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Chapter 18

The Need for Increased Attention to Low-Level Laser Therapy as Treatment for Wounds and Ulcers

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Additional information is available at the end of the chapter

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Abstract

Light amplification by stimulated emission of radiation (lasers) is a device that typically generates electromagnetic radiation of uniform wavelength, phase, and polarization. The term low-level laser therapy (LLLT) is broadly defined as the therapeutic benefit of lasers. This review aims to discuss the positive effects of LLLT on skin wounds, diabetic foot ulcers, and burn healing. Different LLLT protocols have been widely used as treatment for these conditions to accelerate tissue regenerative processes. We have classified eligible papers in the fields of skin wounds, ulcers, and burns into in vivo and in vitro experimental studies and clinical trials that evaluated the use of LLLT as treatments that promote healing. An electronic search of scientific peer reviewed papers was conducted in the PubMed database. Our search has shown that the use of LLLT in biology and medicine is growing rapidly, and advancements in LLLT research dramatically improved the clinicians' ability to safely and effectively treat wounds and ulcers. There is increased clinical use of laser for wound and ulcer treatment. Several recent studies have confirmed the potential beneficial effects of LLLT for wound healing.

Keywords: low-level laser therapy, skin wound, diabetic foot ulcer, burn

1. Introduction

The term low-level laser therapy (LLLT) is broadly defined as the therapeutic benefit of lasers. After Professor Mester from Hungary first revealed the therapeutic importance of lasers, different wavelengths of continuous wave (CW) LLLT have been shown to promote healing in skin from healthy humans and animals, as well as a number of experimental pathological

cases. Different LLLT protocols have been widely used in numerous medical situations with the intent to accelerate the regenerative processes of tissues.

In this review, the author characterized eligible papers into in vivo and in vitro experimental studies and clinical trials that evaluated the use of LLLT on skin wounds for promotion of healing. The author conducted an electronic search of scientific peer reviewed papers in the PubMed database of English language studies published from 2004 to 2016 with the keyword "low-level laser therapy." As inclusion criteria, the author chose articles with availability of access to the full text. This review intended to show the positive effects of LLLT on healing of skin wounds, diabetic foot ulcers, and burns. Initially, the author introduced wounds, ulcers, and burns and showed their importance. Next, a number of important related papers in the field were reported.

2. Definition

Devices that provide light amplification by stimulated emission of radiation (LASERS) typically generate electromagnetic radiation of a uniform wavelength, phase, and polarization. In 1960, Theodore Maiman has originally described a ruby laser. A laser is described as a source of light or radiation energy [1].

3. History

The term "LLLT" is broadly applied to the therapeutic effects of lasers; other terms, such as low power laser therapy, laser biomodulation, laser bioactivation, laser biostimulation, laser irradiation, and laser photostimulation, may be substituted for LLLT. In this review, the author have chosen the term LLLT photostimulation because of the observed stimulatory effects of the laser beam and photochemical nature of its interaction with biological systems. LLLT is a special type of laser that influences biologic systems through nonthermal means [2]. The use of LLLT as a therapeutic modality has originated from Eastern Europe approximately 50 years ago [2]. In 1967, Professor Mester, an employee of Semmelweis University in Budapest, Hungary, observed that applying laser light to the shaven backs of mice could cause more rapid regrowth of hair compared to unshaven mice [3]. He reported that the helium-neon (He-Ne) laser had the capability to promote wound healing in mice [4]. Professor Mester applied these findings to humans when he used lasers to treat patients with nonhealing skin ulcers [5, 6]. The clinical applications of LLLT have become the leading edge of clinical research in several countries, such as the former USSR, Japan, Canada, Australia, United Kingdom, China, and several Scandinavian countries. The history, origin, and development of various lasers are well authorized [2]. The clinical application of laser photobiostimulation is growing rapidly. Several review articles that explain the clinical applications of LLLT have been published [2]. LLLT is currently considered not only as a therapeutic procedure primarily used for relief of inflammation, edema, and chronic joint

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disorders; escalate healing of the wounds, deeper tissues, and nerves; but also as a treatment for neurological disorders and pain [7].

4. Objective

LLLT exposes tissues and cells to low levels of red and near infrared (NIR) and IR light. This treatment is introduced to as "low level" because of usage of light at lower energy densities in comparison to other types of laser therapy such as cutting, ablation, and thermal coagulation of tissue. LLLT is also defined as "cold laser" therapy because of the lower power densities used compared to those needed to produce tissue heating [7]. LLLT is currently used to treat a wide variety of diseases in which a large number of laser parameters such as the energy density, wavelength, pulse structure, power density, and timing of the applied light must be chosen for each treatment. A less than optimal choice of parameters can lead to not only reduced effectiveness of the treatment but also result in negative therapeutic outcomes. Thus, numerous published results on LLLT include negative findings simply because of an inappropriate choice of light source and dosage. This choice is particularly important because of the optimal dose of light needed for any particular application; doses higher or lower than this optimal value may have no therapeutic effect. LLLT is defined by a biphasic dose response: lower doses of light are often more advantageous than high doses [7]. This review aims to discuss the positive effects of LLLT on healing diabetic wounds and burns. Low-level laser energy density (J/cm^2) calculation: power (W) × duration of laser radiation (s)/laser beam surface area (cm^2).

5. Wound healing

Wound healing, which is a normal physiological process, takes places in four particular phases: hemostasis, inflammation, proliferation, and remodeling. For a successful healing process, all four phases must follow in the appropriate sequence and time. Numerous factors can put adverse effects on different phases of this process, resulting in an inappropriate wound healing process. The most important factors that influence healing of the cutaneous wound and the potential cellular and/or molecular mechanisms involved consist of local and systemic factors. Local factors include oxygenation, infections, foreign bodies, and venous sufficiency, whereas systemic factors comprise age and gender, sex hormones, stress, diseases, such as diabetes mellitus (DM), keloids, fibrosis, hereditary healing disorders, jaundice, uremia, obesity, medications (glucocorticoid steroids, nonsteroidal anti-inflammatory drugs), chemotherapy, alcoholism, and smoking, as well as immunocompromised conditions (cancer, radiation therapy, AIDS, and nutrition). A better understanding of the effects of these factors on the wound healing process may lead to therapeutics that accelerate wound healing and resolve impaired wounds. However, the influences of these factors are not mutually exclusive. One or multiple factors may play a role in any of the individual phases by contributing to the overall outcome of the healing process [8].

6. Diabetic wound healing in animals and patients (diabetic foot ulcers (DFU))

DM is the general name for a heterogeneous group of metabolic disorder characterized by high blood glucose levels that result from defects in insulin secretion and/or action [9]. The percentage of the population diagnosed with DM continues to increase. A study projects that as many as one in three US adults may have DM by the year 2050 if current trends continue. The expense of DM in the United States, at more than $174 billion per year in 2007, is anticipated to become an increasingly large financial burden in the future [10].

DFUs are a common problem among individuals with DM. These ulcers are among the most serious complications of DM that may result in amputation and mortality [11]. The prevalence of DFU in people with DM vary from 4% to 10% with a lifetime incidence as high as 25% [12]. Treatment of diabetic foot is extremely hard because these wounds are delineated by delayed healing; often result in chronic wound [13]. It has been reported that the 5-year mortality leading to lower extremity amputations may be as high as 68% [14]. Therefore, successful treatment of diabetic ulcers is a field of huge importance [15].

Many elements considered to be sources for the lack of healing in diabetic wounds involve peripheral neuropathy, the presence of an impaired immune system, peripheral microvascular disease, glycation of hemoglobin that leads to inadequate oxygen delivery to tissues, alterations in the red blood cell membrane [13] due to glycation, interchange in the proportion of type III to type I collagen in the skin [16], impaired biomechanical properties of the diabetic skin [17], impaired proliferation of skin fibroblasts [18], and impaired L-lactate production [19]. The diabetic wound is a disorder of the wound healing process, especially in the inflammatory and proliferative phases [13], pathologic angiogenesis [20], and a significant diminishing of the tensile strength of wound repair, detected in studies on diabetic animal models [21].

According to a review of the literature, numerous in vitro and in vivo studies, as well as clinical trials have reported positive effects of LLLT on the wound healing process both in animals and human patients.

7. Literature review

Dahmardehei et al. have stated that significant numbers of patients in burn centers are diabetics. The healing process in these patients is more difficult due to complications attributed to diabetes. Despite the fact that the gold standard treatment for a grade 3 burn ulcer patient is split-thickness skin grafting (STSG), however in diabetic patients, the rate of graft rejection and organ amputation is high due to impaired tissue perfusion. Previous studies show that LLLT accelerates fibroblast proliferation, increases collagen synthesis and tissue perfusion, and accelerates wound healing. Dahmardehei et al. have recommended a new therapeutic method for improving the healing process with better prognosis for these patients. Their study enrolled type II diabetes patients with 13, grade 3 burn ulcers considered candidates for amputation.

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In these patients, the grade 3 burn ulcers were treated by a 650 nm red laser light at 2 J/cm^2 for the bed of the ulcer and an 810 nm infrared laser light at 6 J/cm^2 for the margins, along with intravenous LLLT with a 660 nm red light, before and after STSG. The results showed complete healing for all patients considered candidates for amputation [22]. Góralczyk et al. reported that that chronic hyperglycemia was the source of endothelial activation. On the other hand, the inflammatory process in DM has been associated with the secretion of inflammatory cytokines by endothelial cells, such as tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6). Góralczyk et al. evaluated the effects of 635 and 830 nm wavelength LLL irradiation on the secretion of inflammatory factors (TNF-α and IL-6) in an endothelial cell culture-human umbilical vein endothelial cell (HUVEC) line under hyperglycemic conditions. Adverse effects of hyperglycemia on vascular endothelial cells might be recovered by the action of LLLT, especially at a wavelength of 830 nm. LLLT decreased TNF-α concentration in the supernatant and improved cell proliferation [23]. Lau et al. carried out a study to investigate the biophotonic effect of irradiance on collagen production in a rat model of a diabetic wound. The skin's tensile strength was a parameter to characterize the wound. The rat models received intravenous injections of streptozotocin (STZ) to induce diabetes. Skin-breaking strength was measured. The experimental animals were treated with an 808 nm diode laser at two power densities of 0.1 and 0.5 W/cm^2. The tensile strength was optimized after treatment with a high-power diode laser. The photostimulation effect was shown by the accelerated healing process and enhanced tensile strength of the wound. Lau et al. concluded that LLLT facilitated collagen production in diabetic wound healing [24]. Sharifian et al. assessed the influence of pulsed wave (PW) LLLT on healing of the diabetic wound in diabetic (STZ-D) rats. They divided rats into two groups: nondiabetic and diabetic. They induced type I DM in the diabetic rat group through injection of STZ. The rats were submitted to two full-thickness skin incisions on the dorsal region of each one. One month after the injection of STZ, wounds of the nondiabetic and diabetic rats were subjected to a pulsed, infrared 890 nm wavelength laser with an 80 Hz frequency and 0.2 J/cm^2 energy density for each wound point. PW LLLT significantly accelerated the numbers of macrophages, fibroblasts, and blood vessel sections in comparison with the corresponding control groups. Semiquantitative analysis of basic fibroblast growth factor (bFGF) gene expression indicated significant increase in gene expression in both nondiabetic and diabetic rats following LLLT [25]. Houreld reported that due to advancements in laser technology, irradiation of diabetic wounds with low-intensity laser irradiation (LILI) or phototherapy has vastly accelerated wound healing. At the correct laser parameters, LILI increased migration, viability, and proliferation of diabetic cells in vitro. A stimulatory effect on the mitochondria that resulted in increased adenosine triphosphate (ATP) was observed. In addition, LILI also showed anti-inflammatory and protective effects on these cells. In light of the continual threat of diabetic foot, infection, and amputation, new better therapies and the developing of wound healing research deserves better prioritization [26]. Esmaeelinejad and Bayat evaluated the effects of LLLT on human skin fibroblasts (HSFs) cultured in high glucose concentration and physiological glucose condition media. Release of IL-6 and bFGF was evaluated by enzyme-linked immunosorbent assay (ELISA). Statistical analysis demonstrated that certain previously mentioned laser doses (energy densities) promoted the release of IL-6 in HSFs which were cultured in high glucose concentration medium in comparison with

nonirradiated HSFs cultured in the same medium. LLLT with 2 J/cm^2 energy density enhanced secretin of bFGF and IL-6 from fibroblast cultured in media mentioned above (hyperglycemic condition media). When HSFs were cultured in physiologic glucose concentration medium during laser irradiation, LLLT more effectively released IL-6 and bFGF [27]. In a single case study, Dixit et al. outlined the possible effect of LLLT on delayed wound healing and pain in a diabetic patient with chronic dehiscent sternotomy. After irradiation, they observed proliferation of healthy granulation tissue with decreased scores from the pressure ulcer scale of healing for sternal According to the results, LLLT could be a new potential treatment for chronic sternal dehiscence following coronary artery bypass graft, as it reinforced wound healing with an early closure of the wound deficit [28]. Fathabadie et al. conducted a study on the influence of PW LLLT on mast cells in wounds of nondiabetic and diabetic rats. The induction of type I DM and LLLT protocol was the same as Sharifian et al.'s study [25]. They assessed mast cell numbers and degranulation in all subgroups at 4, 7, and 15 days after infliction of the wounds. According to the paired *t*-test, there were significantly more total numbers of laser-treated mast cells compared to the placebos in the nondiabetic and diabetic groups. They observed significantly more granulated mast cells compared with degranulated mast cells for all laser-treated mast and placebo mast cells in the nondiabetic and diabetic groups [29]. Aparecida Da Silva et al. performed a study not only to determine if LLLT restored the balance between mRNA expression of matrix metalloproteinases (MMP)-2 and MMP-9 but also to determine the ratio between collagen types I and III during the diabetic wounds healing. The diabetes model was induced efficiently by STZ as demonstrated through increased levels of blood glucose. A diode laser (50 mW, 660 nm, 4 J/cm^2, 80 s) was administered once after scare induction. After LLLT, the rats were euthanized. The scarred areas were collected for MMP-2 and MMP-9 mRNA and histological analyses (inflammation and types I and III collagen). The results determined that scare significantly increased MMP-2 and MMP-9 expressions in untreated diabetic rats compared to nondiabetic rats. LLLT significantly reduced MMP-2 and MMP-9 expressions compared with untreated diabetic rats. Aparecida Da Silva et al. concluded that LLLT altered the expression of MMP-9, stimulated collagen production, and increased the total percentage of collagen type III in diabetic animals [30]. Esmaeelinejad et al. evaluated the effects of LLLT on HSFs cultured in high glucose concentration medium. HSFs were cultured either in physiologic glucose (5.5 mM/l) or high glucose (11.1 and 15 mM/l) media. LLLT was performed with a He-Ne laser unit at energy densities of 0.5, 1, and 2 J/cm^2. The viability and proliferation rate of these cells were determined by MTT assay. The results indicate that LLLT stimulate the viability and proliferation rate of HSFs, which were cultured in physiologic glucose medium compared to their control cultures. LLLT had stimulatory effects on the proliferation rate of HSFs cultured in high glucose concentrations compared with their control cultures. Esmaeelinejad et al. announced that HSFs originally cultured for 2 weeks in high glucose concentration attended to culture in physiologic glucose during laser irradiation increase cell viability and proliferation. Therefore, LLLT had a stimulatory effect on these HSFs [31]. Dadpay et al. studied the effect of LLLT in experimentally induced diabetic rats. They generated two full thickness skin incisions on the dorsal regions of each rat. The healthy (nondiabetic) groups received a pulsed-infrared 890 nm laser with an 80 Hz frequency and 0.03 J/cm^2 for each wound point in the first group and 0.2 J/cm^2

in the second group. Laser-treated diabetic wounds of the animals subjected to the same pulsed-infrared laser treatments as the second group for each wound point. Laser irradiation with 0.03 J/cm^2 significantly diminished the maximum load for wound repair in healthy rats. Laser irradiation with 0.2 J/cm^2 significantly escalated the maximum load in wounds from the healthy control and diabetic groups [32]. Peplow et al. have used a 660 nm laser diode in genetic diabetic mice to promote the healing process of wounds covered with a Tegaderm™ HP dressing that causes delayed contraction (splinted wounds). Possibly, the stimulation of healing could be due to the potential diabetes-modifying properties of laser light. Nonwounded diabetic mice and wounded diabetic mice was subjected to the 660 nm laser to at the same dose and location. They measured body weight and water intake of the mice. The left flank in the experimental group received 660 nm and 100 mW of irradiation 20 s/day for 7 days. There were no significant differences in body weight and water intake over 22 days between mice in the experimental and control groups. On day 14, the mean blood plasma glucose level did not significantly differ between the two groups. There was no glycated hemoglobin A1c detected in the samples. Peplow et al. concluded that irradiation of the left flank in diabetic mice with the 660 nm laser system did not have a significant hypoglycemic effect. The laser-stimulated healing of wounds in diabetic mice resulted from cellular and biochemical changes to the immediate wound environment [33]. Jahangiri et al. studied the effects of combined 670 and 810 nm diode lasers on diabetic wound healing parameters in rats. Two intervention (laser) groups underwent LLLT using 670 nm diode laser (500 mW, 10 J, 48 s) in the wound context and 810 nm diode laser (250 mW, 12 J, 50 s) to the wound margins. Never could they find statistically significant differences between the diabetic and nondiabetic groups in the wound area, percentage of open wound area, and wound healing rate by the repeated measurements. After 7 days of LLLT in the nondiabetic group, urine excretion significantly increased compared with the control group. Jahangiri et al. showed that no significant difference existed between the LLLT and control groups. The increased urine volume in nondiabetic rats after LLLT was an incidental observation that deserved future study [34]. Mirzaei et al. examined the impact of LLLT on cellular changes in organ culture and cell culture of skin from STZ-D rats. Type I DM was induced in rats by STZ. Fibroblasts extruded from the samples were proliferated in vitro and another set of samples were cultured as the organ culture. The researchers used an He-Ne laser. They administered 0.9–4 J/cm^2 energy densities four times to each organ and cell culture. The organ cultures were analyzed by light and transmission electron microscopy. Cell proliferation was evaluated by the MTT assay. Statistically, 4 J/cm^2 irradiation significantly increased the fibroblast numbers compared with the sham-exposed cultures [35].

8. Skin burn healing

Burn injuries are common traumatic injuries that cause considerable mortality and morbidity. Additionally, they are among the most expensive traumatic injuries due to the extended hospitalization and rehabilitation, as well as costly wound and scar treatments [36]. Annually in the United States, 1.25 million burn patients are treated. Of these, at least 50,000 require

hospitalization [36]. Burn wounds generate special interest due to the large numbers of burn cases encountered. These wounds can generate a destructive effect functionally and cosmetically, which necessitates the search for a more efficient cure [37]. LLLT has beneficial effects on burn healing.

9. Literature review

Khoshvaghti et al. studied the effects of LLLT on mast cells in a third-degree burn rat model. Rats from all groups each received third-degree burns at three different locations. The first burn site on group I rats subjected to 890 nm pulsed laser, with 0.924 J/cm^2 energy density. 0.2% nitrofurazone cream was administrated for treatment of the second burn site on both groups of rats. They evaluated mast cell degranulation and numbers at each burn site on each group of rats. Analysis of variance on day 4 showed significantly lower total numbers of mast cells in the laser-treated burn sites compared with the other burn sites in both groups of rats. On day 8, the total numbers of mast cells were significantly lower at the laser-treated burn sites compared with the other burn sites. On day 13, there were significantly lower numbers of types I and II mast cells at the laser-treated burn sites compared with the other burn sites. Khoshvaghti et al. [38] concluded that LLLT significantly declined total numbers of mast cells through the proliferation and remodeling phases of healing in a rat model of third-degree burn. Ezzati et al. investigated the influence of PW LLLT on healing of a deep second-degree burn model in rats. In their study, two groups of laser-treated burns were treated by a 3000 Hz pulsed infrared diode laser that had 2.3 or 11.7 J/cm^2 energy densities, respectively. Treatment response was assessed both microbiologically and macroscopically. The incidence of *Staphylococcus aureus* diminished significantly in group 3 in comparison to group 1 on day 28. Analysis of variance showed that the 11.7 J/cm^2 LLLT significantly increased the wound closure rate at 2 and 3 weeks after infliction of the burn when compared with placebo burns. Independent sample *t*-tests demonstrated that LLLT with 11.7 J/cm^2 significantly enhance the wound closure rate though 4 weeks after infliction of the burn in comparison to the control burns. Ezzati et al. concluded that pulsed LLLT with 11.7 J/cm^2/890 nm of a deep second-degree burn model in rats significantly escalated the rate of wound closure compared with the control burns [39]. Ezzati et al. studied the influence of PW LLLT on the healing process of a third-degree burn in a rat model. They treated two groups of rats with a 3000 Hz-pulsed infrared diode laser that had 2.3 or 11.7 J/cm^2 energy densities and evaluated the response to treatment both microbiologically and macroscopically. They indicated that the incidence of *Staphylococcus epidermidis*, Lactobacillus, and Diphtheria diminished significantly in the laser-treated groups compared to the other groups by the chi-square test. The independent sample *t*-test illustrated that LLLT with 11.7 J/cm^2 energy density significantly escalated the wound-closure rate at 3 and 4 weeks after infliction of the burn compared with the control burns [40]. Vasheghani et al. evaluated 80 Hz pulsed infrared diode LLLT for third-degree burn healing in rats. The laser-treated burns were exposed to an 80 Hz pulsed 890 nm infrared diode laser at 0.396 J/cm^2, three times per week. Burn wounds were clinically examined. There were a significantly higher number of laser-treated burns that closed compared to the controls. The

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paired Student's *t*-test indicated that the wound closure rate of laser-treated burns was significantly longer than the control burns. Chi-square tests showed no significant difference between each microorganism (*Staphylococcus epidermis*, *S. aureus*, and *Pseudomonas aeruginosa*). Vasheghani et al. concluded that LLLT with an 80 Hz pulsed infrared diode laser accelerated third-degree burn healing in rats [41]. Bayat et al. studied the effects of LLLT on mast cell number during the inflammation, proliferation, and remodeling phases of the wound healing process of experimental burns. In the two laser-treated groups, burned areas were subjected to the LLLT with a He-Ne laser at energy densities of 38.2 or 76.4 J/cm^2. They observed that on day 7 in the first laser group, there were significantly more total numbers of mast cells compared with the other groups. On day 16 in the nitrofurazone-treated group, the total number of mast cells was significantly higher compared with the control, first laser, and normal groups [42]. In another study, Vashghani et al. investigated the effect of LLLT administered with a He-Ne laser on mast cell number and degranulation in rats with second-degree burns. All rats received deeply inflicted second-degree burns. In the two laser-treated groups, the burns received daily LLLT, with energy densities of 1.2 or 2.4 J/cm^2. In the fifth group, the burns were treated topically with daily administration of 0.2% nitrofurazone cream. Vashghani et al. concluded that administration of LLLT for deep second-degree cutaneous burns in rats not only significantly enhanced the number of intact mast cells during the inflammatory and proliferative phases of healing but also diminished the total number of mast cells during the remodeling phase [43]. In another study, Bayat et al. researched the effects of LL He-Ne LT on burn healing. The two laser treated groups, underwent daily treatment with LL He-Ne LT at energy densities of 1.2 or 2.4 J/cm^2. The response to treatment was assessed histologically and microbiologically. Analysis of variance demonstrated significantly greater mean blood vessel sections in the 1.2 J/cm^2 laser group compared with the other groups. Compared with the nitrofurazone-treated group, the mean depth of new epidermis in the 2.4 J/cm^2 laser group on day 16 was significantly lower. *P. aeruginosa* and *S. aureus* grew in more than 50% of samples obtained from control group, however these bacteria did not grow in the samples from the 2.4 J/cm^2 laser group. Bayat et al. concluded that LL He-Ne LT stimulated the destruction of *S. aureus* and *P. aeruginosa* in rats with third-degree burns. However, the histological evaluation demonstrated that LL He-Ne LT not only made a significant escalation in the mean blood vessel sections on day 7 after infliction of the third degree burns but also reduced the mean of the depth of new epidermis on day 16 after infliction of these burns in rats [44]. Bayat et al. studied the effects of two different doses of LLLT on healing deep second-degree burns. They inflicted a deep second-degree burn in each rat. The control group burns remained untreated. The two laser treated group burns were irradiated daily with LL He-Ne LT with energy densities of 1.2 or 2.4 J/cm^2. The response to treatments was assessed histologically and microbiologically. *S. epidermidis* was found in the 70% of the rats' wounds in the laser-treated groups in comparison to 100% of rats in the control group. Despite the fact that they found *S. aureus* in 40% of the rat wounds which were treated by nitrofurazone, they did not find this bacterium in the wounds of the laser treated and control groups. Bayat et al. determined that LLLT of deep second-degree burns made significant reduction in the number of macrophages and depth of the new epidermis.

Moreover, this treatment diminished the incidence of *S. epidermidis* and *S. aureus* [45]. It seems that special LLLT protocols have potential antimicrobial activity.

10. Cellular and tissue mechanisms of LLLT

It appears that LLLT not only has a great range of effects at the molecular, cellular, and tissue levels and also its specific modes of action may vary among different applications. Within the cell, there is strong evidence to suggest that LLLT causes the mitochondria [46] to enhance ATP production [27, 31], modification of reactive oxygen species (ROS), and induce transcription factors [47].

LLLT also enhances the proliferation, maturation, and motility of fibroblasts, and increases the production of bFGF [48]. When a chromophore absorbs a photon of light (laser) in the treated cells, an electron in the chromophore has the potential to become excited and move from low-energy orbit to a higher energy orbit [49]. The system can then use this stored energy to achieve various cellular tasks. There are several pieces of data that suggest that a mitochondria chromophore is as the initial LLLT target. Radiation of tissue with light makes mitochondrial products such as ATP, nicotinamide adenine dinucleotide (NADH), proteins, and RNA, as well as a reciprocal augmentation in oxygen consumption to increase. Various in vitro experiments have showed that cellular respiration is upregulated when mitochondria are subjected to a He-Ne laser or other forms of illumination [50]. The relevant chromophore can be detected by matching the action spectra for the biological response to light in the NIR range to the absorption spectra of the four membrane-bound complexes identified in mitochondria. This procedure demonstrates that complex IV or cytochrome *c* oxidase (CCO) is the essential chromophore in the cellular response to LLLT. CCO that consists of two copper and two heme-iron centers (components of the respiratory electron transport chain) is a large transmembrane protein complex [51]. The high-energy electrons are passed from electron carriers through a series of transmembrane complexes (such as CCO) to the final electron acceptor which makes a proton gradient used to produce ATP. Therefore, the administration of light directly affects ATP production by influencing one of the transmembrane complexes in the chain. Especially, LLLT increases ATP production and electron transport [52].

11. Contraindications and precautions

11.1. Contraindications

Direct irradiation of the eyes, within 4–6 months after radiotherapy, hemorrhaging region, locally to the endocrine glands [53].

11.2. Precautions

Epilepsy, fever, malignancy, to the low back or abdomen during pregnancy or menstruation, embryo or fetus, over the gonads, epiphyseal lines in children confused or disoriented patient,

area of decreased sensation, infected tissue, sympathetic ganglia, vagus nerves, or cardiac region in patients with heart disease [53].

12. Conclusion

The effects of LLLT depend on the physiological state of the target cells, type of laser, radiation wavelength, energy density, and number of laser sessions. The biostimulation efficiency of LLLT is also dependent on the delivered energy density, which appears to be restricted to a very narrow therapeutic window. Compared with CW LLLT devices, PW LLLT devices provide more laser parameters. By investigating different values of these parameters, research models can be more effectively studied in these devices (PWLLLT) in comparison with CW LLLT devices, with the purpose of achieving better outcomes [54]. There were different LLLT protocols for different tissues. Clinical applications of LLLT have significantly impacted medicine and attracted the interest of clinicians, the public, and the media. The use of LLLT in biological applications and medicine is growing rapidly; advances in LLLT research have dramatically improved the clinician's ability to safely and effectively treat various medical conditions. According to several studies if the general condition of patients (such as blood glucose level, hydration, Na level, etc.) is controlled, LLLT can be useful for the treatment of diabetic foot ulcer. Nevertheless, additional research is required to elucidate the exact mechanism of laser photostimulations action at the cellular and molecular levels. Standardized treatment parameters of LLLT should be followed. Efforts should be made to evaluate precise dosimetry for skin wounds, DFUs, and burns.

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