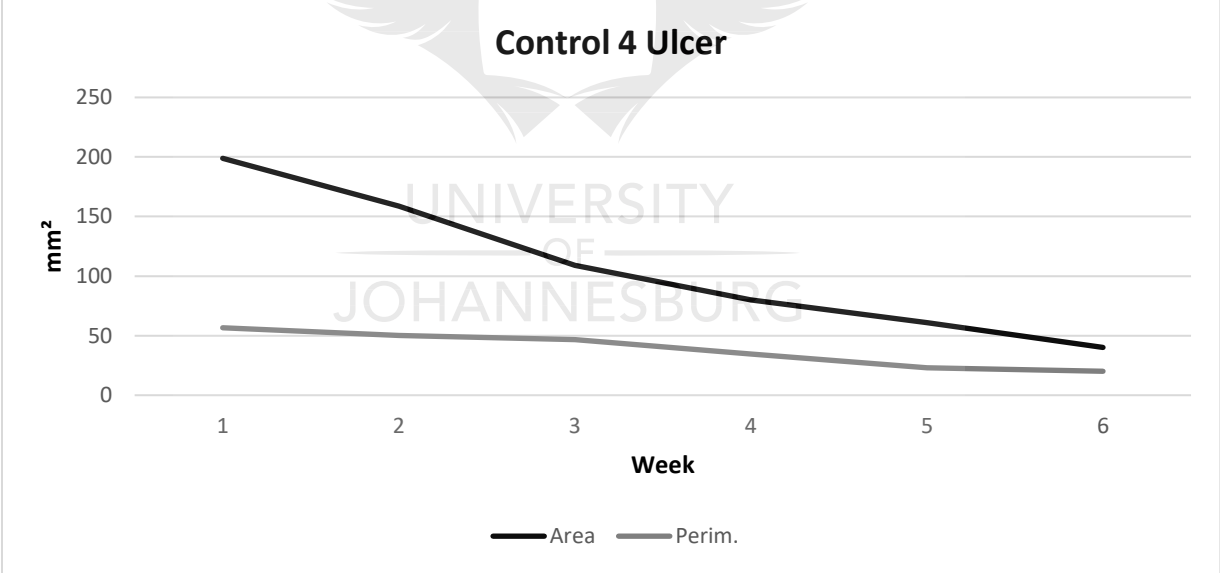

Figure 14.2. Control 4 ulcer progress graph shows how the ulcer area decreased by ~ 80% in six weeks.

4.4.5 Control 5

A 74-year-old Indian male participant who presented with a Grade 1 ulcer on his left foot plantar aspect. Ulcer duration: 24 months and diagnosed with diabetes 27 years ago.

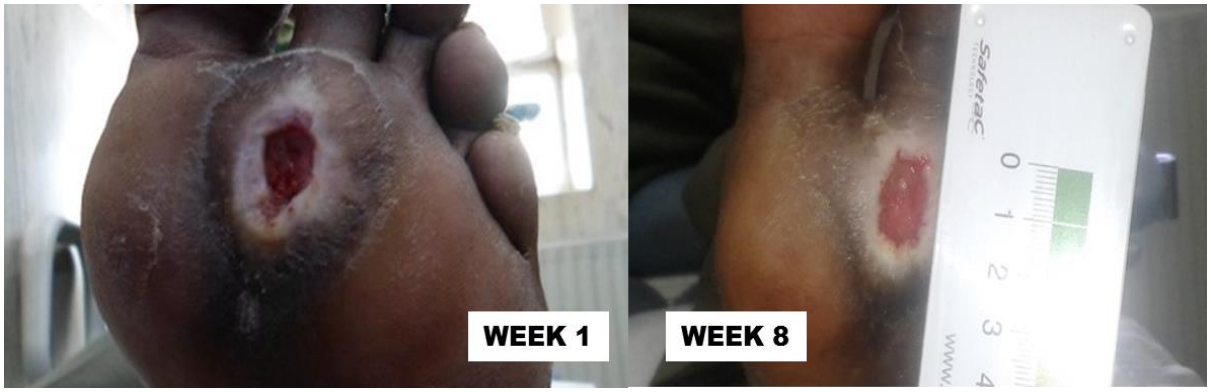

Figure 15.1 Control 5 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 8). Participant left the study.

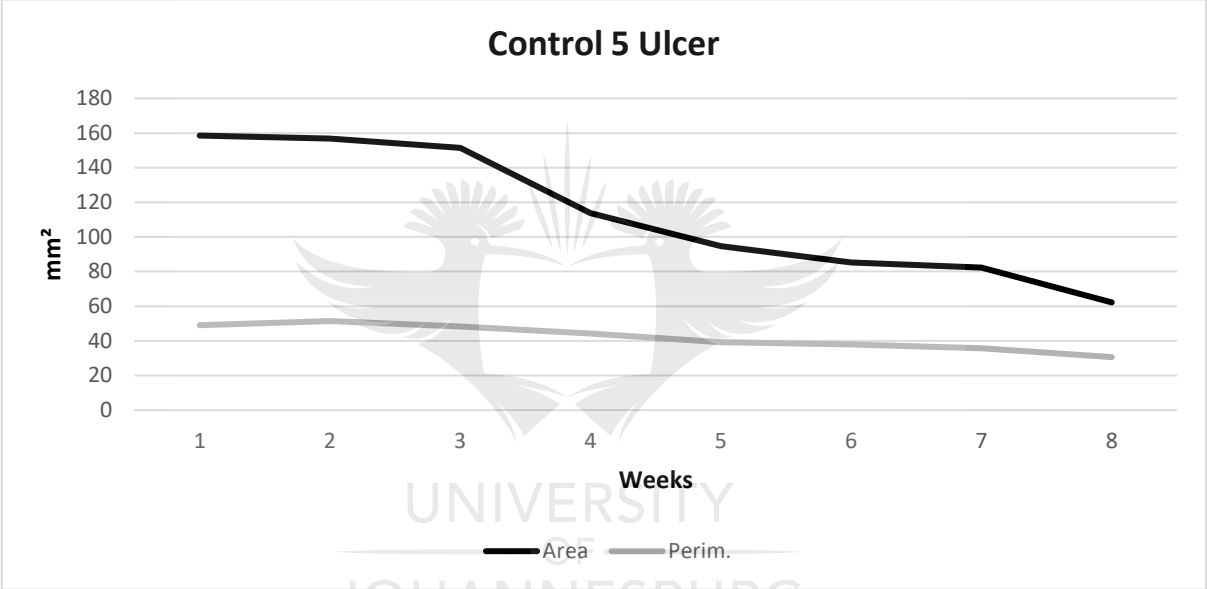

Figure 15.2. Control 5 Ulcer progress graph shows how the ulcer area decreased by ~ 63% in eight weeks.

4.4.6 Control 6

A 44-year-old Black African male with two Grade 2 ulcers on both feet plantar metatarsal area. Ulcer of two-year duration and diagnosed with Diabetes and Hypertension eight years ago.

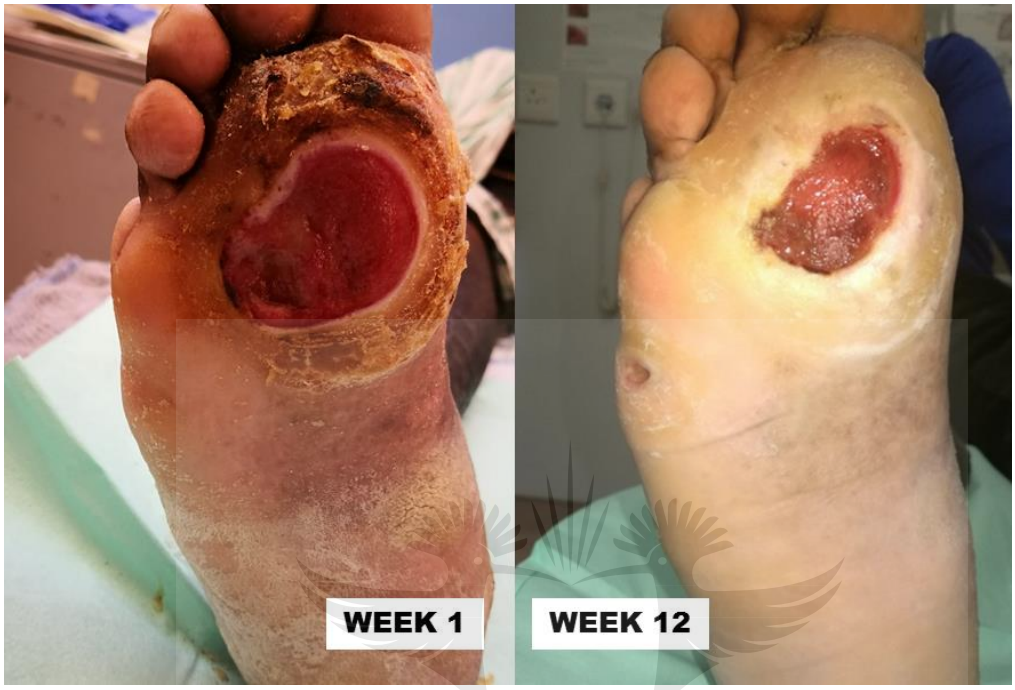

Figure 16.1. Control ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 12).

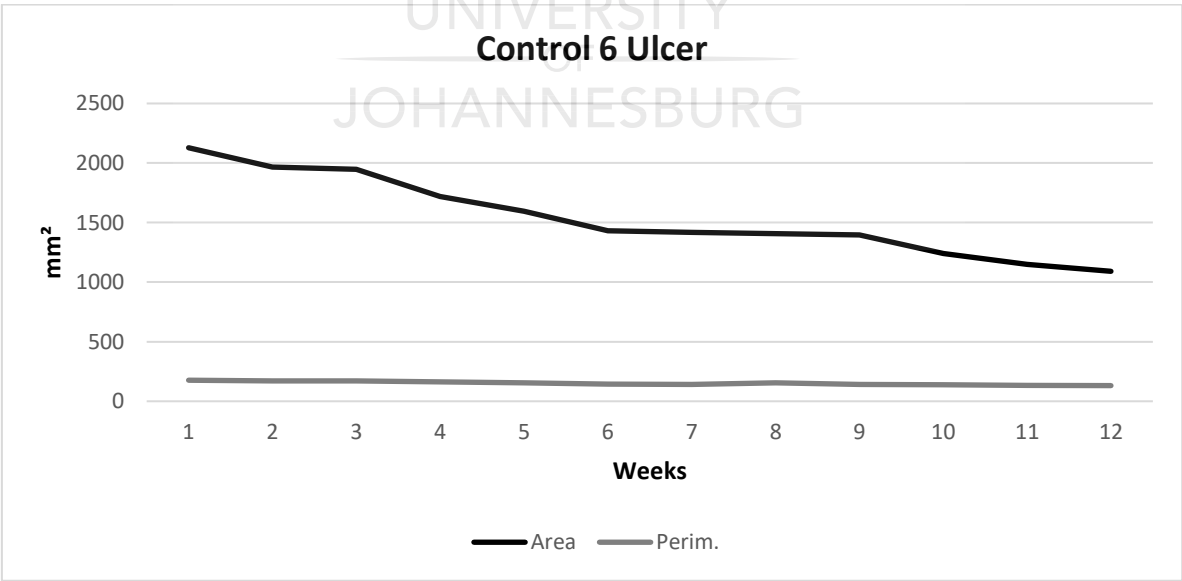

Figure 16.2. Control 6 Ulcer progress graph shows how the ulcer area decreased by ~ 51% in 12 weeks.

4.4.7 Control 7

A 54-year-old Indian male who presented with a Grade 1 interdigital ulcer (post digit amputation). Ulcer of three months duration and diagnosed with DM and Hypertension for six years.

Figure 17.1 Control 7 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 12).

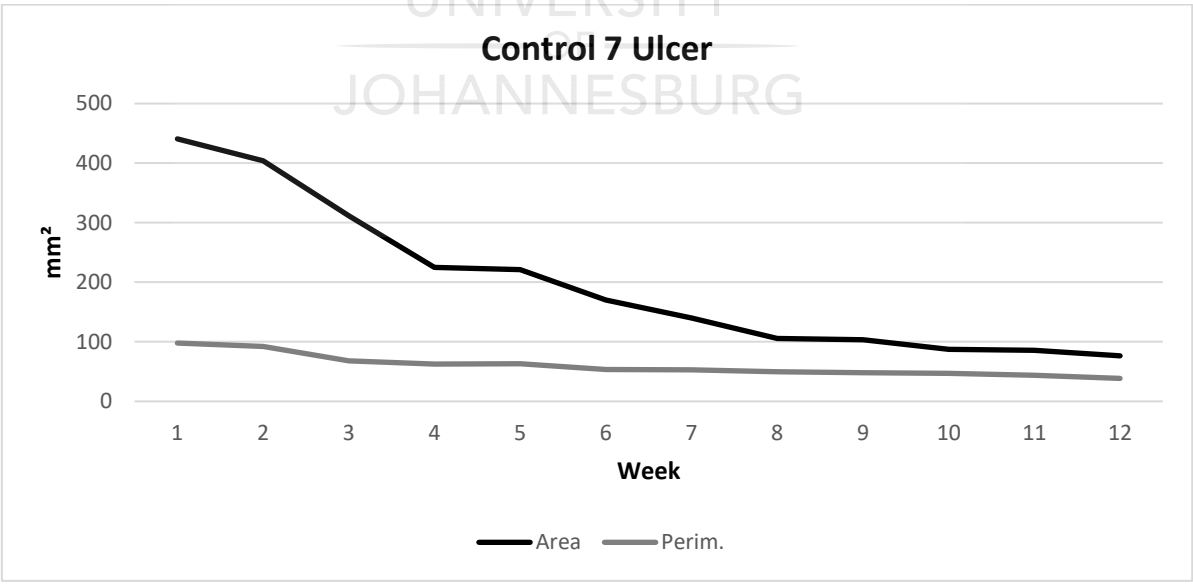

Figure 17.2. Control 7 ulcer progress graph shows how the ulcer area decreased by ~ 83% in 12 weeks.

4.4.8 Control 8

A 57-year-old Coloured female who presented with a Grade 1 ulcer on the 5th plantar metatarsal aspect of the right foot. Ulcer of 3 months duration and diagnosed with DM and Hypertension for eight years.

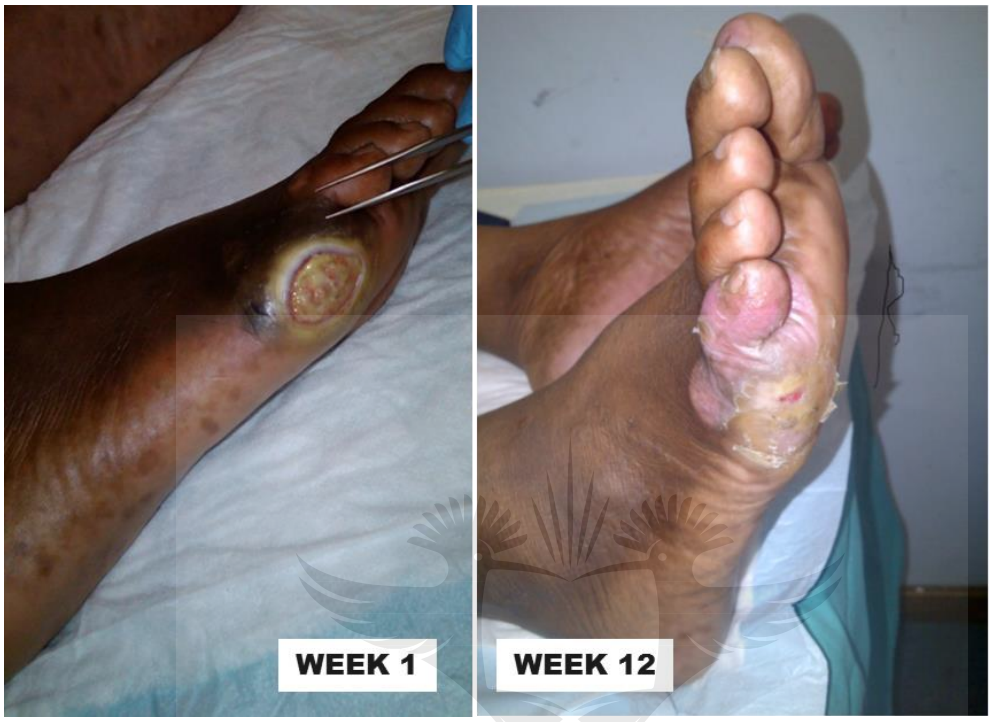

Figure 18.1 Control 8 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 12).

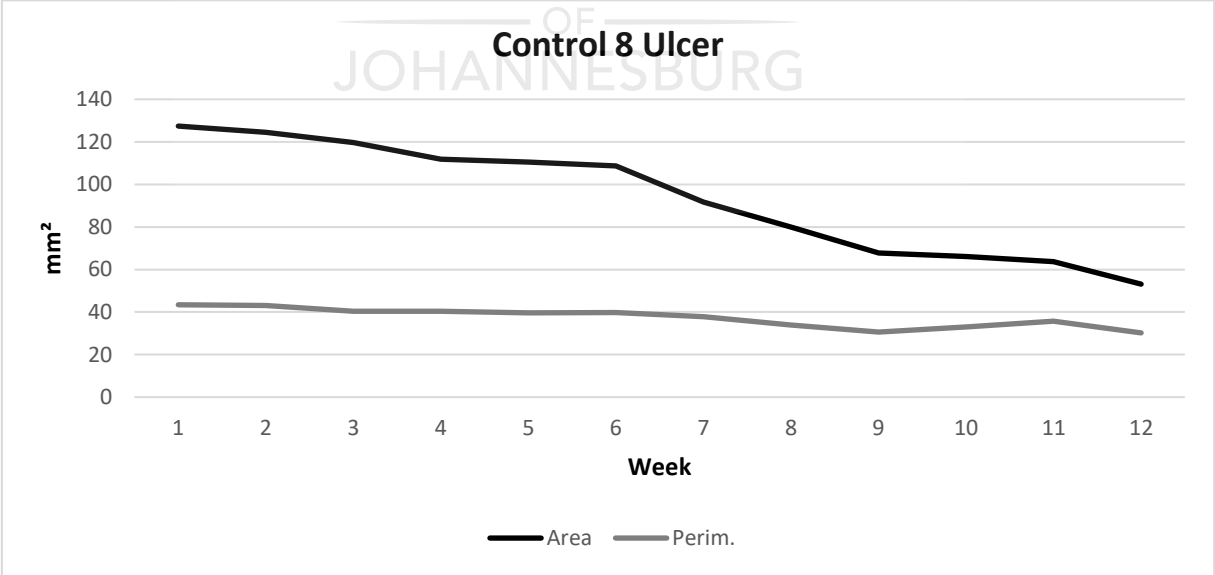

Figure 18.2. Control 8 ulcer progress graph shows how the ulcer area decreased by ~ 58% and healed in 12 weeks.

4.4.9 Control 9

A 65-year-old Caucasian male who presented with a Grade 1 ulcer on the plantar metatarsal area of the right foot. Ulcer of six months duration, diagnosed with DM ten years ago and a smoker.

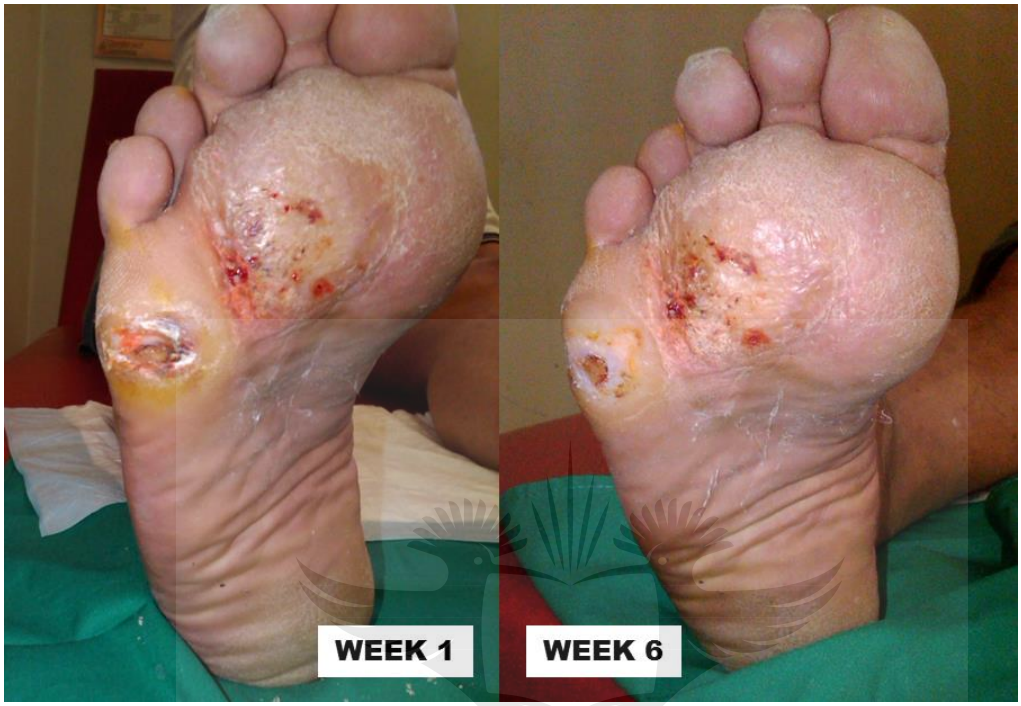

Figure 19.1 Control 9 ulcer: shows the ulcer before podiatric intervention (Week 1) and after podiatric intervention (Week 6). Participant left the study.

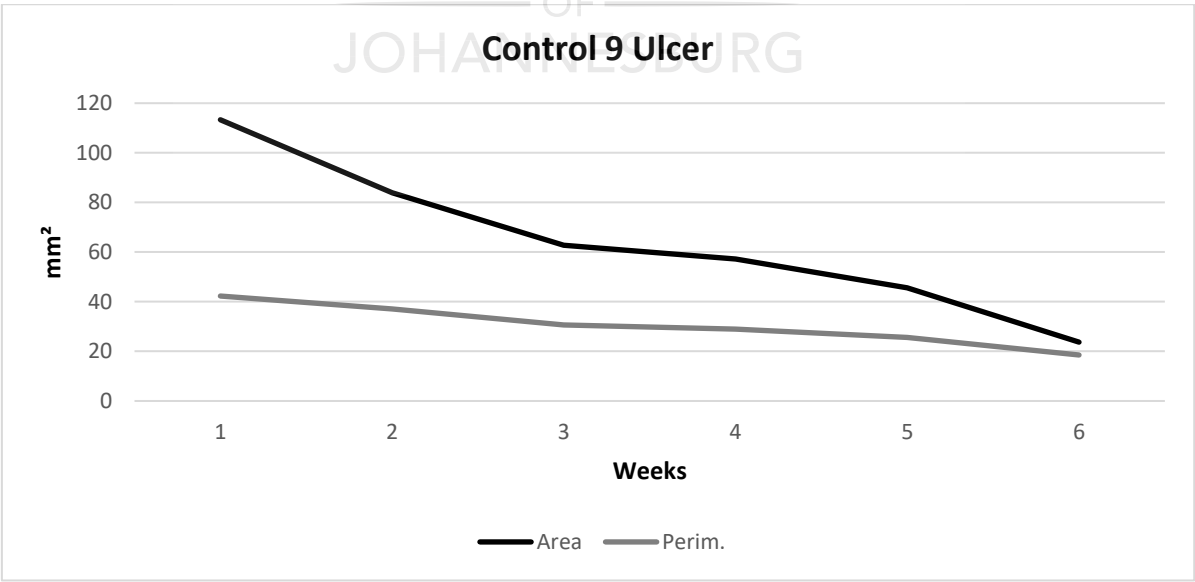

Figure 19.2. Control 9 ulcer progress graph shows how the ulcer area decreased in six weeks before the participant left the study.

4.5 Photobiomodulation group results

Overall, 12 ulcers received irradiation in the treatment group over the 12 weeks, and one participant decided to withdraw from the study at week four. This section presents visual results from participants 1 to 10 in pictures and line graphs to show ulcer-healing progress.

4.5.1 Participant 1

A 57-year-old Indian male diagnosed with Diabetes 25 years ago and is a smoker. He presented with two Grade 1 ulcers of three-month duration on his below the knee amputation site.

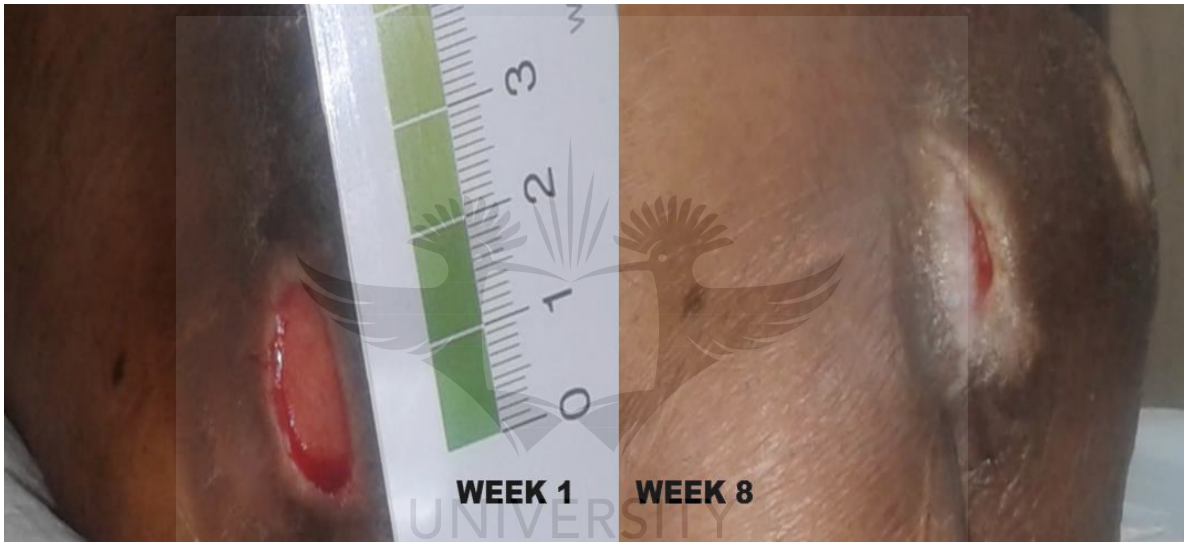

Figure 20.1. Participant 1 Ulcer 1: shows the ulcer before PBM (Week 1) and after PBM (week 8).

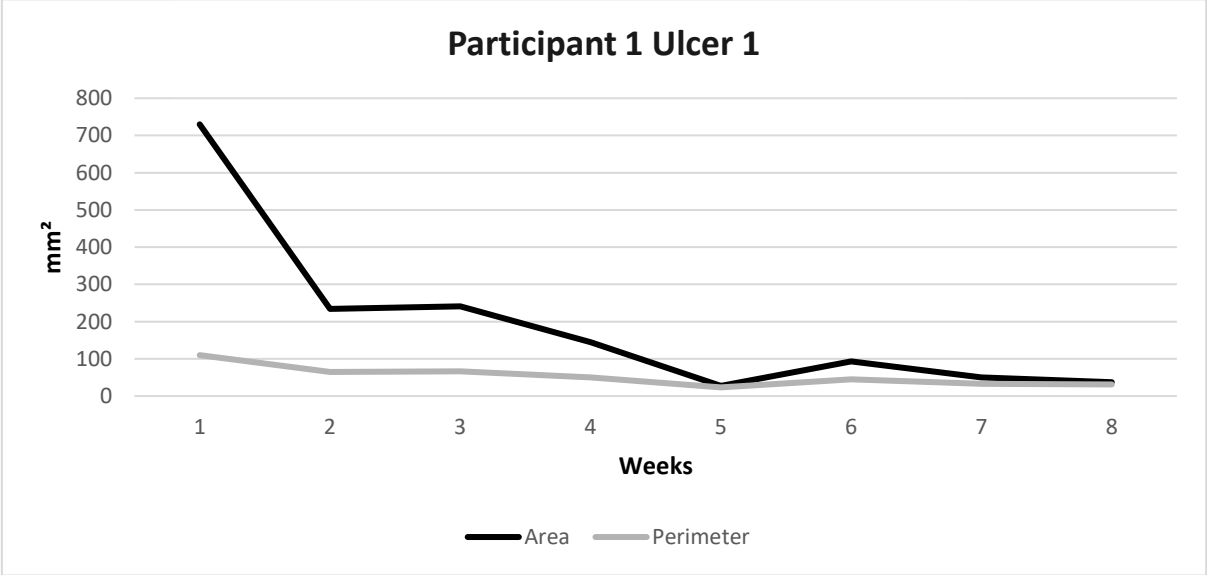

Figure 20.2. Participant 1 Ulcer 1-progress graph shows ulcer healing in eight weeks.

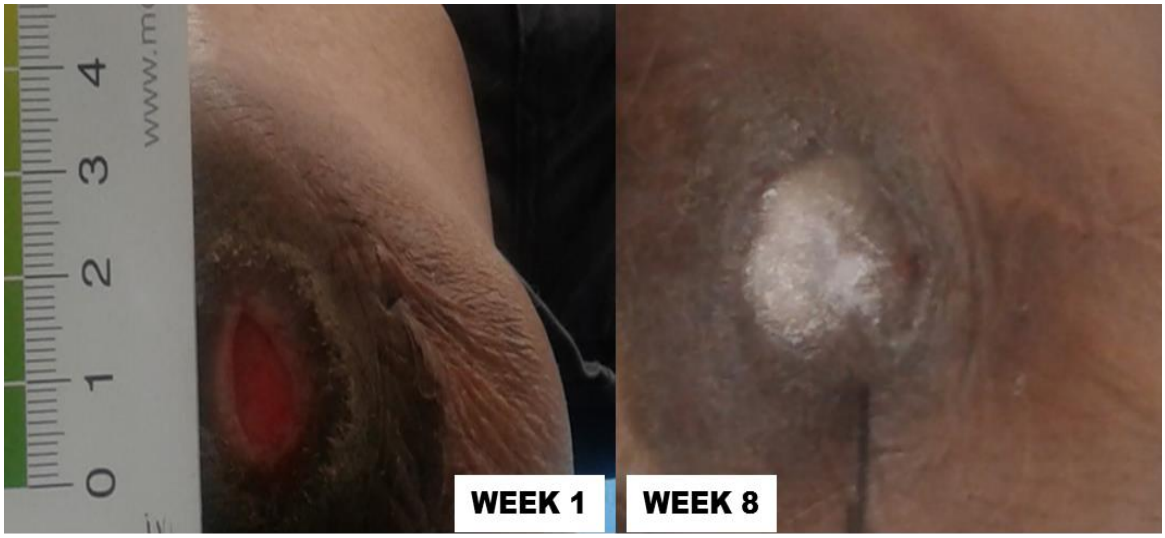

Figure 20.3. Participant 1 Ulcer 2: shows the ulcer before PBM (Week 1) and after PBM (Week 8).

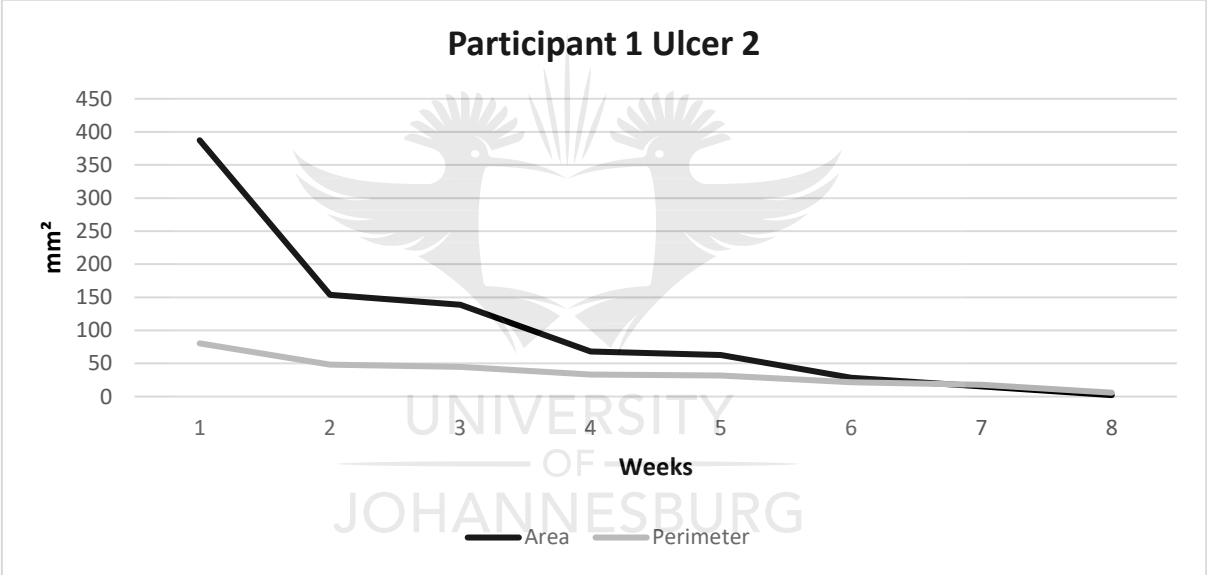

Figure 20.4 Participant 1 Ulcer 2-progress graph shows ulcer healing in eight weeks.

4.5.2 Participant 2

A 60-year-old Caucasian female diagnosed with diabetes for six years. She had a previous history of amputation of all digits due to non-healing ulcers. Presented with a Grade 2 ulcer of 24-month duration on the plantar aspect of her right foot.

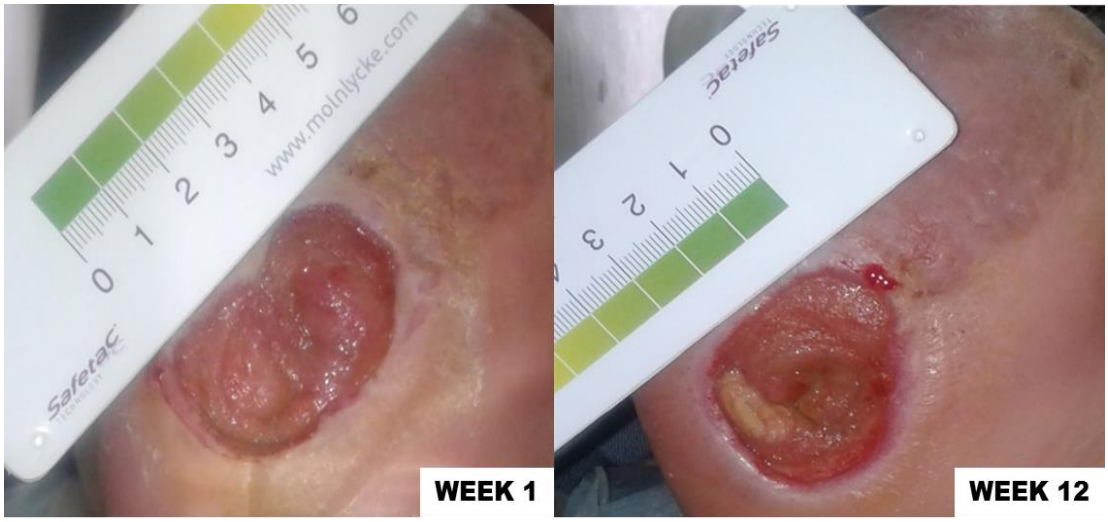

Figure 21.1. Participant 2 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

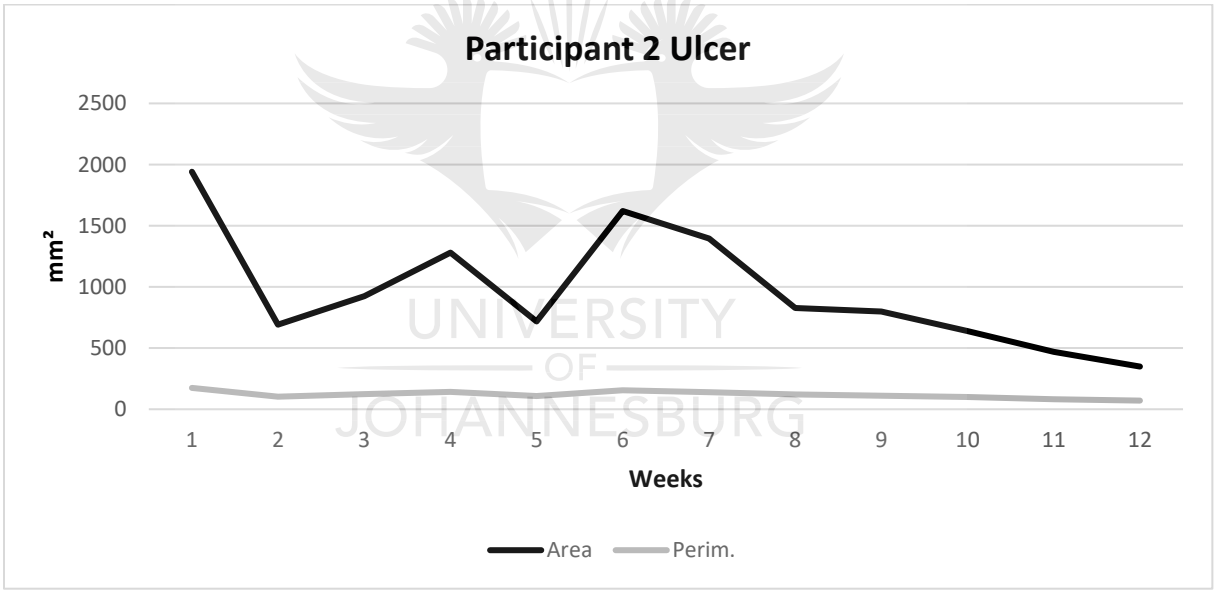

Figure 21.2. Participant 2 Ulcer progress graph shows the perimeter was constant whereas the area decreased significantly by ~82% in 12 weeks of PBM.

4.5.3 Participant 3

A 49-year-old Black African male with a Grade 1 ulcer on the forefoot (post-amputation site) of seven weeks duration. Diagnosed with Diabetes and Hypertension 11 years ago.

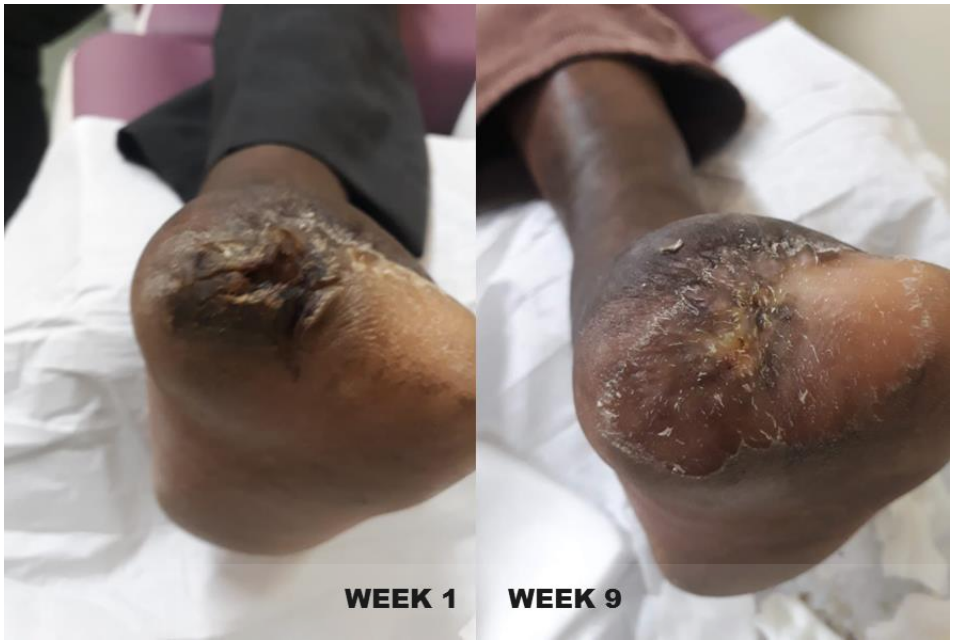

Figure 22.1. Participant 3 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 9).

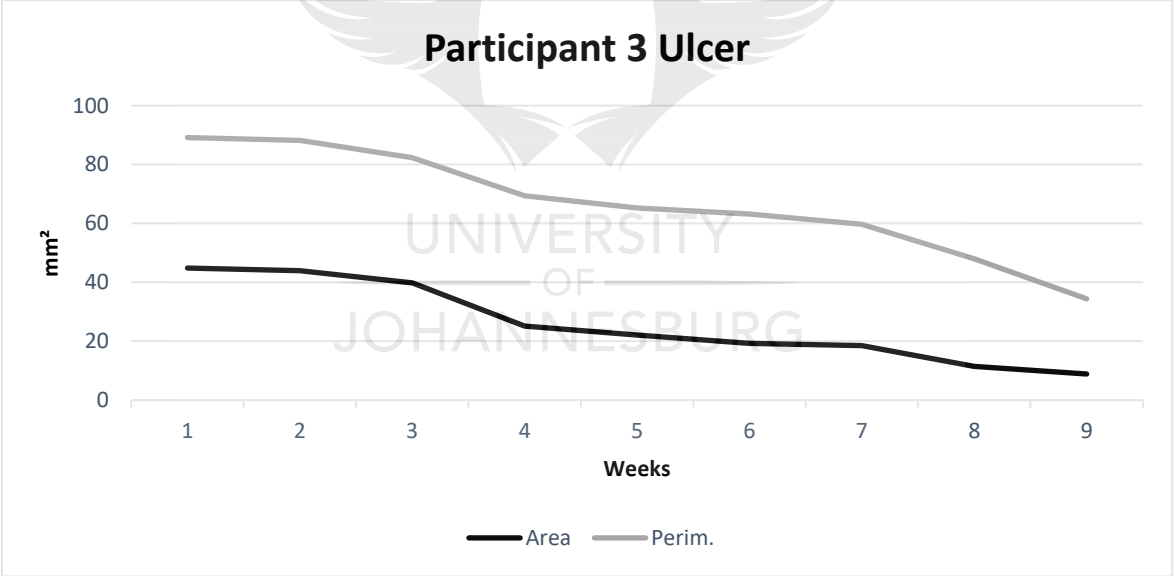

Figure 22.2. Participant 3 Ulcer progress graph shows ulcer healing in nine weeks.

4.5.4 Participant 4

The participant was a 52-year-old Caucasian female diagnosed with diabetes 22 years ago. She presented with a Grade 1 ulcer of 12-month duration on her left plantar aspect of the first metatarsal head.

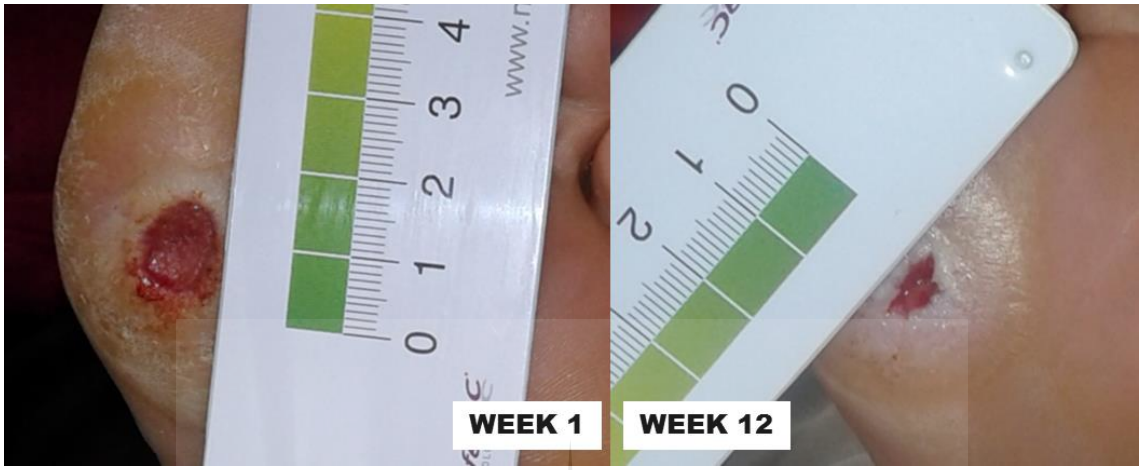

Figure 23.1. Participant 4 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

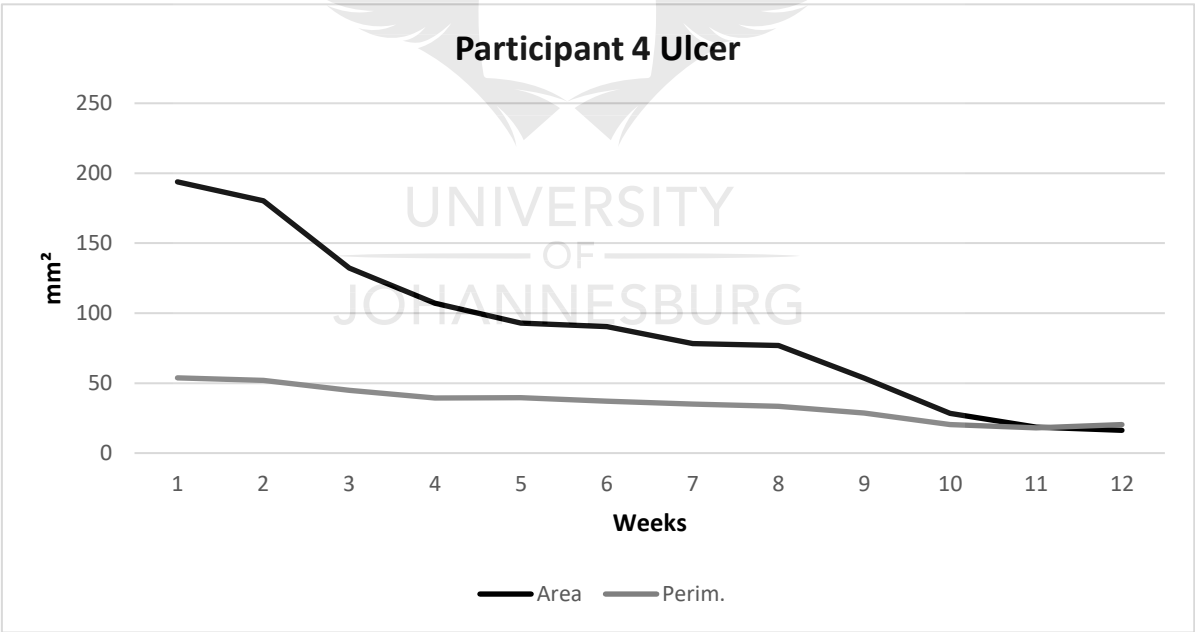

Figure 23.2. Participant 4 Ulcer progress graph shows significant improvement of the ulcer in 12 weeks. Ulcer area decreased by ~ 92% and parameter decreased by 62%.

4.5.5 Participant 5

A 62-year-old Black female participant who presented with a Grade 1 ulcer of 8-month duration on her right foot plantar aspect of the fifth metatarsal. Diagnosed with diabetes 16 years ago.

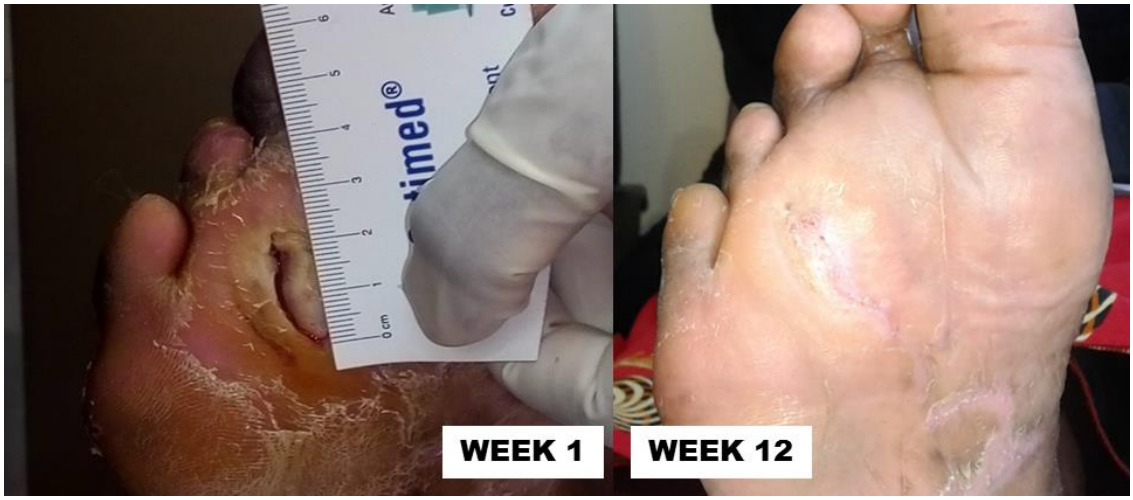

Figure 24.1. Participant 5 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

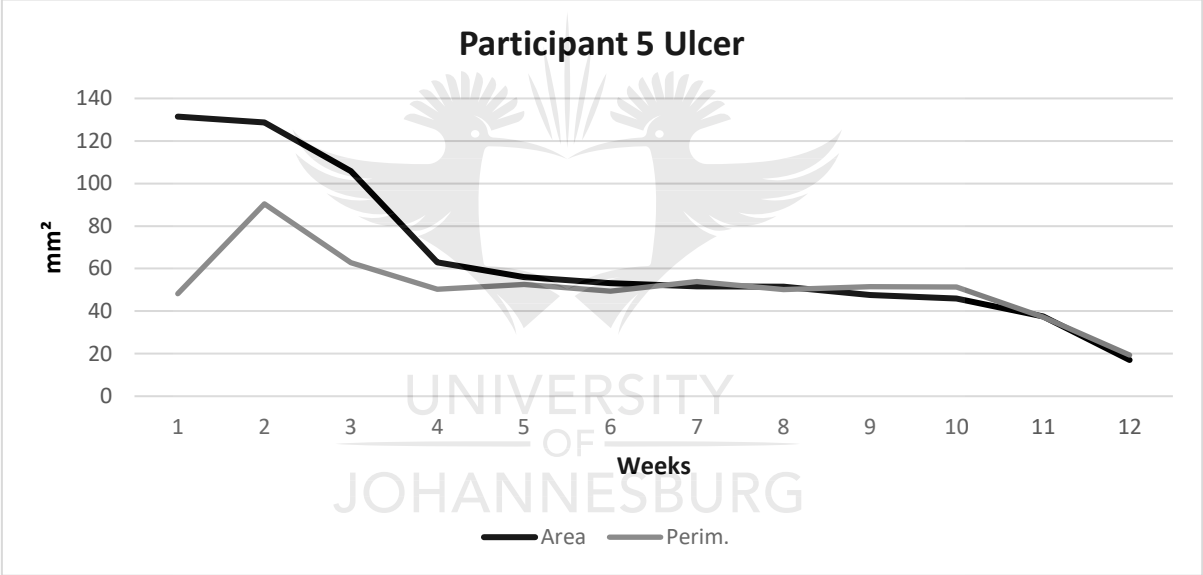

Figure 24.2. Participant 5 ulcer progress graph shows ulcer healing in 12 weeks.

4.5.6 Participant 6

This participant was a 52-year-old Caucasian male who presented with a Grade 2 ulcer on his left foot on the plantar aspect of his second metatarsal head. Ulcer duration: 19 months. The participant is a smoker, diagnosed with diabetes two years ago.

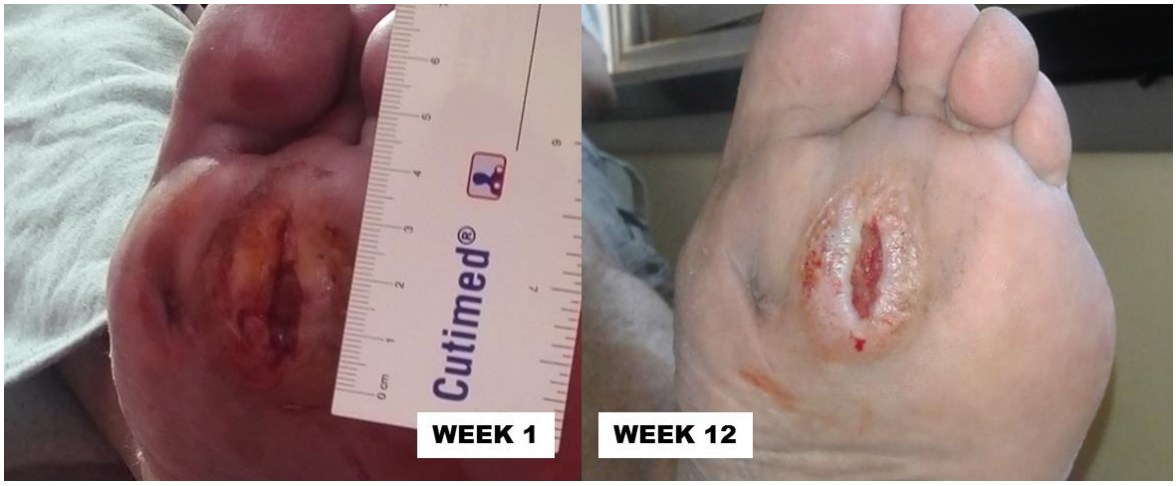

Figure 25.1. Participant 6 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

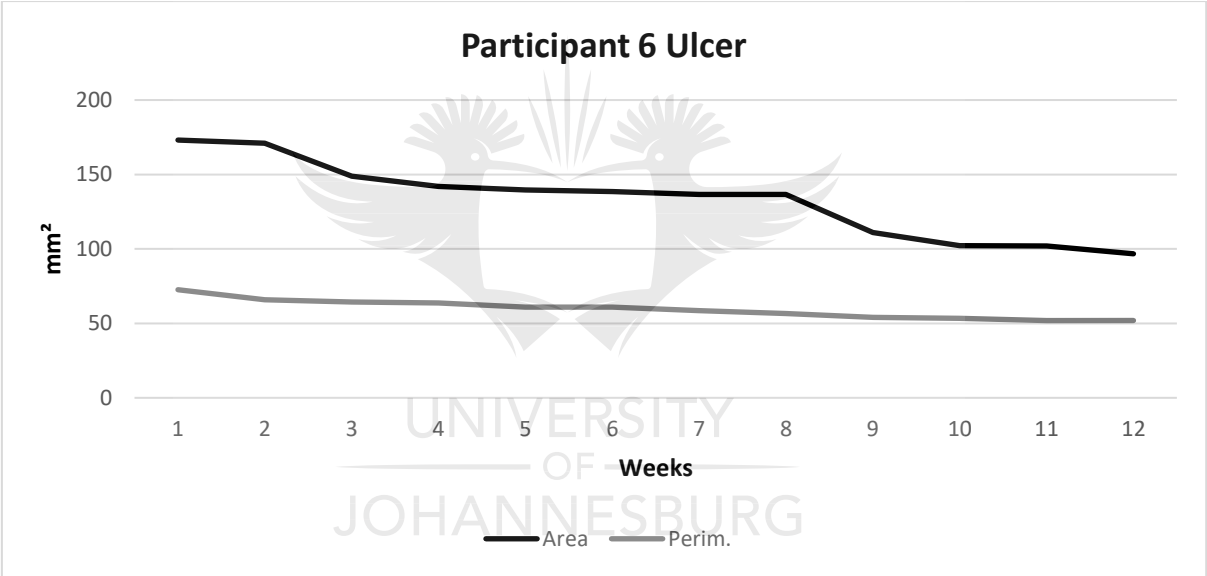

Figure 25.2. Participant 6 Ulcer progress graph shows the ulcer did not significantly improve in its perimeter and area. Ulcer area decreased by ~ 44% and parameter decreased by ~ 28%.

4.5.7 Participant 7

A 56-year-old Indian male participant who presented with two ulcers on his right foot plantar aspect. Ulcer duration of 3 months and diagnosed with diabetes 16 years ago.

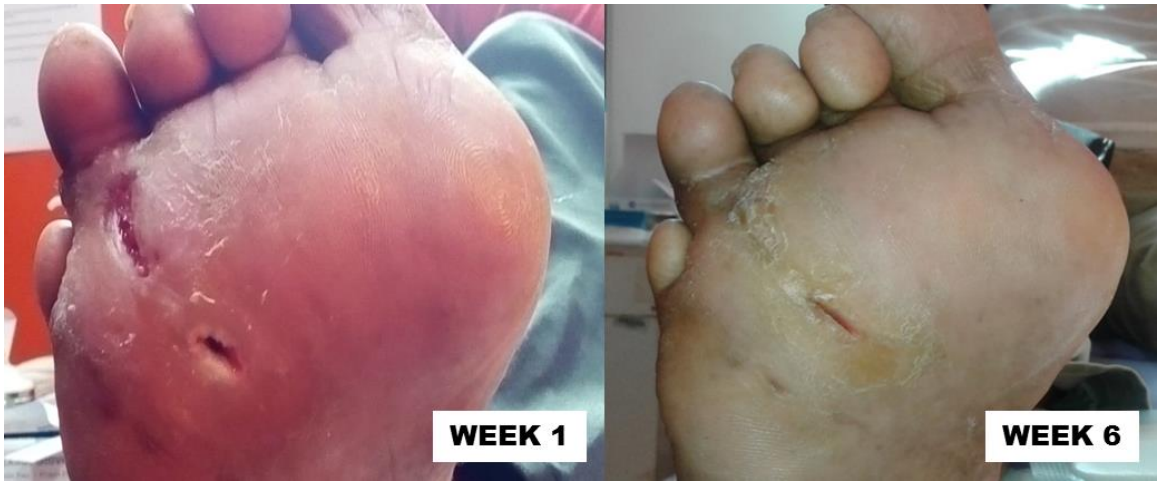

Figure 26.1. Participant 7 ulcers before PBM (Week 1) and after PBM (Week 6).

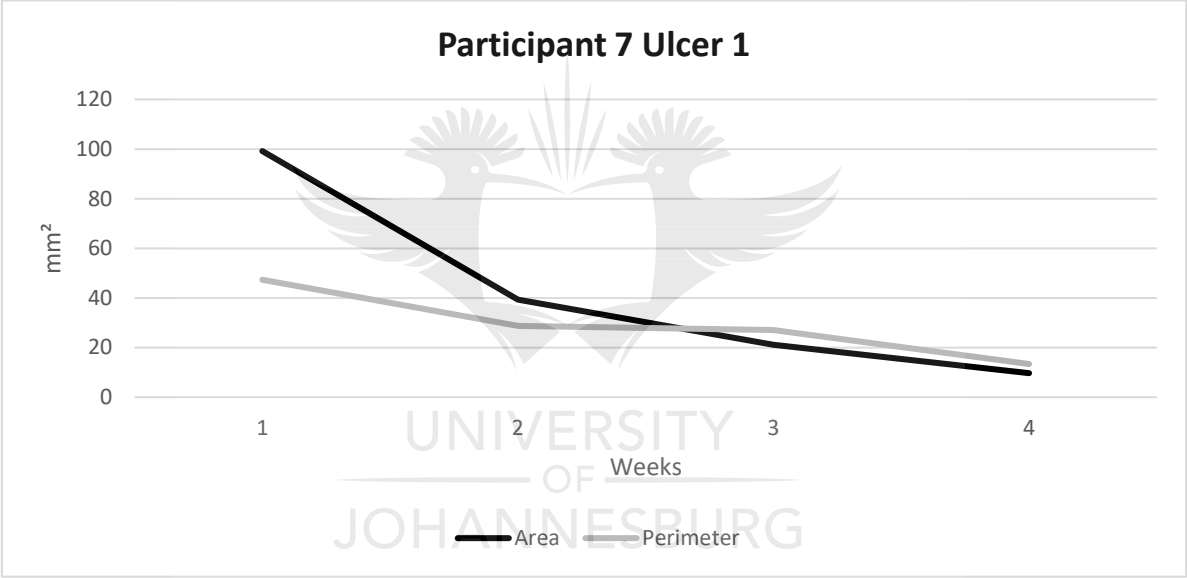

Figure 26.2. Participant 7 Ulcer 1(Grade 1) progress shows ulcer healed in four weeks.

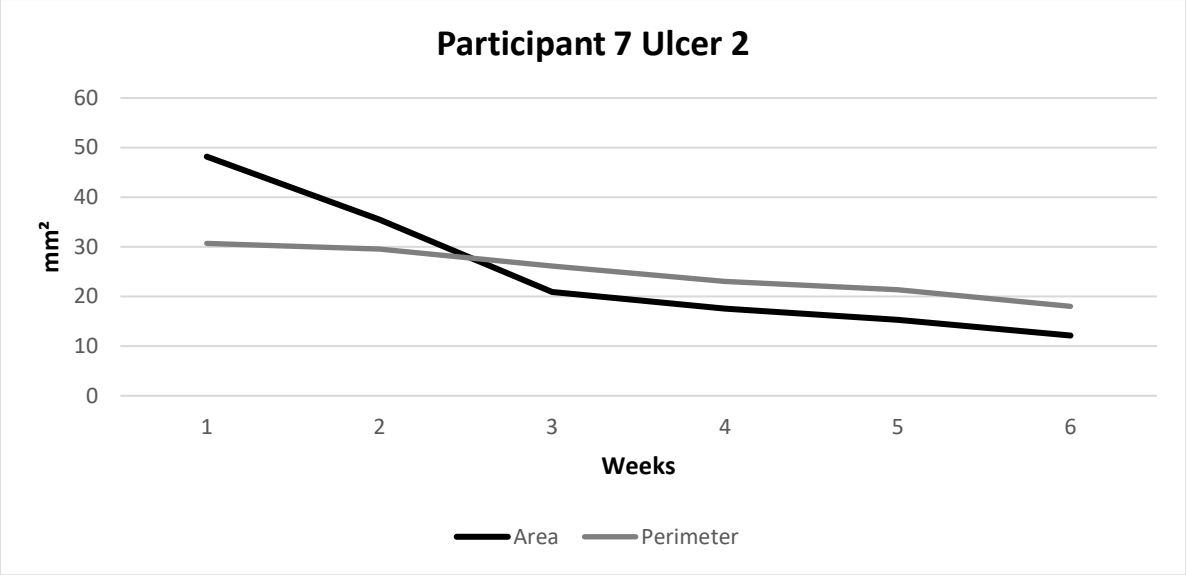

Figure 26.3. Participant 7 Ulcer 2 (Grade 2) progress shows ulcer significant improvement in six weeks. Ulcer area decreased by ~ 75% and parameter decreased by ~ 41%.

4.5.8 Participant 8

This participant was a 46-year-old Black female who presented with a Grade 2 ulcer on her right lateral-dorsum aspect of the fifth toe. Ulcer of one-month duration and diagnosed with DM and Hypertension 5 years ago.

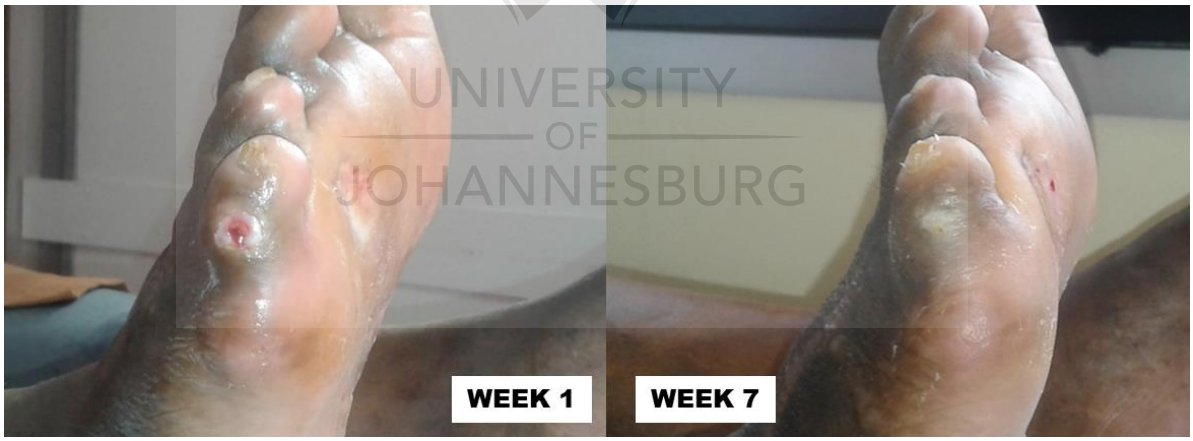

Figure 27.1. Participant 8 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 7).

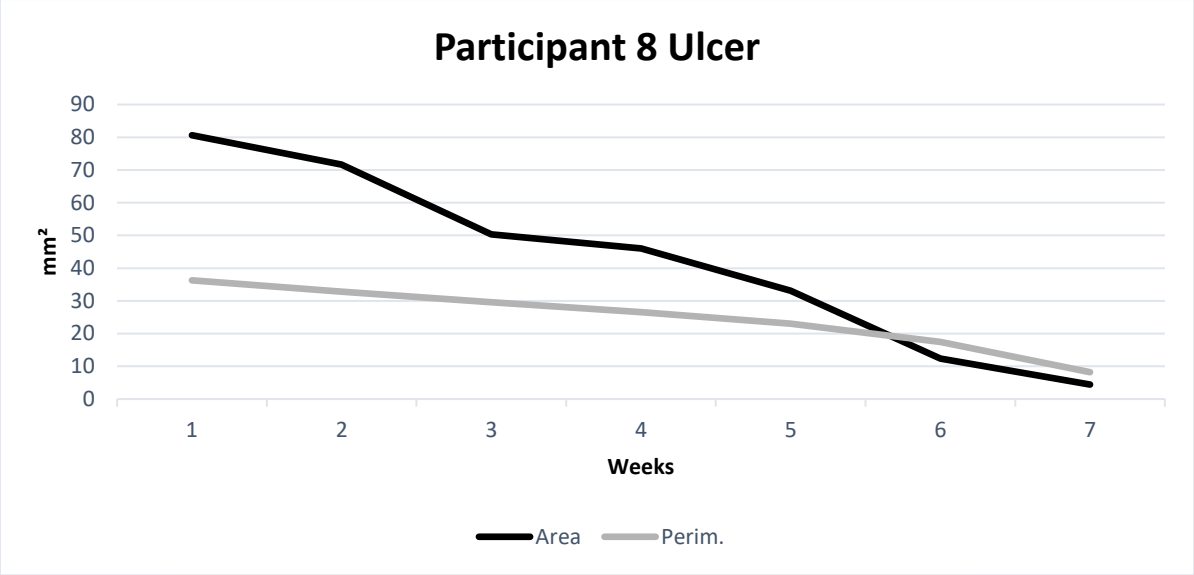

Figure 27.2. Participant 8 Ulcer progress graph shows ulcer healing in seven weeks.

4.5.9 Participant 9

A 44-year-old Black African male diagnosed with Diabetes and Hypertension eight years ago. Who presented with two Grade 2 ulcers on both feet plantar metatarsal area. Ulcer of two years duration. The ulcer on the left foot was on the PBM treatment as participant 9, and the right foot was control 6.

Figure 28.1 Participant 9 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

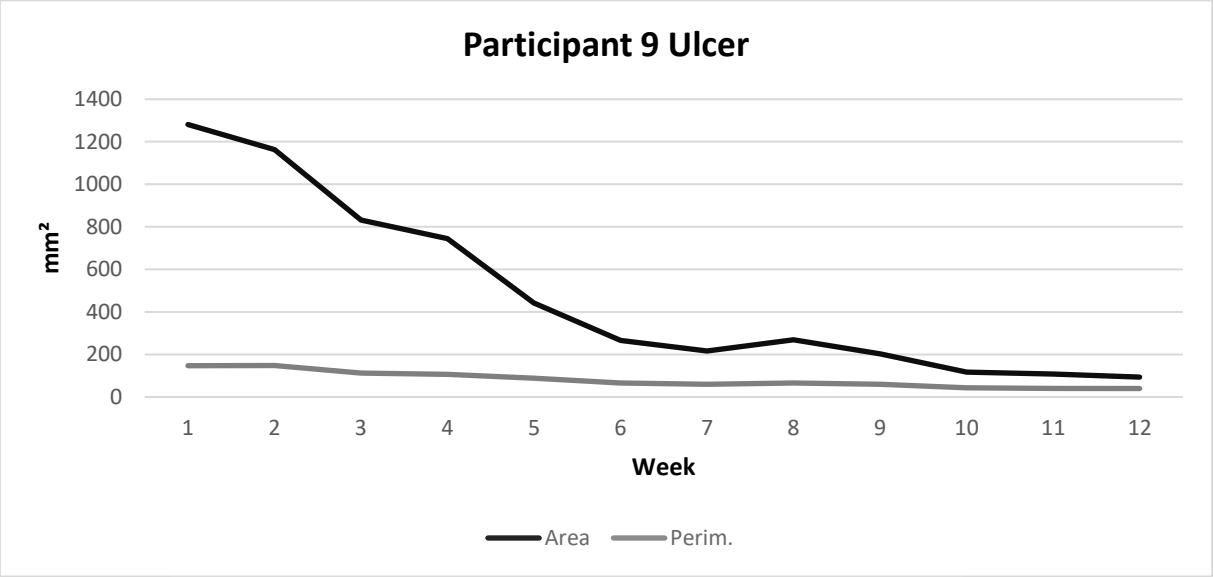

Figure 28.2. Participant 9 Ulcer progress graph shows the ulcer significantly improve in 12 weeks. Ulcer area decreased by ~ 93% and parameter decreased by ~ 73%.

4.5.10 Participant 10

A 44-year-old Coloured male who presented with a Grade 1 ulcer on the plantar metatarsal area of the right foot. He smokes and presented with an ulcer of two months duration and a diabetic for three years.

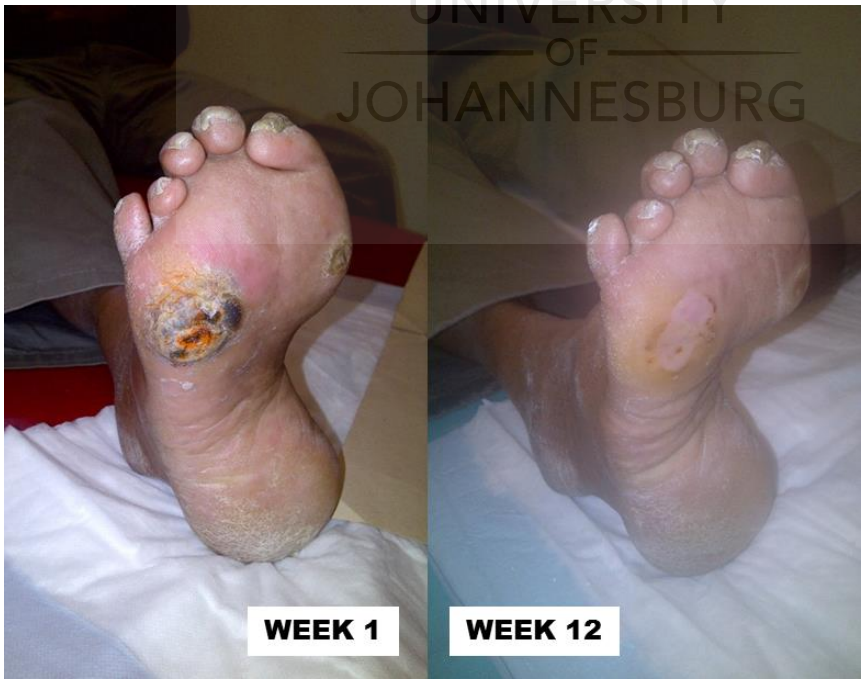

Figure 29.1 Participant 10 ulcer: shows the ulcer before PBM (Week 1) and after PBM (Week 12).

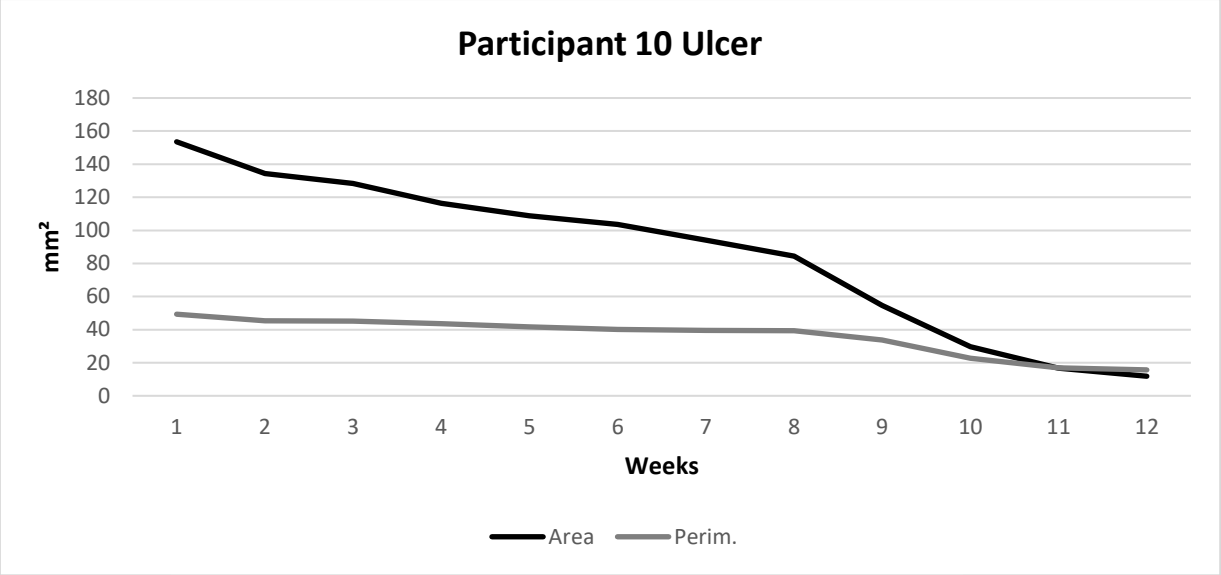

Figure 29.2. Participant 10 Ulcer progress graph shows the ulcer healed in 12 weeks.

4.6 The Pain Intensity Assessment results

In this study, each participant had to complete a pain intensity assessment (Appendix G) after each Low-Level Laser irradiation session. **Tables 11-15** present the reported changes in pain, heat, erythema, pricking and itching/tingling sensations; experienced during irradiation/treatment between week one and week 12.

The results in **Table 11** shows that by week 12, 100% of the participants did not experience pain.

Table 11 Pain scale in Week 1 and 12.

Group			Week12 Pain Scale
			None
Week 1 Pain Scale	None	Count	7
		%	58.3%
	Mild	Count	4
		%	33.3%
	Moderate	Count	1
		%	8.3%
Total		Count	12
			100.0%

The results in **Table 12** show that 90% of the participants did not experience heat by week 12 and only 10% experienced mild heat.

Table 12 Heat scale in Week 1 and Week 12.

Group			Week12 Heat Scale		
			None	Mild	Total
Week 1 Heat Scale	None	Count	6	0	6
		%	100.0%	0.0%	100.0%
	Mild	Count	1	1	2
		%	50.0%	50.0%	100.0%
	Moderate	Count	2	0	2
		%	100.0%	0.0%	100.0%
Total		Count	9	1	10
			90.0%	10.0%	100.0%

The results in **Table 13** show that 70% of the participants did not observe erythema by week 12 of the study.

Table 13 Erythema scale in Week 1 and Week 12.

Group			Week12 Heat Scale			
			None	Mild	Moderate	Total
Week 1 Erythema Scale	None	Count	6	0	2	8
		%	75.0%	0.0%	25.0%	100.0%
	Mild	Count	1	0	0	1
		%	100.0%	0.0%	0.0%	100.0%
	Moderate	Count	0	1	0	1
		%	0.0%	100.0%	0.0%	100.0%
Total		Count	7	1	2	10
			70.0%	10.0%	20.0%	100.0%

The results in **Table 14** show that only 10% of participants still experienced mild to moderate pricking sensation at the end of this study where 80% did not.

Table 14 Pricking sensation scale in week 1 and 12.

Group			Week12 Pricking Scale			
			None	Mild	Moderate	Total
Week 1 Pricking Scale	None	Count	5	0	0	5
		%	100.0%	0.0%	0.0%	100.0%
	Mild	Count	3	1	1	5
		%	60.0%	20.0%	20.0%	100.0%
		%	0.0%	100.0%	0.0%	100.0%
Total		Count	8	1	1	10
			80.0%	10.0%	10.0%	100.0%

The results in **Table 15** show that only 10% of participants still experienced itching at the end of the study whereas 90% did not.

Table 15 Itching/Tingling sensation scale in week 1 and 12.

Group			Week12 Itching/Tingling Scale		
			None	Mild	Total
Week 1 Itching/Tingling Scale	None	Count	6	0	6
		%	100.0%	0.0%	100.0%
	Mild	Count	3	1	4
		%	75.0%	25.0%	100.0%
Total		Count	9	1	10
		%	90.0%	10.0%	100.0%

CHAPTER 5: DISCUSSION

5.1 Introduction

Non-healing wound is a wound that does not improve after four weeks of standard treatment and supportive measures on time, and these commonly include diabetic foot ulcers (Frykberg and Banks, 2015). Diabetes increases the risk of developing a wide range of foot complications, including foot ulceration. Foot ulceration always precedes major leg amputations, and evidence suggests that a lower leg is lost every 30 seconds due to diabetes somewhere in the world (IDF, 2015). Diabetes-related amputations have a dramatic effect on the quality of life and life expectancy and are a substantial financial burden on the health care system (Rheeder, 2006; Brem and Tomic-Canic, 2007).

Thus, there is an urgent need to look at all available treatment interventions in the management of diabetic foot ulcers (DFUs). Such an approach is more suitable for low-resources countries like South Africa (RSA), which should include instigating technology intervention such as PBM. People with diabetes can ill afford chronic DFUs that takes a long time to heal, arguably in the I.R 4.0 era; technological advancements should begin to influence patient care. To date, ulcers treated using conventional podiatric interventions have been shown to take too long to heal. Low-level laser therapy is a growing technology that is gaining evidence for efficacy in a variety of specialities. Despite some scepticism, PBM has achieved reliable status in wound healing, skin rejuvenation, pain attenuation, and allergy-related conditions. Recent studies support its effectiveness in various areas such as wound healing, skin rejuvenation, and pain alleviation (Kim & Calderhead, 2011). However, in RSA, the efficacy of PBM in the treatment of chronic wounds remains unknown and in fact, under-researched. In this study, for the first time, DFUs in diabetic patients were treated with PBM and found evidence of its effectiveness in reducing wound healing time.

The preliminary findings of this study, which aimed to assess the potential efficacy of the PBM system used in DFUs treatment are encouraging. However, the researcher would like to acknowledge the small treatment patient population as a limitation. However, as alluded to in chapter three, an experimental design study aims to show that two variables are statistically related. That is to show that

the independent variable caused the observed changes in the dependent variable. The researcher and supervisor feel that despite the limited participant numbers, the findings of the study shows that PBM irradiation led to reduced wound healing times. Thus, despite the limited study participants, the range of wound types and stages provides insightful findings on the efficacy of PBM when compared with podiatric interventions.

The researcher recruited participants from SOPD due to the nature and holistic treatment of DFUs. Only a few patients were willing to participate, as they were not familiar with PBM and their clinicians were uncomfortable with them having this unknown intervention. The scepticism by both treating clinicians could help explain the low number of participants despite the large population of patients with diabetes seen at hospitals.

In South Africa, there is limited data on the overall treatment of, and the healing time of DFUs. The use of phototherapy in vitro has shown significant improvement in DFU cell. Until this study, there has been limited evidence on the effectiveness of phototherapy in treating diabetic foot ulcers in vivo.

This preliminary study used PBM irradiation on chronic diabetic lower limb ulcers in Type II Diabetic patient with Fitzpatrick skin type III and V. The findings have shown a good response of DFUs healing time to a combined treatment of podiatric intervention and PBM.

5.2 Role of podiatrists in DFUs management.

Podiatrists have become the point persons on the wound management team, often the first to recognise the presence of or the impending formation of a limb- and life-threatening wound. A typical lower extremity examination with a podiatric focus considers the patient from four essential viewpoints: vascular, dermatologic, orthopaedic, and neurologic. Assessment that includes these four points is essential to treat a lower extremity wound properly.

However, in RSA, despite podiatrists inclusion amongst the healthcare professionals that deal with or manage DFUs ulcers, their clinical interventions remain ill-defined. Thus, nurses and surgeons manage the majority of DFUs either in a vascular outpatient department or the surgical outpatient department (SOPD). There is a limited number of 45 podiatrists in RSA employed in the

Gauteng Department of Health (GDoH) (Bodenstein, 2018). Thus only a few clinicians (doctors and nurses) refer to these healthcare professionals due to their limited availability and poor understanding of what they do.

Podiatrists play an essential role in the multidisciplinary team in DFUs management. They use treatment which includes both conservative and surgical modalities. Understanding the biomechanics of the lower extremity is principally emphasised in the education and training of a podiatrist. Understanding biomechanics is particularly crucial in the context of the diabetic foot where structural and subsequent biomechanical abnormalities often precede ulcer development. Preventive ulcer development strategies employed by a podiatrist include regular monitoring, routine care of calluses, and orthoses or shoe recommendations. Further, podiatrists use simple interventions like regular callus debridement to prevent increases in focal pressures in order to reduce the likelihood of ulcer formation. However, there continues to be a poor understanding of the podiatrists' role in the management of DFUs in RSA.

The lack of awareness about the Podiatry service and Diabetic foot specialist seems to be a problem not only in RSA but also in other low-middle-income countries such as Nigeria and Ethiopia. According to Edo et al. (2013), there is a shortage of trained Diabetic foot specialist in Nigeria, and an incomplete multidisciplinary team manages DFUs. According to Mishra et al. (2017), podiatrists understands the importance of foot care education, as it controls the risk factors of developing foot problems in patients with diabetes. Therefore the exclusion of podiatrist in the multidisciplinary team for diabetic foot care results into the absence of adequate health education and emphasis on diabetic foot care practised in developing countries. If this continues, peripheral neuropathy and other risk factors will continue to be a significant component in delayed wound healing for these patients (Mishra et al., 2017).

5.3 Mechanism of PBM and its effect on DFUs

Low-Level Laser Therapy is the application of light to a biologic system to promote tissue regeneration, reduce inflammation and relieve pain. Low-Level Laser Therapy does not have an ablative or thermal mechanism, unlike other medical laser procedures, but rather a photochemical or photobiomodulation

effect (Farivar et al, 2014). Photobiomodulation effect is beneficial in diabetic patients on accelerating wound healing in chronic diabetic foot ulcer (Enwemeka, 1988). Low-Level Laser Therapy is a treatment that uses low-level lasers to change cellular function and is a clinically accepted tool in regenerative medicine. It has been especially beneficial in dermatology and dentistry to improve healing processes and management of functional disorders (Rochkind et al,1989) .

The skin is the organ with the most exposure to light more than any other organ; thus, it responds well to light wavelengths. The mitochondrial chromophores in skin cells absorb photons. Consequently, electron transport, adenosine triphosphate (ATP) nitric oxide release, blood flow, reactive oxygen species increase activating diverse signalling pathways. To achieve sufficient wound or tissue healing and tissue repair, sufficient stem cells activation must be achieved (Avci et al, 2013) . Current conventional podiatric interventions cannot achieve stem cell activation. Thus, interventions like PBM could have a place in the treatment of DFUs.

Several in vivo and in vitro studies have demonstrated the positive effects of PBM on tissues (Nteleki and Houreld, 2012). Low-Level Laser Therapy enhances the survival of Adipose-derived mesenchymal stem cells (ASCs) and stimulates the secretion of growth factors in the wound bed (Kim et al, 2012). Additionally, PBM seems to exert biostimulatory effects on various cell types, including osteogenic cells, and bone tissue due to its stimulating effects on osteoblast-like cells and accelerates the repair process of the bone (Huertas et al, 2014, Stein eta al, 2005). Other cellular activities such as enhanced alkaline phosphatase activity and improved osteocalcin gene expression are other effects observed with the use of Low-Level laser therapy (Renno et al, 2010). Low-level laser therapy interventions results indicate a higher inflammatory cells recruitment and a better tissue organisation at the site of the injury, with the presence of granulation tissue and new bone formation (Bottino, (2005) cited by Amid et al, 2014). The noted effects of PBM make it one of the ideal addition in the treatment of DFUs. The findings of the current study show the ability of PBM to activate wound healing at a cellular level and thus achieve the results noted in this study. Low-Level Laser Therapy achieves this by providing direct biostimulative light energy to cells, which are the main target of low-level laser therapy. Laser energy results in the

stimulation of molecules of cells while having no significant increase in tissue temperature, as illustrated in **Figure 29**.

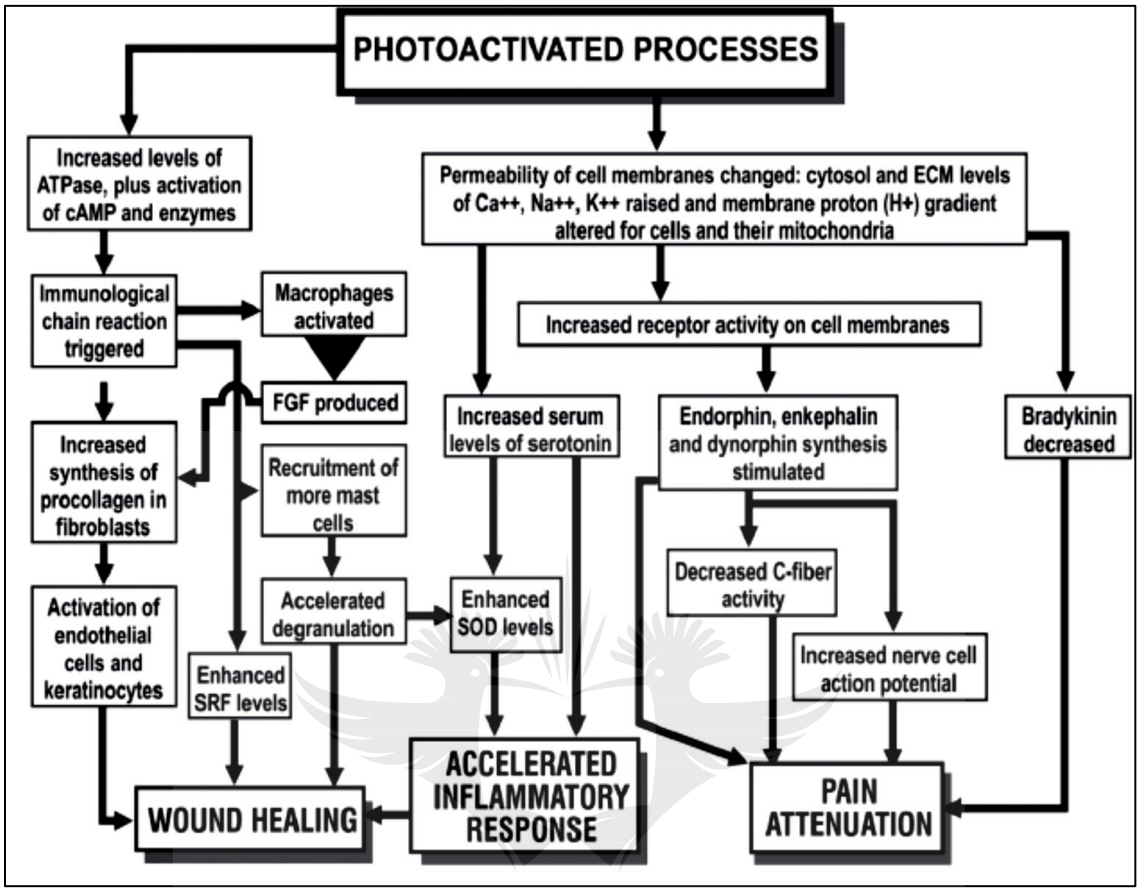

Figure 30. Photobiomodulation and the biostimulative processes underlying its three primary endpoints: Wound healing, Inflammatory response and Pain reduction (Kim, W. and Calderhead, 2011).

Despite the evidence on the effects of PBM on different cell lines, without knowing its effects on actual DFUs, it is has been challenging to suggest its inclusion in DFUs clinical treatment protocol. This study was designed to provide such preliminary evidence by trying to provide primary evidence about the effects of PBM on DFUs.

Significantly, there was a high healing rate of 58.3% in the PBM group compared to 25.0% in control. Additionally, 42.9% of ulcers healed before completion of the study 12 weeks. Thus, indicating the capabilities of PBM to improve wound healing in DFUs. The effect of PBM is seen to enhance wound healing when compared to standard podiatric interventions. Intentionally, the majority of ulcers 59.1% received irradiation with blue light (625nm and 850nm). This approach enabled the researcher to demonstrate the ability of PBM to treat DFUs and to

observe the effects of PBM on more ulcers and could still allow for comparison with validated podiatric interventions.

The specific characteristics of the tissue within the wound bed play an essential role in the wound-healing continuum. When wound bed tissue is nonviable or deficient, it delays wound healing. Furthermore, it might provide an opportunity for infection to develop, prolongs the inflammatory response, mechanically obstructs contraction and impedes re-epithelialisation (Dowsett and Hallern, 2017). Podiatrists use debridement as a process of removing devitalised tissue and foreign material from a wound. Ranges of techniques of debridement including surgical, sharp, autolytic, enzymatic, and mechanical debridement, are available. However, these techniques are dependent on the patient, the wound and the expertise of the clinician. Thus, the current podiatric wound management techniques might fail to address this critical area of wound healing adequately.

Wound healing is a complex process requiring highly coordinated biochemical processes at the wound site and immune responses needed for restoring tissue integrity. Along with these complex processes involving cellular players, wound healing also requires several coordinated biochemical pathways and reactions that lead to collagen synthesis and disposal of damaged tissues (Nair, 2018). Thus, a treatment modality that can act at a cellular level must accompany podiatry interventions to achieve desired healing times. Current evidence suggests that PBM can achieve this and allow podiatric interventions to address wound healing at this level. PBM can alter the cellular redox state that induces the activation of numerous intracellular signalling pathways and alters the affinity of transcription factors concerned with cell proliferation, survival, tissue repair and regeneration (Peplow, Chung, Ryan & Baxter, 2011)

5.4 Ulcer grades and duration

To predict the outcome DFUs outcomes and appropriate diabetic foot ulcer treatment, clinician usually use a transparent descriptive classification system. The (i) Wagner and (ii) University of Texas (UT) classification are the two classification systems used worldwide. Wagner classification focuses on the depth of the wound, presence or absence of osteomyelitis or gangrene and the extent of tissue necrosis. On the other hand, UT classification considers not only

the depth and penetration of wound but also the presence or absence of infection and ischemia (Gul et al, 2006).

A number of studies have observed healing time of DFUs, although mostly focused on the healing of ulcers on the sole (Kirsner et al, 2010). On the contrary, the current study evaluated all ulcers regardless of position. The reported rates of healing usually defined as the percentage of wounds healed by 12 weeks, 20 weeks, six months, or 12 months vary widely. However, the majority of the ulcer will heal entirely between 20 and 52 weeks (Ince et al, 2007). In their review, Ince et al (2007) stated that some studies reported healing by 12 weeks in only 18.3% of control subjects, whereas others reported 38% healing by 12 weeks (Ince et al, 2007). Meta-analysis of patients receiving standard care in randomised controlled trials found that only 31% of DFUs receiving conventional podiatric therapy heal within 20 weeks, and only 24% heal within 12 weeks (Kirsner et al, 2010).

Therefore, to evaluate the efficacy of any DFUs treatment intervention, it is essential to ascertain its ability to reduce the healing times is critical. This study demonstrated improved healing times of all DFUs treated using PBM. The findings of the study show that PBM has the potential to increase ulcer healing times. Thus, this intervention might have a space in the management of DFUs.

Literature confirms that wound duration, is related to wound healing times and that old wounds are less likely to heal (Bosanquet and Harding, 2014). Additionally, the severity of the ulcer has a direct influence on its healing time (Smith-Strøm et al., 2017). Thus, in the current study, the researcher used the Wagner classification system to classify or grade all ulcers and recorded the duration of each presenting ulcer. This method allowed the researcher to predict how long each ulcer could be expected to take before it healed, as indicated in literature that links ulcer duration and severity to healing times. The duration of the majority of ulcers 63.63% was between 1 and 5 months for both groups and 59.1% were Grade 1 in both groups. In the PBM group, the majority 53.8% were Grade 2 ulcers. Therefore, the healing times recorded in this study are remarkable when one considers both the duration and severity of ulcers treated using PBM.

In their study, Smith-Strøm et al. (2017), found that patients referred to specialist health care by general practitioners ≥ 52 days after ulcer onset had a 58% decreased healing rate compared to those referred earlier. They also reported that ulcers classified as high severity (grade 2/3) were associated with a decreased healing rate when compared to low severity ulcers (grade1). Thus, early-targeted treatment and referral are essential in the management of DFUS. Currently, there is a limited referral of these patients to podiatry services in RSA (Ntuli et al, 2018).

Concerning the relationship between the healing rate, ulcer grade and duration, the findings of the current study are in line with current literature. In the current study it was noted that subacute ulcers (superficial grade 1 and of 1-5 month duration), healed faster (reduce in size) when compared to chronic ulcers (deep grade 2 and of more than five months duration). This study produced an interesting finding in that, in the PBM group, even deeper ulcers older than five months, which notoriously take longer to heal, showed quicker healing rates 57.1%. Furthermore, in the PBM group, 42.9% of these ulcers had healed entirely before week 12. Therefore, the findings suggest that the inclusion of PBM as a treatment modality in DFUs might be of some benefits. The main aim of any chronic wound management is to reduce healing times and limit or control any infections. The PBM seems to do both of these, as noted in the findings of this study. Thus, it may be worth considering PBM as a modality for the management of chronic wounds.

5.5 Risk factors for DFUs and their impact on healing

According to literature, the risk factors for DFUs include male gender, diabetes duration of more than ten years', peripheral neuropathy, abnormal foot structure, peripheral arterial disease, smoking, previous history of ulcer or amputations, and poor glycemic control (Kajagar et al, 2011). There is an association between these risk factors and poor healing of diabetic ulcers. Therefore, part of any DFUs management strategy should address these factors. Hence, the current study recorded presenting risk factors, including comorbidities in all the participants. The researcher did this to evaluate the PBM intervention in an authentic environment, similar to all other DFUs treatment strategies/ interventions.

Concerning male gender as being a risk factor for developing DFUs, the current study findings were in line with the literature (Amin and Doupis, 2016). In the current study, 68.2% ulcers were on male participants, thus supporting literature as already stated. The findings of this study showed the ability of PBM to heal ulcers in the male gender effectively who are usually associated with longstanding DFUs. In this group, the study found complete healing rate in 80% of Grade 1 ulcers and 25% Grade 2 ulcers in the PBM group compared to 33.3% Grade 1 and none of the Grade 2 ulcers in the control group. Overall, 40% of ulcers healed completely and 26.67% improved from Grade 2 to Grade 1 ulcers in both groups. The findings of this study provide preliminary evidence that PBM modality is effective in inducing wound healing; however, a larger cohort is needed to validate the current findings.

Another significant risk factor that is associated with DFUs is the duration of diabetes. Diabetes Mellitus of more than ten years of duration and peripheral neuropathy is associated with DFUs (Shahi et al., 2012; Ahmad et al., 2017). In this study, 45.5% of ulcers were on participants who had diabetes duration of >10 years and 59% in this study were on participants diagnosed with peripheral neuropathy. These findings confirm suggestions by literature, which states that DFUs occur in the presence of peripheral neuropathy (Bergin et al., 2012). In this study, healing was noted in 80% Grade 1 ulcers in the PBM group when compared to control.

Other comorbidities such as smoking and hypertension are also associated with delayed wound healing. In 54.5% and 81.8% of ulcers, smoking and hypertension respectively were risk factors seen in ulcers, in the current study. In this study, however, 75% of ulcers, with hypertension and smoking were healed in both groups compared to 60% of ulcers with hypertension alone. These findings differ from Musa and Ahmed's findings in 2012, where 65% of smokers did not have ulcer healing versus 35% of nonsmokers. Hypertension, on the other hand, did not have an effect on wound healing correlating with the current study (Musa and Ahmed, 2012).

5.6 PBM and its ability to induce wound healing at a cellular level.

The PHOTOTHERAPY blue light laser, used in the PBM group in this study has bactericidal effects. Several studies have found that, at different wavelengths, the blue light laser is bactericidal to different infectious organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), *Propionibacterium acne* and *Pseudomonas aeruginosa* (Houreld, 2014). Enwemeka et al. (2009) found that 470-nm light kills Hospital Acquired-MRSA and Community Acquired-MRSA *in vitro*, suggesting that using blue light laser might have a similar effect in human cases of cutaneous and subcutaneous MRSA infections. These results were already found in a study by Lipovsky et al. (2008), which demonstrated that high-intensity broad-spectrum polychromatic light with wavelengths in the range of 400–1000 nm kills bacteria in infected diabetic ulcers.

Wound infections are among the most common problems in diabetic people, and an essential factor that prolongs the inflammation stage of wound healing (Ranjbar and Takhtfooladi, 2016). These ulcers produce copious amount of exudate if there is an infection as it prolongs the inflammation stage (Speak, 2014; Kavitha et al., 2014; Ranjbar and Takhtfooladi, 2016). During the first consultation and wound assessment of the participants in the current study, no signs of severe infection (pus and cellulitis) were present. However, the research noted wound weeping of clear and sometimes discoloured (tan and brown) exudate that is suggestive of low-grade infection. Significantly, weeping reduced dramatically with the use of PBM, suggesting the ability of this modality to deal with bacteria in the wound. Moreover, there were no reports of new or secondary infections during the study in the PBM group. The current study findings are in line with literature with other recent studies and thus, provide initial evidence on the efficacy of PBM.

The current study used a combination of 625nm and 850nm to irradiate the diabetic ulcers to promote both healing and reduce (chances of) infection. A study by Figurova et al. (2016) found that the combination of red and blue laser improved the healing of sutured skin incisions in piglets and observed no wound infection in either control or treated piglets.

In the current study, the dressing used was a silver-based dressing. Silver dressings are ideal to use in wounds where the infection is possible due to their antibacterial qualities (Wall, 2010). However, literature shows the limited result in the ability of silver-containing dressings inhibit wound infection in DFUs (Storm-Versloot et al., 2010). This approach allowed the researcher to investigate the blue laser ability in preventing or clearing secondary infection of all the ulcers. Of course, more research needs to be conducted to investigate whether phototherapy alone can prevent wound infection in chronic DFUs in Podiatry alone or combination with silver dressing. If a blue light laser is bactericidal to one of the persistent infection strain (MRSA), some suggest that phototherapy can also be an alternative to drug treatment (Enwemeka et al., 2009). Using it could even help avoid polypharmacy and adverse drug effects in patients with DFUs.

Healing of chronic DFUs can undergo an extended period without any response due to multiple complex cellular pathophysiological mechanisms involved in patients with diabetes. These involve factors such as hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularisation, high levels of metalloproteases, damage from oxygen radicals and advanced glycation end products (Petrova & Edmonds, 2006; Guo & DiPietro, 2010). The current podiatric interventions and other conventional methods do not address all these factors as part of DFUs treatment, which might explain the long duration currently observed in the treatment of DFUs.

In this context, the current study findings might provide critical input and variation in the management of DFUs. Current podiatric interventions are limited in their ability to address or initiate healing at a cellular level. However, the properties of PBM shows that the use of phototherapy allows for the clinician to target wound healing at a cellular level. PBM, phototherapy or photobiomodulation refers to the use of photons at a non-thermal irradiance to alter biological activity. The mechanism associated with the cellular photobiostimulation by PBM involves a wide range of effects at the molecular, cellular, and tissue levels (Avci, Gupta, Sadasivam, Vecchio, Pam, Pam & Hamblin, 2013).

The underlying biological mechanism behind the effects of PBM is thought to be through absorption of red and NIR light by mitochondrial chromophores, in

particular, cytochrome c oxidase (CCO) contained in the respiratory chain located within the mitochondria, and perhaps also by photoacceptors in the plasma membrane of cells (Karu and Kolyakov, 2005).

Consequently, a cascade of events occurs in the mitochondria, leading to biostimulation of various processes (Oron, 2011). It is implicit that this absorption of light energy may cause photodissociation of inhibitory nitric oxide from CCO9 leading to enhancement of enzyme activity, electron transport, mitochondrial respiration and adenosine triphosphate (ATP) production (Avci, Gupta, Sadasivam, Vecchio, Pam, Pam & Hamblin, 2013) as illustrated in **Figure 31**. Thus, PBM alters the cellular redox state that induces the activation of numerous intracellular signalling pathways and alters the affinity of transcription factors concerned with cell proliferation, survival, tissue repair and regeneration (Peplow, Chung, Ryan & Baxter, 2011).

Thus, the improvement perceptible in the treatment group in this study is arguably due to PBMs' ability to influence wound healing at a cellular level. The targeting of wound healing at a cellular level using PBM is a unique way. It might enable podiatrists to enhance wound healing. This technology is entirely contrary to current podiatric interventions, which focuses on offloading and necrotic tissue debridement. Admittedly, these methods have stood the test of time and have produced excellent results. However, the treatment time on these methods can take up to a year (Kirsner, Warriner, Michela, Stasik & Freeman, 2010).

In vitro studies have shown that phototherapy PBM can positively stimulate diabetic ulcer, thus promoting healing and wound closure. The ability of PBM induce this action is due to its ability to act on fibroblasts resulting in increased viability, proliferation, ATP, growth factors, cytokines and nitric oxide as well as a decrease in cellular damage and proinflammatory cytokines (Houreld & Abrahamse, 2010; Beckmann et al., 2014; Houreld, 2014).

The findings of this study have shown that PBM can produce similar results in vivo as those produced mostly in vitro studies to date in RSA. The findings should be well-thought-out in the context of RSA podiatric diabetic foot management strategies, which have remained stagnant, and without any innovation. The podiatry and wound care professionals should consider the PBM

technique/technology as a methodology that can allow clinicians to initiate treatment at the most effective level of wound healing, as illustrated in **Figure 31**.

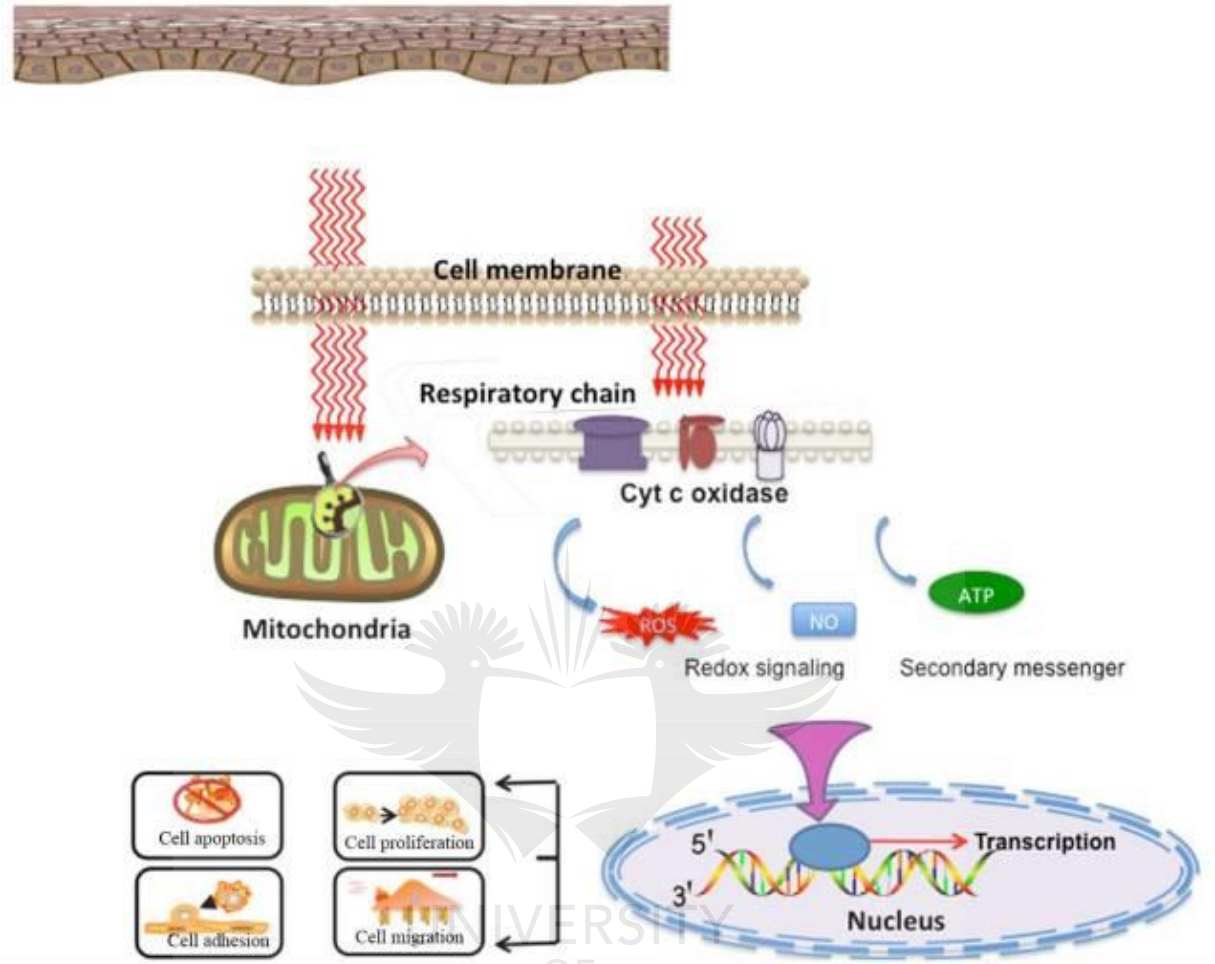

Figure 31. Mechanism of PBM at a cellular level (Avci, Gupta, Sadasivam, Vecchio, Pam, Pam & Hamblin, 2013)

In this study, 58.3% ulcers healed in the PBM group compared to 25.0% in the control group. The study results are similar with Minatel et al. (2009) who treated chronic diabetic leg ulcers in 23 patients that were unresponsive to other forms of treatment, where thirteen ulcers were treated with phototherapy (combined 660 and 890 nm) twice a week until healed, or for a maximum period of three months. In the group of ulcers that were irradiated, 58.3% resolved completely, and 75% of the ulcers achieved 90-100% healing by day 90 (Minatel et al., 2009).

A study by Priyadarshini et al.(2018), conducted over 15 days found that 66.6% grade 1 ulcers and 4.4% of grade 2 ulcer healed completely, whereas 96.6% grade 2 ulcers improved to grade 1 by day 15 (Lenifa Priyadarshini and Kishore

Babu, 2018). To date, no studies have documented the average healing times of DFUs in RSA. The current study is the first study (limited as it may have been) to provide some idea of DFUs healing times.

The current study found that 80.0% Grade 1 ulcers and 42.9% Grade 2 ulcers entirely healed in the PBM group, whereas 57.1% Grade 2 ulcers improved to grade 1 ulcers. Significantly, only 20% of grade 1 ulcer remained as grade 1 ulcer in the PBM group compared to 66.7% of grade 1 ulcers in the control group. The findings of this study are the first to indicate good improvement in DFUs healing times using a combination of PBM with podiatric intervention in the management of DFUs. Importantly also, the findings highlight the possible value add that can come from using PBM in combination with podiatric interventions. Any DFUs that treated successfully within 12 weeks signifies a measurable improvement in the patient's quality of life. Additionally, successful DFUs management means a reduction of possible amputations.

Priyadarshini et al. (2018) study findings are similar to those of Kajagar and Godhi (2011). Both studies reported positive results in ulcers irradiated daily over 15 days. The researcher could not achieve this in the current study and ulcers were treated twice a week in this study. Treating ulcers twice a week meant that participants had to come to the hospital twice a week, all participants complained about this due to financial constraints. Depending on the clinician's decision, participants would have come to the hospital once a week or two weeks for podiatric management and between one to four weeks for a wound dressing change by nurses. This presented a challenge, as no treating clinicians were happy about their patients receiving treatment twice a week. The noticeable changes in the ulcer that is healing were what motivated participants in the PBM group to continue with the study despite the stated challenges.

In the current study, participants in the PBM group received treatment twice a week as compared to daily treatment, which could have been a reason for decreased healing rate of some of the ulcers in this study compared to participants of Priyadarshini et al. (2018) and Kajagar (2012). However, the current study compares adequately with literature concerning the treatment of

chronic ulcers. Literature suggests that chronic wounds should be treated once or twice a week considered as the maximum (Samaneh et al., 2015).

5.7 PBM and skin type reaction

The skin is the organ exposed to light more than any other organ; thus, it responds well to light wavelengths. The mitochondrial chromophores in skin cells absorb photons. Consequently, electron transport, adenosine triphosphate (ATP) nitric oxide release, blood flow, reactive oxygen species increase activating diverse signalling pathways. Stem cells can be activated to increase tissue repair and healing (Avci et al, 2013).

Low Level Laser Therapy (PBM) is an adverse effect on free treatment modality in the management of ulcers (Priyadarshini et al. 2018; Kazemi-Khoo, 2006). However, early studies in dermatology showed some unwanted side effects (thermal effects) such as blistering, transient or permanent depigmentation, textural change and scarring (Battle & Hobbs, 2003; Battle & Soden, 2009), especially in the dark skin tones: Fitzpatrick skin type IV to VI. Notably, recent studies show that PBM appears to have a wide range of applications of use in dermatology, especially in indications where stimulation of healing, reduction of inflammation, reduction of cell death and skin rejuvenation are required (Avci et al, 2013). Thus, PBM is used in inflammatory skin conditions without inducing any dermatological adverse effects (Kim et al, 2012; Kim & Calderhead, 2011).

However, the pathogenesis of sensitive skin remains poorly understood. Recent studies suggest that an impaired barrier function of stratum corneum in sensitive skin facilitates the penetration of irritants, resulting in marked cutaneous responses to otherwise harmless stimuli (Farage, 2009). In the histopathologic findings examination, exhibits vasodilation and an inflammatory infiltrate in people with sensitive skin (Reilly et al, 2000).

Therefore, the researcher in this study felt it was essential to investigate the skin reactions of participants in this study. This approach, the researcher thought it would be essential in developing a protocol for the inclusion of PBM in the management of DFUs. No participant in the PBM group reported any skin complaint during the treatment period. The findings are noteworthy, as they show that PBM can play a significant role in the treatment of DFUs.

In the current study, 69.2% of the ulcers were from the participants with skin type V compared to 30.8% skin type III, in the PBM group. This group of participants experienced mild to moderate heat and only one participant in skin type III experienced increased heat during her few sessions of treatment. However, there was no blistering or depigmentation observed or reported in this participant. These results differ from Joensen et al. (2011), who found that irradiating with a 200 mW, 810 nm laser-induced three to six times more heat in dark skin than in the other skin tone groups.

Erythema was the only “depigmentation” observed in the current study. Notably, this was immediately after treatment and was reported to subside between 10 and 15 minutes. Erythema seen in the participants was not a side effect but rather a sign of increased blood flow to the area due to mild heat from PBM, which promotes healing. Studies confirm the ability of PBM to improve skin circulation in patients with diabetic microangiopathy, as low-level laser irradiation accelerates collateral circulation, and enhance microcirculation, thus promoting healing (Kazemi-Khoo, 2006).

Initially, in the first week of study, participants reported mild discomfort, pricking and tingling sensation, but by week 12, no participant (100%) reported pain. However, by week 12 mild tingling sensation and pricking sensation was reported by 10% of the participants. Notably, these were only reported when asked by the researchers and were not considered as an issue by the affected participants. The reason for the reduction in pain can be due to PBM mechanism of action. Furthermore, reduction of tingling and pricking can be due to PBM ability to increase ATP production by mitochondria and increase cellular oxygen consumption thus promoting nerve regeneration and increased microcirculation to the periphery (Beckmann et al., 2014; Houreld, 2014; Kazemi-Khoo, 2006).

Significantly, all ulcers that healed completely was on the skin type V participants. Therefore, these results suggest that PBM for wound management in dark skin tone patients is an adverse thermal effect free treatment that promotes wound healing. The study is significant in the RSA context as the majority of the population most likely fall in this skin tone group. The findings of the study suggest that this skin tone population might respond favourably to PBM interventions.

CHAPTER 6: CONCLUSION AND RECOMMENDATIONS

Diabetic ulcers still prove to be a significant health care problem worldwide. Despite optimal wound care, complete wound healing rates are still as low as 60% after one year (Cavanagh et al., 2005; Smith-Strom et al., 2017). If a wound is in the process of healing, it should show signs of healing within four weeks and heal entirely in three months. However, chronic DFUs undergo an extended period without any response due to multiple complex cellular pathophysiological mechanisms involved in patients with diabetes. Such delays are because the standard podiatric wound treatments are limited in their ability to address and initiate healing at a cellular level.

Several in vitro and clinical studies suggest PBM (red and blue) to promote wound healing and bactericidal or prevent infections in diabetic wounded cells and patients. However, before this study, no clinical studies were found in RSA that have investigated the use and effects of PBM (blue) to manage DFUs or any other ulcers presenting in the lower limb in different skin tones.

This study showed that treating chronic diabetic foot ulcers in skin type III and V with PBM in combination with podiatric interventions is more successful than treating these ulcers with podiatric interventions alone. This study also showed that there are no significant adverse effects with the use of PBM in the darker skin individuals, but complete wound healing. . It is also essential to understand that if any DFU treated successfully within 12 weeks signifies a measurable improvement in the patient's quality of life. Additionally, successful DFUs management means a reduction of possible amputations for these patients.

The researcher achieved the main aim and objectives of this study despite the challenges concerning participant attrition

6.1 Study Limitations

The main limitation of this study was the number of participants. The researcher identified two reasons that might have led to low numbers seen.

i. **Study protocol.**

   The study protocol required each ulcer on the PBM group to receive treatment twice a week. Having treatment, twice a week conflicted with the

standard dressing protocol set out at the hospital where the participants receive their treatment.

ii. **Dropouts.**

The high dropout rate might have been primarily due to costs, as coming to the hospital twice a week proved too costly for most if not all participants.

The acceptance of PBM in treating DFUs would have led to lower attrition rate by patients with diabetes. Thus, the main recommendation in this study would be to repeat this study after registering it as a clinical trial.

6.2 Recommendations for future research

- The larger sample size is recommended to corroborate the findings of the current study further.
- A study should be done to compare the effectiveness of blue laser therapy and a silver-based dressing in the prevention and management of local infection in chronic diabetic ulcers.

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Appendix A: Research design (Flow diagram)

PARTICIPANTS

-19 patients (22 ulcers)
-Type II diabetes
- Fitzpatrick Type III and V
-Lower extremity ulcer >4 weeks in stable or worsening condition
-Meet all inclusion criteria
-Draw up full patient history and complete study specific questionnaire

↙ ↓ ↓ ↘

GROUP 1 (15 patients) Skin Type III Control	GROUP 2 Skin Type III Experiment	GROUP 3 Skin Type V Control	GROUP 4 Skin Type V Experiment
-Placebo laser -Standard podiatric treatment	-Phototherapy (480 nm & 850 nm) -Standard podiatric treatment	-Placebo laser -Standard podiatric treatment	-Phototherapy (480 nm & 850 nm) -Standard podiatric treatment

↓ ↓ ↓

TREATMENT

-Twice a week, until ulcer heals/3 months
-Clean the ulcer – 0.9% physiological saline and dry
-Standard podiatry treatment
-Irradiation – phototherapy with 480nm & 850nm
-Wound setting
-Contact mode
-Placebo irradiation
-Dress ulcer

↓

ULCER MEASUREMENTS

-Visual assessment
-Digital photography at 30 cm distance
-Ulcer area and area of ulcer granulation tissue measured using ImageJ® software

INCLUSION CRITERIA:

1. Diagnosis of type II diabetes with neuropathic or mixed ulcers.
2. Ulcer located on the lower extremity.
3. Ulcer present for a minimum of 4 weeks during which it has been either stable or worsening.
4. Willingness to participate in the study and commitment to follow-up protocol.
5. Sign a written consent to participate in the study.

EXCLUSION CRITERIA:

1. Evidence of cellulitis, osteomyelitis or gangrene anywhere in the affected extremity.
2. Presence of any of one or more medical conditions such as renal, hepatic, haematologic, neurologic, or immune disease, which in the opinion of the co-principal investigator (MACF) constitutes a confounding variable.
3. Presence of malignant disease (other than basal cell carcinoma) not in remission for more than 5 years.
4. Use of oral or parenteral corticosteroids, immunosuppressive, or cytotoxic agents.
5. Known infection with HIV or presence of AIDS.
6. Use of other investigational drug or device within 30 days of recruitment into the study.
7. Other leg ulcers, such as ulcers due to arterial insufficiency, decubiti, or vasculitis.

Appendix B: HDC Approval letter.

UNIVERSITY OF JOHANNESBURG

FACULTY OF HEALTH SCIENCES

HIGHER DEGREES COMMITTEE

26 MARCH 2015

TO WHOM IT MAY CONCERN:

Student: SITHOLE, N
Student Number: 200829848

TITLE OF RESEARCH PROPOSAL: Phototherapy and Podiatric Interventions for the Management of Chronic Lower Limb Ulceration in Patients with Type II Diabetes Mellitus and Skin Type III and V

DEPARTMENT OR PROGRAMME: PODIATRY

SUPERVISOR: Prof H Abrahamse CO-SUPERVISOR:

The Faculty Higher Degrees Committee has scrutinised your research proposal and confirms that it complies with the approved research standards of the Faculty of Health Sciences; University of Johannesburg.

The proposal has been awarded a Code 02 – Approved with suggestions without re-submission. Attached recommendations were made by the Committee which will add value to your proposal.

Please make these amendments to the satisfaction of your supervisor/s and submit a corrected copy of the proposal to the Faculty Research Administrator after which your clearance number will be issued.

The HDC would like to extend their best wishes to you with your postgraduate studies.

Yours sincerely,

Prof Y Coopoo
Chair: Faculty of Health Sciences HDC
Tel: 011 559 6944
Email: yogac@uj.ac.za

Appendix C: REC Approval letter.

UNIVERSITY OF JOHANNESBURG

FACULTY OF HEALTH SCIENCES

RESEARCH ETHICS COMMITTEE

NHREC Registration no: REC-241112-035

REC-01-186-2015

12 JUNE- 2015

TO WHOM IT MAY CONCERN:

STUDENT: SITHOLE, N
STUDENT NUMBER: 200829848

TITLE OF RESEARCH PROJECT: "Phototherapy and Podiatric Interventions for the Management of Chronic Lower Limb Ulceration in Patients with Type II Diabetes Mellitus and Skin Type III and VI"

DEPARTMENT OR PROGRAMME: PODIATRY

SUPERVISOR: Prof H Abrahamse **CO-SUPERVISOR:**

The Faculty Research Ethics Committee has scrutinised your research proposal and confirm that it complies with the approved ethical standards of the Faculty of Health Sciences; University of Johannesburg.

The REC would like to extend their best wishes to you with your postgraduate studies.

Yours sincerely,

Prof M Poggenpoel
Chair : Faculty of Health Sciences REC
Tel: 011 559 6686
Email: mariep@uj.ac.za

Appendix D: Helen Joseph Hospital Research Committee Approval letter.

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Gauteng Department of Health
Helen Joseph Hospital
Enquiries: Dr. M.R. Billa
Chief Executive Officer
Tel :(011) 489-0306/1087
Fax :(011) 726-5425
E mail: Raymond.Billa@gauteng.gov.za
Date: 27 February 2017

Dr.M.R. Billa
Chief Executive Officer
Helen Joseph Hospital

Dear Nozipho Sithole

STUDY: PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATION IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND SKIN TYPE 111 AND V.

RESEARCHERS: Nozipho Sithole

The above was discussed at the Research Committee Meeting. We recommend that permission be granted for Helen Joseph Hospital to be used as a site for the above research. However, since this is a research project involving voluntary participation. We cannot guarantee participation of individuals/patients.
Upon completion of the study, a copy thereof should be submitted to Helen Joseph Hospital.
Furthermore, please ensure that your research is captured in the national research registry.

DR. Murimisi Mukansi
CHAIRPERSON
DATE: 03-03-2017

Approved

DR. M.R. BILLA
CHIEF EXECUTIVE OFFICER
DATE: 01.03.2017

Appendix E: Information and Consent form

INFORMATION AND CONSENT FORM

PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATIONS IN PATIENTS WITH TYPE II DIABETES MELLITUS AND SKIN TYPE III AND V

Dear Sir/Madam,

My name is Nozipho Sithole and I am a Podiatry Postgraduate student at the University of Johannesburg. I am busy conducting a research study under the supervision of Prof Heidi Abrahamse, as a fulfillment for my M.Tech degree in Podiatry.

I would like to invite the to participate in this clinical study which is investigating the effects of phototherapy in the treatment of non-healing lower limb ulcers in patients with Type II Diabetes. Please take a few moments to read the attached information and consent form (including the terms and conditions thereof). Please inform your podiatrist of you decision whether or not to participate in this research.

Should you have any questions that I or the clinical supervisor is unable to answer, please do not hesitate to ask to forward those particular questions onto the Laser Research Centre. A speedy response will be made to such questions.

We hope that you will be able to assist us in our research efforts with your participation in this study.

Kind regards

_____

Miss Nozipho Sithole

University of Johannesburg

INFORMATION AND CONSENT FORM

PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATIONS IN PATIENTS WITH TYPE II DIABETES MELLITUS AND SKIN TYPE III AND V

In order to decide whether or not you wish to participate in this study, you should know enough about the risks and benefits of phototherapy to make an informed decision. This form gives you information about the research. Once you understand the process, you will be asked if you wish to participate, if so, you will then be asked to sign a form prior to treatment.

What is Phototherapy?

Phototherapy, also known as Low-Level Laser Therapy and photobiostimulation, is a form of light therapy that involves the application of low power laser light to injuries and lesions in order to stimulate healing. The exact mechanism of PBM is not completely understood. However, it is known that the laser light is absorbed by photoacceptor molecules, or chromophores, inside the cells. The effects are known to be chemical not thermal. This absorbed energy then stimulate cellular metabolism. PBM has been found to stimulate blood flow and in doing so improve wound healing and reduce pain as well as inflammation. It has also been shown to stimulate the immune system. Many studies have shown that PBM improves healing of slow-to-heal/non-healing diabetic ulcers.

There are no known side effects associated with PBM. Although no pain associated with laser irradiation is expected, a light tingling sensation may be felt. To help assess this, a short pain questionnaire will be completed after each visit.

Phototherapy has shown to improve the healing of diabetic ulcers. We hope that the information gained from the research studies will increase our knowledge of human health and disease, and that this information will lead to better treatments.

Economic consideration

You will not receive any payments for participating in this study. The information we will get from participation may help to develop new products and treatments and promote the use of phototherapy.

Treatment Regime

If you meet the criteria and decide to participate in the study, you will need to complete a questionnaire. You will then be treated with low-level laser light twice a week until the ulcer heals, or for a maximum of period 3 months (90 days).

Time to complete such a treatment will depend on the size of the ulcer, the ulcer as well as the number of ulcers to treat. The ulcer will first be cleaned with physiological saline and allowed to dry. The laser light will then be applied to the ulcer and the surrounding area. Following phototherapy, the ulcer will then be dressed and covered. At each treatment the ulcer will be visually inspected and a digital photograph of the ulcer will be taken. A short pain intensity assessment will also need to be completed.

Participants will be randomly assigned to one of four groups based on the skin colour (white and dark brown). Each group will receive a standard podiatric treatment for diabetic ulcers; the difference comes with the phototherapy. Two groups will be receiving placebo irradiation of the ulcer/s and the other two will receive irradiation of the ulcer/s.

Confidentiality

All identifiable information that is obtained in connection with your participation will remain confidential. When the result of the research are published or discussed in conferences, no personal information will be included. By agreeing to participate, you give permission for the researcher to use any findings/results emanating from the study in research publications/reports and conference presentations. You also have a right to refuse to participate.

Voluntary Participation and Withdrawal

You are free to choose not to participate in the study, however if you do participate you are free to withdraw from the study at any time. If you choose not to participate it will not harm your relationship with your podiatrist.

Access to information or results of the study

Results of the study will be made available to participants on request; however no names or personal information will be included.

Questions

We have used some technical terms in this form, so please feel free to ask about anything you don't understand and consider participation and consent carefully before you make a decision.

Authorization

I have read (or someone has read to me) the Information and Consent Form and have decided to participate in this clinical study being conducted at the Podiatry Clinic in conjunction with the Laser Research Centre at the University of Johannesburg. Its general purposes, the particulars of my involvement and possible hazards and inconveniences have been explained to my satisfaction. By signing below, I give permission for the described treatment and disclosures of information. My signature also indicates that I have received a copy of the consent/ authorization form. I do not give up any of my legal rights by signing this form.

TICK ONE:

_____ I wish to participate in this study.

_____ I do not wish to participate in this study.

_____ _____

Signature of subject Date

_____

Print name of subject

_____ _____

Signature of Person Obtaining Consent Date

_____ _____

Signature of Researcher Date

Important contact details:

Researcher: Miss Nozipho Sithole:

Clinic Supervisor: Miss Meesha Purbhoo: 011 559 6442

Study Supervisor: Prof Heidi Abrahamse: 011 559 6550

Appendix F: Questionnaire

QUESTIONNAIRE
PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATIONS IN PATIENTS WITH TYPE II DIABETES MELLITUS AND SKIN TYPE III AND V

Personal Details:

Name and Surname: _____File no.: _____
Date of birth (YY/MM/DD): _____ Age: _____
Gender (please tick one): Male____ Female_____
Race (please tick one): Black___White____Coloured____Indian____ Asian___

Clinical Details:

1. **Have you been diagnosed with type II diabetes (please tick one)? Yes ___ No___**
2. **How many years have you been diagnosed with type II diabetes?**
3. **Are you on any treatment for your diabetes? Yes___ No___**
4. **If you answered yes to question 3, what treatment are you on? _____**
5. **How many weeks/months has the lower limb ulcer/s been present?_____**
6. **Do you have known infection with HIV (please tick one)? Yes___ No___**
7. **Do you or have you had a malignant disease? Yes___ No___**
8. **If you answered yes to question 7, are you in remission? Yes___ No___**
9. **If you answered yes to question 8, how long have you been in remission?_____**
10. **Are you using any corticosteroids, immunosuppressive or cytotoxic agents/drugs? Yes___ No___ If yes please specify: _____**
11. **Do you have any of the following illnesses/diseases (please tick the boxes that apply):**

    Renal ☐ Hepatic ☐ Hematologic ☐

    Neurologic (not related to diabetes) ☐ Immune (not related to diabetes) ☐

    Please specify the nature of the disease: _____
12. **Have you been using other investigational drug or device within the last 30 days? Yes___ No___**

Appendix G: Pain Intensity Assessment

PAIN INTENSITY ASSESSMENT

PHOTOTHERAPY AND PODIATRIC INTERVENTION FOR THE MANAGEMENT OF CHRONIC LOWER LIMB ULCERATIONS IN PATIENTS WITH TYPE II DIABETES MELLITUS AND SKIN TYPE III AND V

Name and Surname: _____

File no.: _____

Date: _____

Instructions: Please circle the one that best describes what you experienced during or after phototherapy.

Pain

Mild Moderate Severe None

Heat

Mild Moderate Severe None

Erythema (redness)

Mild Moderate Severe None

Pricking

Mild Moderate Severe None

Itching/Tingling sensation

Mild Moderate Severe None

If you experienced any discomfort after the treatment, state the discomfort i.e. burning or hot sensation, swelling or other signs that you have experienced: _____

_____

Appendix H: Turnitin Report

Final Dissertation

ORIGINALITY REPORT

15%	15%	5%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.diabetesjournal.co.za Internet Source	6%
2	www.laser-therapy.us Internet Source	2%
3	Bahle Nteleki, Heidi Abrahamse, Nicolette N. Houreld. "Conventional podiatric intervention and phototherapy in the treatment of diabetic ulcers", Seminars in Vascular Surgery, 2015 Publication	1%
4	ujdigispace.uj.ac.za Internet Source	1%
5	info.med.yale.edu Internet Source	1%
6	www.uj.ac.za Internet Source	1%
7	epdf.tips Internet Source	1%
8	onpointneuro.com Internet Source	1%