

# The use of phototherapy in the treatment of diabetic ulcers

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## Abstract

Chronic ulcers are a common complication in diabetes. The nature of diabetic foot ulcers makes them difficult to manage and treat. A dynamic management plan is required to treat diabetic lower limb ulcerations. This involves a strategic approach, including mechanical offloading, wound debridement, wound dressing, patient education and surgical intervention. Alternative methods have been developed, of which phototherapy is one. Phototherapy, or low-level laser therapy (LLLT), is a therapeutic treatment modality that has been found to enhance wound healing. Its therapeutic properties have been determined by means of in vitro, in vivo and animal studies. Some studies have shown that the clinical application of phototherapy has a positive effect on the process of wound healing. Therefore, LLLT has the potential to decrease the level of secondary complications, improve wound regeneration, and ultimately improve patient quality of life. This review will discuss the concept of chronic wound management by means of LLLT in patients who suffer from type 2 diabetes.

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## Introduction

Diabetes mellitus is a common metabolic disease that is increasing in prevalence worldwide. This increase has highlighted the importance of understanding both the complications and metabolic consequences of the condition.<sup>1</sup> Africa is estimated to experience the second highest increase in prevalence of diabetes in the world. The greatest surge is expected to occur within the next 15-20 years.<sup>2,3</sup>

According to Hedefort et al, there has been a fourfold leap in the number of foot ulcerations that affect patients with type 2 diabetes mellitus.<sup>4</sup> It follows that there is an expected increase in the number of patients who suffer from the complications that are associated with diabetes mellitus. The literature stipulates that the lifetime risk of developing a diabetic ulcer can be as high as 13-25%.<sup>5,6</sup> It is important to acknowledge that diabetes predisposes the patient to the development of lower limb lesions since the foot is a target of peripheral neuropathy and ischaemia.<sup>1,7</sup> Chronic diabetic foot ulcerations are known to be a notorious problem in patients with diabetes mellitus. Nonhealing ulcerations are associated with substantial cost and poor outcomes generally, such as decreased quality of life and nontraumatic lower limb amputations. The nature of chronic diabetic foot ulcerations disables the normal stages of healing, which in turn induces a state of pathological inflammation. This results in the overall healing process becoming incomplete or delayed.<sup>8</sup>

The disabled healing process has become a significant problem within the diabetic community, since it predisposes patients to secondary infections. More than 12% of this population undergo possible lower limb amputations.<sup>9</sup> Diabetic lower limb ulcerations tend to heal slowly and require intensive multidisciplinary care. The management of chronic diabetic foot ulcerations requires a consistent and reliable treatment plan.<sup>10</sup>

Peripheral sensory neuropathy is a major contributor to diabetic foot ulcerations, and is frequently the most common microvascular complication of both type 1 and type 2 diabetes. It is progressive and irreversible.<sup>11</sup> Neuropathy alone cannot induce ulceration as it is not sufficient. Trauma acts as an accomplice to neuropathy. Consequently, it is vital to understand that the loss of sensation in high-pressure areas predisposes a patient to ulcers and hinders wound healing.

Ischaemia is one of the most destructive complications of diabetes. It has become clear that this condition may predispose a patient to ulcerations, as well as gangrene, which may result in lower limb amputations. The literature has shown that endothelial and smooth muscle cell dysfunction contributes to impaired microcirculation in patients with diabetes. The red blood cells become less flexible as a result of glycosylation. This increases the risk of obstruction within the blood vessels and reduces the rate of perfusion. Disturbed microcirculation, in association with neuropathy, is linked to the development of diabetic gangrene,

and ulcerations and infections of both the skin and the bones in patients with long-term diabetes.<sup>12,13</sup> Impairment of the small blood vessels in parts of the body may also induce poor wound healing.

Although infection may not be a primary cause of diabetic ulcers in the lower extremities, it is a major contributor to non-healing wounds in patients with diabetes. It is important to comprehend that these patients are at greater risk and require constant monitoring. Patients with diabetes are often unable to respond appropriately to an infection. Local signs, such as pain and erythema, can be less apparent, because of factors such as neuropathy and ischaemia.<sup>10</sup>

### Phototherapy

The application of phototherapy or low-level laser therapy (LLLT) has generated considerable interest within surgery, dentistry, dermatology, somatology, pain management and wound healing. It is a therapeutic method that involves the application of laser light, at a particular wavelength and at low intensities, to the tissue to stimulate biological processes. The choice of wavelength is dependent on the depth of penetration. In some instances, light from light-emitting diodes (LEDs) is used. It is important to understand that the effects of LLLT arise because of chemical and biological changes within a cell, and not because of thermal changes. Photon energy is absorbed by photoacceptors or chromophores within a cell. The main photoacceptor is thought to be the mitochondrion. Research has shown that following laser irradiation, there is an increase in mitochondrial metabolism.<sup>14</sup> This leads to an escalation in adenosine triphosphate (ATP)<sup>15,16</sup> and cell membrane permeability, which leads to the activation of secondary messengers. In turn, these activate a cascade of intracellular signals.<sup>17</sup> Numerous studies have established the effect of phototherapy in vitro and in vivo, as well as in animal studies. Despite this, LLLT is still not an established treatment modality. This is mainly owing to poorly controlled studies and a lack of knowledge of the underlying mechanisms.

### Effect of LLLT on diabetic ulcers

Phototherapy has been shown to positively affect the healing process in wounds that are associated with diabetes.<sup>18</sup> Several studies have acknowledged that LLLT stimulates angiogenesis and microcirculation and promotes vasodilation, thereby improving blood circulation and reducing tissue damage that is caused by ischaemia.<sup>13,19-21</sup>

### In vitro studies

A review of the literature that was published between 2002 and 2009 by Peplow et al showed that there was a clear positive effect on cells when LLLT was applied.<sup>22</sup> LLLT stimulated cellular proliferation in a wide variety of cell types, including fibroblasts, endothelial cells, smooth muscle cells, stem cells, osteoclasts, osteoblasts and keratinocytes.

According to the literature, phototherapy stimulates mitochondrial oxidative metabolism in vitro, and increases cell and tissue repair in vivo. In vitro experimentation has demonstrated a significant increase in cell growth in a variety of cell lines which include murine fibroblasts, rat osteoblasts, rat skeletal muscles and normal human epithelial cells.<sup>23</sup> AlGhamdi et al conducted a review of the literature and suggested that a dose of 0.5-4.0 J/cm<sup>2</sup>, and a wavelength ranging from 600-700 nm, were the most beneficial and helpful in enhancing cellular proliferation.<sup>24</sup> At the correct laser parameters, LLLT has been shown to positively stimulate diabetic-wounded fibroblast cells. An increase in viability, proliferation, ATP, growth factors, cytokines and nitric oxide results, as well as a decrease in cellular damage and proinflammatory cytokines.<sup>25-28</sup> A study conducted by Gavish et al<sup>29</sup> on smooth muscle cells demonstrated that LLLT stimulated proliferation and collagen synthesis, and modulated equilibrium between the degradation and synthesis of the extracellular matrix; a very important aspect in diabetic wound healing. LLLT has a direct influence on the mitochondria of irradiated cells.<sup>14,30,31</sup> This results in increased ATP production which leads to the release of secondary messengers and the modulation of cellular processes, leading to cell survival and repair.

### Animal studies

Several studies have been conducted on animals with diabetes to evaluate the effects of phototherapy on the healing process of diabetic wounds. Positive results have been shown in wound healing in mice with diabetes.<sup>32-35</sup>

Peplow et al conducted a review of the literature on the use of phototherapy in wound healing in diabetic rat and mice animal models. Their review consistently showed that phototherapy was able to stimulate wound healing and that there is a strong case for further controlled studies in vitro. Kawalec et al<sup>32</sup> and Agnol et al<sup>36</sup> showed that LLLT has the ability to significantly reduce the size of a wound that was inflicted in diabetic mice and rats respectively. Al-Watban<sup>37</sup> demonstrated that streptozotocin-induced diabetic rat burns and wounds responded favourably to irradiation at a wavelength of 633 nm. Akyol et al<sup>38</sup> made use of a laser, not only to induce a wound, but

also to treat the wound, in male diabetic Wistar rats. They found that wounds created by a scalpel healed slower than those induced by a laser. They also noted that wounds treated with LLLT had the least amount of tissue injury and the fastest resolution of inflammatory response, as determined histologically.

Rabelo et al<sup>39</sup> irradiated full-thickness wounds in streptozotocin-induced diabetic rats (632.8 nm). They found that irradiation promoted efficient wound healing at a faster rate than in control rats. It has been shown that a single treatment of LLLT (wavelength of 660 nm, fluence of 4 J/cm<sup>2</sup>) is enough to accelerate the inflammatory phase, angiogenesis and leukocyte chemotaxis in burn wounds on the backs of rats.<sup>40</sup> At a wavelength of 890 nm (pulsed at a frequency of 80 Hz) and a fluence of 0.2 J/cm<sup>2</sup> per point, LLLT has been found to increase wound tensile strength in diabetic rats. A fluence of 0.03 J/cm<sup>2</sup> per wound point decreased wound tensile strength.<sup>41</sup> There was a significant improvement in the maximum stress and repair of tenotomised Achilles tendons in diabetic rats who were exposed for 10 consecutive days to a wavelength of 632.8 nm and a fluence of 2.9 J/cm<sup>2</sup>.<sup>42</sup>

A recent study has shown that the consequences of irradiation on diabetic wound healing in mice was not as a result of the effects on the plasma glucose levels. LLLT did not have a hypoglycaemic effect. The effects on wound healing relate directly to cellular and biochemical changes that are induced at the wound site.<sup>43</sup> Not all studies have shown positive effects. Abdi et al<sup>44</sup> found that laser irradiation (632.8 nm) did not enhance bone repair of a partial transversal standardised osteotomy in streptozotocin-induced diabetic rats.

### In vivo studies

Accelerated wound healing has been observed in vivo following phototherapy. It resulted in increased rates of epithelisation in human studies<sup>45</sup> and the promotion of connective tissue stability.<sup>46</sup> Recent studies using laser to treat diabetic foot complications demonstrated a positive effect on wound healing. According to a study that was conducted by Schindl et al, phototherapy improved microcirculation at the irradiated site, and caused a systemic effect on microcirculation, thereby improving the skin circulation.<sup>13</sup> A study conducted on 30 Egyptian patients with diabetic-linked skin lesions (dryness, hair loss, infections, itching, eczema and nail changes) showed that combined irradiation of the affected area with visible red and infrared lasers improved blood flow and partially reversed the condition in the affected area.<sup>47</sup>

In a double-blinded, randomised, placebo-controlled experimental trial, Minatel et al treated the chronic diabetic leg ulcers of 23 patients that were unrespon-

sive to other forms of treatment.<sup>48</sup> Thirteen ulcers were treated with phototherapy (combined 660 and 890 nm) twice a week until healed, or for a maximum period of three months. The rest were sham irradiated (10 ulcers). In the group of ulcers that were irradiated, 58.3% resolved completely, and 75% of the ulcers achieved 90-100% healing by day 90. Minatel et al found that phototherapy promotes tissue granulation and rapid healing of diabetic ulcers.<sup>48</sup>

In another study, Caetano et al used phototherapy (combined 660 and 890 nm) in a randomised, placebo-controlled, double-blinded study to treat venous ulcers that failed to respond to other forms of treatment.<sup>49</sup> A total of 32 ulcers were divided into three groups. Group 1 (a total of 11 ulcers) received placebo irradiation. Wounds were cleaned and dressed with 1% silver sulphadiazine cream. In Group 2 (a total of 14 ulcers), the wounds were irradiated twice a week and the wounds dressed with 1% sulphadiazine. In Group 3 (a total of seven ulcers), the wounds were dressed with 1% sulphadiazine. Treatment continued for three months. Seven of the 32 ulcers were small in size and healed within 60 days, regardless of treatment. The remaining ulcers (medium and large sized) were compared, and on days 30, 60 and 90 respectively, 75%, 50% and 75% of the medium-sized ulcers in Group 2 had healed, compared to 0%, 33% and 67% of ulcers in Group 1. None of the ulcers in Group 3 had healed. A comparison of the large ulcers showed that 0%, 43% and 57% of ulcers in Group 2 had healed, and 0%, 20% and 20% of ulcers in Group 1, while none of the ulcers in Group 3 had healed at the same time points. It was evident that medium- and large-sized ulcers that were treated with phototherapy had a  $\geq 40\%$  faster healing rate per month.<sup>49</sup>

The literature has clearly indicated that phototherapy has the ability to help to resolve chronic diabetic lower limb ulcerations. In a recent study, 30 male and female patients with diabetes were divided into two equal groups, comprising a control group and a laser-treated group (850 nm). Patients were treated over a four-week period. Patients who received phototherapy experienced a 26.4% decrease in pain levels, while electrophysiological parameters and foot skin microcirculation were significantly improved.<sup>50</sup> This shows that phototherapy may have the ability to improve the electrophysiological parameters of the peroneal motor nerve and the sural sensory nerve, resulting in decreased pain intensity.<sup>50</sup> This is very beneficial, even though the exact mechanism of pain relief that is induced by phototherapy is still largely unknown. Even though very little clinical research has been carried out on laser therapy and diabetic ulcers, Schindl et al noted that this treatment modality might constitute a side-effect-free route for the healing of neuropathic ulcers in patients with diabetes.<sup>51</sup>

## Effect of LLLT on infection and inflammation

Different wavelengths are used for different applications in phototherapy. This is based largely on the wavelengths' penetrative depths into the tissue, as well as their absorption properties. Light in the visible red to near-infrared spectrum has been shown to be absorbed by cytochrome c oxidase, while light in the blue spectrum is absorbed by flavins.<sup>52</sup> Blue light has been shown to have bactericidal effects. Enwemeka et al established that blue light (470 nm) was able to kill methicillin-resistant *Staphylococcus aureus* (MRSA) in vitro.<sup>53</sup> This is an important breakthrough, since the treatment of MRSA is extremely difficult. A number of other studies have found that blue light is bactericidal to *Propionibacterium acne*,<sup>54</sup> *S. aureus*<sup>55</sup> and *Pseudomonas aeruginosa*.<sup>55</sup> Lipovsky et al revealed that high-intensity visible light in the range of 400-1 000 nm was bactericidal to several pathogenic bacteria, namely *S. aureus*, *P. aeruginosa*, *Escherichia coli* and *Serratia marcescens*.<sup>56</sup> Ancri et al showed that a wavelength of 480 nm LLLT was optimal when treating infected wounds and should be used first, followed by irradiation at 730 nm to enhance wound closure.<sup>52</sup> Further studies should be conducted, as it may be useful to use a combination of wavelengths in the treatment of infected diabetic foot ulcers.

It has been established that mast cells play an important role in wound healing, as well as in the inflammation process. LLLT may have an influence on mast cells and result in their degranulation,<sup>57</sup> together with the production of several cytokines that are contained within their cytoplasmic granules. Xavier et al showed that phototherapy reduces inflammation in collagenase-induced tendinitis in rats.<sup>58</sup> Post-irradiation (LED 880 nm), there was a reduction in the amount of inflammatory cells, as well as a decrease in inflammatory cytokines interleukin-1 beta (IL-1 $\beta$ ), IL-6, tumour necrosis factor alpha (TNF- $\alpha$ ) and cyclooxygenase 2. Aimbire et al investigated the effect of LLLT on immune modulation (TNF- $\alpha$ ) in bronchoalveolar fluid after immune complex-induced lung injury in male Wistar rats.<sup>59</sup> They also found that at the correct dose, LLLT was able to significantly reduce TNF- $\alpha$ . Rabelo et al reported that irradiated streptozotocin-induced diabetic rats (632.8 nm) had a less intense inflammatory response.<sup>39</sup> Sekhejane et al investigated the effect of LLLT (636 nm) on proinflammatory cytokines, IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , in a diabetic and hypoxic fibroblast cell model in vitro.<sup>60</sup> They demonstrated a decrease in these cytokines and the translocation of nuclear factor kappa B. There was also an increase in the proliferation of these cells as they were directed into a cell survival pathway. Gavish et al demonstrated that the irradiation of porcine smooth muscle cells inhibited proinflammatory cytokine IL-1 $\beta$ .<sup>29</sup>

## Conclusion

Phototherapy or LLLT may be considered from a range of alternative treatment options, such as biological therapies, hyperbaric oxygen and negative-pressure therapy, which help to enhance the wound healing process. However, in practice, the management of diabetic lower limb ulcerations depends on clinicians and available resources. It is important to note that new technologies are not optimally effective unless they are coupled with appropriate overall wound management. The scientific community is dependent on comprehensive wound care studies in order to establish standard guidelines when assessing new approaches to chronic wound management. Standard treatments for diabetic lower limb ulcers seem to be ineffective and to reduce the quality of life of most patients.<sup>61</sup> In the last 20 years, new treatment procedures have been developed and tested. These have resulted in minimal improvements to previously available treatment options.<sup>49</sup> The clinical application of phototherapy is still to be fully investigated. It is unfortunate that more well-controlled clinical studies have not been explored in the past. Phototherapy has been evaluated as noninvasive and constitutes a promising treatment option with which to treat diabetic wounds.<sup>32,62</sup> If phototherapy can be shown to have beneficial effects on chronic diabetic lower limb ulcerations, and if the underlying mechanisms are better understood, the treatment regime could be reconstructed and improved.

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