Low-level laser therapy for diabetic foot wound healing. (Wound care)

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Introduction

An alternative to traditional treatment modalities for diabetic ulcers is low-level laser therapy (LLLT). Several published studies demonstrate the beneficial effects of LLLT (Ribeiro et al, 2002), although several other studies also exist which indicate results to the contrary (Malm and Lundeberg, 1991; Loevschall and Arenholt-Bindslev, 1994). Further work focusing on cellular and molecular mechanisms of responses to laser irradiation is required to establish LLLT as a reliable, safe, and inexpensive treatment modality. This article reviews LLLT as a treatment modality for diabetic ulcers.

KEY WORDS

* Wound healing

* Laser therapy

* Photobiostimulation

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Due to its serious complications diabetes remains an important cause of morbidity and mortality. The principal complications arise from macro- and microangiopathy. The nervous system is also affected, which can lead to sensory loss and subsequent damage to the limbs. Atrophy of fat and muscle tissue, combined with sensory loss, can result in pressure sores on the feet, which, in turn, can lead to lower-limb amputation. Approximately 15% of people with diabetes will develop foot ulcers, and 6% of these will require hospitalization for the treatment of such ulcers (Carrington et al, 2001). Diabetes accounts for 50% of all non-traumatic amputations (Schindl et al, 1998). Changes to the vascular system results in delayed wound healing. People with diabetes have poor circulation, poor resistance to infection, and poor local nutrition, thus these wounds are highly susceptible to infection.

Low-level laser therapy

Low-level laser therapy (LLLT; also known as bio stimulation and photobiostimulation) is a form of phototherapy that involves the application of low-power monochromatic and coherent light to injuries and lesions in order to stimulate wound healing. LLLT has been shown to increase the speed, quality, and tensile strength of tissue repair, resolve inflammation and provide pain relief (supporting literature is reviewed later in the article). Lasers are already used in a variety of medical and surgical fields, including dentistry, chiropractic, osteopathy, physiotherapy, cosmetic, pain attenuation, wound healing, and acupuncture to name but a few (e.g. Walsh, 1997).

The effects of LLLT are photochemical, not thermal, and the responses of cells occur due to changes in photo acceptor molecules (also known as chromophores [molecules which are able to absorb photonic energy]; Tuner and Hode, 2002), such as porphyrin. The exact mechanism of action of LLLT is not completely understood. However, it is known that during laser irradiation cells absorb photonic energy that is incorporated into chromophores, which, in turn, stimulates cellular metabolism (Pinheiro et al, 2002).

The chromophore is able to transfer the absorbed energy to other molecules and thus cause chemical reactions in surrounding tissue. The acceptor molecules' kinetic energy is increased, thereby activating or deactivating enzymes, which, in turn, are able to alter the physical and/or chemical properties of other macromolecules (for example DNA and RNA; Matic et al, 2003; Takac and Stojanovic, 1998) in order to facilitate wound healing. Energy which is delivered to the cells produces insignificant and minimal temperature changes, typically in the range of 0.1-0.5[degrees]C (Nemeth, 1993).

LLLT and wound healing

Normal wound healing requires both destructive and reparative processes in controlled balance. Proteases and growth factors play an important role in regulating this balance, and if disrupted in favor of degradation then delayed healing ensues, which is a trait of chronic wounds (Cullen et al, 2002). It has been shown that low-level laser irradiation at certain fluences and wavelengths can enhance the release of growth factors and stimulate cell proliferation (Yu et al, 2001).

The effects of LLLT include wound epithelialization, reduction of edema and inflammation, and re-establishment of arterial, venous and lymph microcirculation. Increased rates of ATP, RNA and DNA synthesis are also observed (Takac and Stojanovic, 1998). Major changes seen in wounds treated with LLLT include increased granulation tissue, early epithelialization, increased fibroblast proliferation, increased extracellular matrix synthesis and enhanced neovascularization (Walsh, 1997), all of which lead to better tissue oxygenation and nutrition, and, in turn, enhanced wound healing. The effects of LLLT on wound healing are summarized in Table 1.

It has been shown that low-level irradiation of fibroblasts stimulates the production of basic fibroblast growth factor and stimulates the transformation of fibroblasts into myofibroblasts (Walsh, 1997). LLLT also affects immune cells and acts directly and selectively on the immune system (Tadakuma, 1993). Stimulation of the immune system means that infected wounds can be cleared more readily. The use of low-level lasers in wound healing has been shown to speed up the healing of leg ulcers and burn wounds; it has also been shown to improve skin-healing capabilities (Ribeiro et al, 2002).

LLLT and wound healing in vitro

It has been shown that exposure to a 308nm excimer laser reduces bacterial growth in vitro (Folwaczny et al, 1998). This may be of significant clinical importance in bacterially infected wounds: not only could LLLT increase wound closure, but it may also speed up the clearing of an infected wound--a definite benefit to people with diabetes.

LLLT and diabetic wound healing in rodents

Yu and colleagues (1997) evaluated whether low-level laser irradiation could improve wound healing in mice with diabetes. Genetically diabetic mice (C57BL/KsJ-db/db) were exposed to an argon dye laser (wavelength: 630nm; power density: 20mW/[cm.sup.2] [see Table 2 for definitions]). They demonstrated that laser irradiation enhanced wound closure over time; histological evaluation indicated improved wound epithelialization, cellular content, granulation tissue formation and collagen deposition as compared to the negative control group.

LLLT has also been shown to enhance cutaneous wound tensile strength. Stadler and colleagues (2001) exposed the wounds of wounded female C57BL/KsJ-db/db mice to low-level laser irradiation and measured tensile strength. The wounded mice were exposed to low-level laser irradiation daily for 5 days, (wavelength: 830nm; power density: 79mW/[cm.sup.2]; energy density: 5.0J/[cm.sup.2] [see Table 2 for definitions]) starting either on the day of wounding or 3 days later. Compared with control mice (which received no irradiation) there was an increase in tensile strength in exposed mice sacrificed on days 11 and 23 post-injury. Higher tensile strengths were noted at 23 days in mice that received their course of irradiation 3 days after wounding. Stadler and colleagues (2001) felt that further investigation of the mechanism of LLLT in primary wound healing is warranted.

Reddy and colleagues (2001) concluded that photobiostimulation promotes tissue repair by accelerating the production of collagen and promotes overall connective tissue stability in wound healing. Male rats with streptozotocin-induced diabetes received circular wounds 6mm in diameter either side of the spine--one wound was treated with a helium--neon (He--Ne) laser (wavelength: 632.8nm; energy density: 1.0J/[cm.sup.2]) 5 days per week until there was wound closure. The other wound received no laser irradiations and was used as the control. In 2003, Reddy compared these results with wounded rats with streptozotocin-induced diabetes exposed to a gallium--arsenide (Ga--As) laser (wavelength: 904nm; energy density: 1.0J/[cm.sup.2]). The wound to the left of the spine was irradiated 5 days per week for a period of 3 weeks, while the wound to the right was used as a control. After 3 weeks, the rats were sacrificed and the wound sites analyzed (Reddy, 2003). Measurements of the He--Ne-irradiated wounds indicated there was an increase in maximum load, stress, strain, energy absorption and toughness compared with the controls (Reddy et al, 2001). There was an increase in tensile strength and toughness of the wound exposed to the Ga--As laser as compared with the control wounds. There were no changes in energy absorption between the control and irradiated wounds (Reddy, 2003).

Biochemical analysis revealed that the amount of total collagen was significantly increased in laser-treated wounds over control wounds, with an increase in the concentration of acid- and salt-soluble collagen and insoluble collagen. There was also a decrease in proteolytic digestion as measured by a decrease in pepsin-soluble collagen (Reddy et al, 2001; Reddy, 2003). It is the opinion of Reddy (2003) that irradiation with an He--Ne laser for wound healing in mice with diabetes is better than irradiation with a Ga--As laser, and that the different biochemical responses may be wavelength and coherence dependent.

LLLT and diabetic wound healing in humans

Exposure to low-level laser irradiation abates the inflammatory reaction and stimulates the immune system, leading to an increase in wound healing in infected wounds in people with diabetes (Khurshudian, 1989). Khurshudian treated 174 people with diabetes with suppurative diseases. Patients were exposed to a helium--cadmium laser beam of wavelength 441.6nm. A single exposure to 4.5J/[cm.sup.2] led to a rapid decrease in the inflammatory reaction, and there was a cleansing and acceleration of regeneration processes in the infected wounds.

This was supported by work conducted by Kuliev and Babaev (1991). They studied the immune status after laser irradiation in 152 people with diabetes with purulent soft tissue injuries. There was a rapid stabilization of the immune system, thus reducing the duration of treatment. Potinen (1992) determined the stabilization of the immune system by the observation of the increased release of various cytokines upon LLLT. He also observed an increase in the leucocyte population and an arrest in bacterial growth.

Kuliev and colleagues (1992) determined the effectiveness of including both a magnetic field (provided by various methods such as magnetic bracelets and wraps) and LLLT in the treatment of 119 people with diabetes with suppurative wounds. Immunological status was stabilized in a shorter time and the process of wound healing followed a quicker course, resulting in a shortened treatment time. It was suggested that the magnetic laser combined effect has an advantage over the separate use of these factors.

Low-level laser irradiation induces wound healing in conditions of reduced microcirculation. Schindl and colleagues investigated the effect of LLLT in patients with diabetic microangiopathy by infrared thermography on skin blood circulation (Schindl et al, 1998; Schindl et al, 2002). In the first study (Schindl et al, 1998), 30 people with diabetic ulcers or gangrene received either a single low-intensity laser irradiation (He--Ne laser; wavelength: 632.8nm; beam power: 30m/W; energy density: 30J/[cm.sup.2]), or a sham irradiation over both forefoot regions. At 20 minutes of laser irradiation, there was a significant rise in skin temperature in the forefoot area, with an increase of 0.58 [+ or -] 0.68[degrees]C (P<0.001). The increase was 1.06 [+ or -] 1.03[degrees]C at the end of irradiation (50 minutes; P<0.001) and 1.22 [+ or -] 1.01[degrees]C (P<0.001) 15 minutes after the end of irradiation. There was a slight, but significant, drop in skin temperature in the placebo group (P<0.001).

In the second study (Schindl et al, 2002), patients were exposed once to an He--Ne laser, (wavelength: 632.8nm; energy density: 30J/[cm.sup.2]), or a sham irradiation over the forefoot region of one foot. A rise in skin temperature in both feet in the laser group was noted, whereas a drop in both feet in the placebo group was noted. The group showed that athermic laser irradiation on one foot in people with diabetes with angiopathy causes a significant increase in skin circulation in both feet and points to the possibility of systemic effects.

Schindl and colleagues (Schindl et al, 1999) conducted a study on a person with diabetes with sensory neuropathy, macroangiopathy and microangiopathy. The patient was exposed (in 16 sessions within a 4-week period) to a 670nm diode laser, as well as conventional treatments (such as using dressings and antibiotics). There was complete healing of the ulcer with no recurrence after 9 months, despite the patient's unstable metabolic condition. Despite the fact that LLLT was not applied alone, LLLT may be a useful alternative treatment modality for the induction of wound healing of ulcers in people with diabetes which is free of side effects.

Exposure of blood to LLLT results in a decrease in free radical oxidation (Grigor'eva et al, 1991). Grigor'eva and colleagues investigated the activity of primary and secondary products of lipid peroxidation and antiperoxide protection enzymes. The blood of 33 people with diabetes was irradiated for 60 minutes with the help of a light guide. After laser irradiation, there was a decrease in the activity of processes of free radical oxidation compared with blood samples taken before laser irradiations. This decrease is probably due to the effect of LLLT on antiperoxide enzymes. The group also found an increase in microcirculation, which is in accordance with the work of Schindl and colleagues (Schindl et al, 1998; 2002).

Current literature

Currently there is no accepted theory to explain the mechanism of low-level laser biostimulation, and this lack of knowledge complicates the evaluation of conflicting reports in the literature. Lasers have been shown to be both stimulatory and inhibitory. These differences in the literature can be explained by the different treatment parameters used, such as wavelength, fluence, output power and treatment regimens (Baxter et al, 1991). Few articles provide all the relevant laser parameters, making it difficult to reproduce the work. Patient status, size, and type of wound also play important roles. LLLT has been used extensively in former Eastern bloc countries, thus there is a vast amount of experience and information available, although most of this work is published in Russian journals, and during the translation of these papers' information can become lost.

According to the American Diabetes Association (1999), the following criteria should be included when evaluating new treatments for diabetic foot wound care: randomized controlled studies; a sufficient number of patients; relevant outcomes; control patients; primary end point, with a proportion of patients with complete wound healing within the study period; and evaluation of the cost and effectiveness of the treatment and the quality of the patient's life. Of all the studies mentioned in this paper, none of them make mention of the costs and quality of patient life. The paper by Schindl and colleagues (1999) was written on a single patient.

Conclusion

The exploitation of phototherapy in medicine and surgery is of great interest, and there is a growing interest in the use of lasers for the treatment of various conditions and disorders, including the treatment of diabetic wounds. There is a need to develop alternative treatment modalities which can improve the endogenous capacity of the healing process, particularly during disease conditions with impaired wound healing. Using lasers as a source of photobiostimulation looks to be an attractive branch of medicine for the future.

Chronic skin ulcers present a challenge in dermatology, and among the various non-invasive treatments used in wound healing, LLLT has steadily increased in its applications to include a wide variety of medical and surgical specialties (such as physiotherapists, dentists, dermatologists and rheumatologists, and also in nerve regeneration; Karu, 2003). LLLT as a treatment is a choice that appeals to people (Forney and Mauro, 1999), it is a simple and non-invasive treatment that offers pain relief and has no reported side effects. As outlined above, LLLT has been shown by various studies to be effective in the treatment of diabetic wound healing.

Due to disturbances of the circulation in people with diabetes, wounds heal slowly and are susceptible to infection. LLLT has been shown to speed up the time needed for wound closure in people with diabetes (Khurshudian, 1989; Kuliev and Babaev, 1991; Yu et al, 1997; Reddy et al, 2001); and there is improved wound epithelialization, increased cellular content, increased granulation tissue formation and increased collagen deposition (Yu et al, 1997). There is a decrease in the inflammatory reaction (Khurshudian, 1989), and a stimulatory effect on the immune system (Khurshudian, 1989; Kuliev and Babaev, 1991). LLLT has also been shown to increase microcirculation (Grigor'eva et al, 1991; Schindl et al, 1998; Schindl et al, 1999; Schindl et al, 2002), enhance wound tensile strength (Stadler et al, 2001), accelerate collagen production (Reddy et al, 2001; Reddy, 2003), and decrease free radical oxidation processes (Grigor'eva et al, 1991) in people with diabetes.

Due to the increasing cost of care of diabetic wounds, and the burden incurred by the patients and society, there is a need to develop new, inexpensive, and safe treatment modalities which increase wound healing. From the results of published studies on diabetic wound healing, large, properly controlled studies seem justified. At the correct wavelength, intensity and fluence, LLLT can be a complementary therapy modality in the treatment of impaired wound healing and future research should be developed to find adequate wavelengths and doses.

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RELATED ARTICLE: ARTICLE POINTS

1 Low-level laser therapy (LLLT) is an alternative treatment modality for diabetic wounds.

2 LLLT increases the speed, quality, and tensile strength of tissue repair, and resolves inflammation and provides pain relief.

3 LLLT is a noninvasive treatment with no reported side effects.

4 LLLT improves wound epithelialization and increases cellular content, granulation tissue, collagen deposition and microcirculation.

5 LLLT stimulates the immune system, enhances wound tensile strength, and decreases free radical oxidation processes.

RELATED ARTICLE: PAGE POINTS

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RELATED ARTICLE: PAGE POINTS

1 Due to the increasing cost of care of diabetic wounds, and the burden incurred by the patients and society, there is a need to develop new, inexpensive, and safe treatment modalities, which increase wound healing.

Table 1. Summary of events during wound healing and the effects of low-level laser therapy (LLLT; adapted from Pearl and Kanat, 1988).

Phase	Duration	Events
Lag	0-10 days	Inflammation Clot formation Epithelialization Fibroblast migration
Proliferation	2-4 weeks	Mitogenesis Fibrinogenesis Cellular migration Wound contraction Angiogenesis Granulation tissue formation Epithelialization
Remolding	[greater than or equal to]1 year	Scar formation Collagen maturation Collagen synthesis and lysis in balance

Phase	Effects of LLLT at all phases
Lag	Increased epithelialization Re-establishment of arterial venous and lymph microcirculation Decreased edema Pain attenuation Increased ATP, RNA and DNA synthesis
Proliferation	Increased granulation tissue Increased mitogenesis Increased neovascularization Increased matrix synthesis Increased fibrinogenesis Decreased inflammation Increased cytokines and growth factors Increased stimulation of immune system
Remolding	Increased tissue nutrition and oxygenation Increased wound closure Increased angiogenesis Increased tensile strength

Table 2. Explanation of units used for LLLT.

Power density refers to the light output per unit area of the target tissue being irradiated. This is measured in watts per square centimeter

(W/[cm.sup.2]) or milliwatts per square centimeter (mW/[cm.sup.2]).

Energy density is equivalent to dose (or fluence) and is measured in joules per square centimeter (J/[cm.sup.2]). Energy density refers to the amount of energy per unit area brought to bear on the tissue being irradiated. It is measured using the following formula.

Energy density (D;J/[cm.sup.2]) = [power (W; watts) X time (s; seconds)]/[area treated ([cm.sup.2])]

The wavelength of the lasers used is always measured in nanometers (nm).