

Review Article

Photobiomodulation Therapy in Diabetic Wound Healing: Review

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Abstract

Background: The diabetic wounds that are likely to result in amputation and/or death are receiving particular attention of medical and healthcare community in recent years. Photobiomodulation therapy (PBMT) is an alternative medical technique that uses low energy light to stimulate cellular process in order to improve the biological response and function. A number of researchers have explored the positive effects in in-vivo and in-vitro studies.

Objective: In this review, we highlight and discuss the mechanism of laser therapy that affects cellular processes by bio-stimulation on inflammation and proliferation phase based on diabetic model.

Methods: Review of literature related to PBMT and its application in diabetic wound healing. Literatures were collected from PubMed, Google Scholar and Scopus using keywords PBMT, diabetic wound healing and photobiostimulation.

Results: The respective wavelength of visible red and near infrared light are considered as most effective for stimulating the cellular responses. Although both ranges of wavelengths have different penetrative power but they can provide therapeutic benefits on specific cellular functions.

Conclusion: Literatures suggest that PBMT have stimulatory effects that lead to enhance diabetic wound healing. However, for comprehensive understanding of cellular and light interaction, a detailed study of PBMT is further required.

Keywords: Diabetic Wound; Healing Process; Photobiomodulation Therapy (PBMT)

Introduction

Photobiomodulation therapy (PBMT) is one of the biophotonic technique, it denotes a stimulation of biological processes upon incident by photons [1]. Many researchers have revealed that PBMT has great impact in wound healing specifically on pain reduction, cell regeneration, anti-inflammatory, activating metabolism, increasing cell signaling pathway and/or restore damaged tissue [2-4]. High attention are required on diabetic wound because its healing process is notoriously slow, and can worsen rapidly

often resulting in ulcer formation. Diabetes mellitus considered as a complication of metabolic disorder disease (high blood pressure, high blood sugar, and abnormal cholesterol levels) that cause cellular signaling dysfunction to disturb intracellular signal transduction and decrease cellular responses [5-7]. Cell dysfunction, immune system deficiency and poor blood circulation are the factors that delay the healing process [8]. Numerous of conventional treatment and pharmaceutical drugs such as antibiotics and ointments which were taken either in orally or directly applied on the wound in order to promoting the healing process or preventing the spread of bacterial infections, these might have adverse effect on kidney, resistance to drugs or allergic reaction [9]. Light-based

therapy has advantage of being safe, easy to operate and able use as a supplementary therapy parallel to conventional treatments as well as minimizing the medication side effects. In this review, we highlight the function of laser therapy on diabetic wound healing.

Mechanism of Photobiomodulation Therapy

Photobiomodulation Therapy (PBMT) is rapidly becoming the alternative approach for a wide variety of treatment, it has introduced as painless, non-invasive and drug free therapies in wound healing [10]. It is stimulate biological items with light based on the principles of photobiomodulation or photobiostimulation [11]. Some studies have speculate that the light are absorbed by certain electronic absorption band belonging to the multitude of molecular photo-acceptor in tissues causes rotations and vibrations of molecular, excitation of molecule, and energy transduction that were trigger a series of bio-reaction in motion cellular metabolism, which eventually leads to accelerate healing process [12]. There were evidence shows that the action of light involves the photo-activation of enzymes in mitochondria [13-15]. Mitochondrion described as nature light receptors or photoacceptor, which is the house for energy production and respiration processes. Mitochondria contain an Electron Transport Chain (ETC) and a huge amount of respiratory complexes as well as transmembrane protein complex such as cytochrome c oxidase [16]. cytochrome c oxidase has been proposed as a primary photoacceptor for the infrared range, its absorption spectra was found to be very close to the action spectra for biological responses to light [17]. Therefore, modulation of cytochrome c oxidase activity and transport chain have been demonstrated as an important role in laser therapy for acceleration of wound healing via oxidative phosphorylation and pathway to changes in the redox status of the mitochondria [18,19]. PBMT was increase the activity of mitochondria to provoke the production of adenosine triphosphate (ATP), which is a coenzyme uses as an energy currency of cells [20]. The light was trigger ADP/ATP exchange cycle from conversion of ATP (contain three phosphate groups) to ADP (adenosine diphosphate contains two phosphate groups) through breakdown of the phosphate group and to release energy vice versa [21]. Simultaneously, ADP/ATP exchange cycle as a signaling molecule to communicate and control cellular activities. The signaling cascade to recruitment the cells and growth

factors immigrate to wound area take responsibility for their duties [22]. These effect of PBMT increase the activity of mitochondria respiratory chain and ATP/ADP exchange cycle production in turn lead to promote the cellular metabolism, cell proliferation and migration may induce accelerate the healing process [23].

Wound Healing Assessment

Wound healing is a natural and complex process of our body to repair the damaged skin. Diabetic wound that also have to pass through the same phase as ordinary wound that are homeostasis, inflammation, proliferation and remodeling. By definition, any therapeutic methodology altering the healing process by accelerating transition periods between inflammation and proliferation [24]. The inflammatory process is play the role as “alarm signal” to awake and provoke a series of response that released many of factor such as extracellular fluid, macrophages, mast cell and leukocytes to establish of a clean wound bed for repair process [25]. Furthermore, inflammatory response also induces the signal to release and activate the cell, factor and mediate to trigger into proliferation stages. Proliferation is a growth process by the rapid production of new tissues or cells. In this review, the effects of PBMT with various biology cells at inflammation and proliferation phase have discussed.

Drawing conclusive results from PBMT has proven difficult especially in clinical trials due to the myriad of assessment methods from experimental outcomes, but since the mechanism of natural wound healing depends critically on the availability of fibroblast cells for its ability to synthesize extra-cellular matrix and collagen, quantifying it has almost become a standard for most PBMT investigations. For non-human investigations, skin tensile tests by sacrificing the test subject are often applied to study the breaking strength of the healed wound [26]. Several assessments have been used to quantify the analysis such as wound size, healing time, pain intensity, tensile strength of skin and image analysis [27,28]. Cellular assessment has also used to monitor tissue details such as bacteria colony count, macrophage count, leukocyte count, mitochondrial enzyme activity, keratin level (mRNA), protein level, level of enzyme cathepsin B, level of hidroksiprolin, uronik acid level, level of hydrolyzate and cytotoxicity [29,30]. Studies

Parameter/ Grade	0	1	2	3	4
Necrosis	none	few	partial	thin	thick
Epithelialization	none	minimal (at edge of the wound)	moderate (more than half of the wound)	complete (entire wound with thin layer)	complete and thick layer
Inflammation Infiltrate	none	mild	mild to moderate	moderate	severe
Leukocytes	none	mild	mild to moderate	moderate	abundant
Macrophages	none	mild	mild to moderate	moderate	abundant
Dermal Regeneration	none	loose and sparse	dense and a lot of hole	dense and regular orientation	dense and irregular orientation
Granulation Tissue	none	thin layer at edges	thin layer across wound	uniformly thick	uniformly thicker
Collagen Deposition	none	few collagen fibers	moderate collagen fibers (migrate to wound center)	abundant with regular orientation	abundant with irregular orientation
Fibroblasts	none	mild	mild to moderate	moderate	abundant
Vascularization	none	few capillaries	moderate	extensive	well-defined capillary system
Keratinocytes	none	mild	moderate	thin	Thick

Table 1: Wound healing histological scoring system.

Note. Based on scoring system reported in previous investigators [31-33].

Photo-Absorption of Living Tissues

The PBMT is an alternative method of treatment, a number of experimental procedures have been deployed for independent studies. However, it was the lack of standardization and comprehensive up-to-date reviews leading in conclusive outcome for PBMT. Thus, due to complex nature of biological interactions coupled with the light-sources for PBMT, there still have some limitations. Effectiveness of PBMT was dependent by wavelength, radiation dose, power density, target area, waveform intensity, penetration depth, exposure time and treatment frequency [34]. Besides, effect of PBMT not only dependent on the treatment parameter, it is also directly affected by the properties of skin. Skin properties are depend by model (animal or human), age, gender, pigmentation, part of body, and skin types (oily, pimples, sensitive, dry and normal). For the *in vivo* studies, animal models are frequently used as a replacement for human being. Laboratory rat have served as an important animal model for research in wound healing because their properties, genetic and physiology are similar to those of human [35]. The skin of rat is made up of three primary layers same as human skin, there are epidermis, dermis and hypodermis. Epidermis is the outermost layer of skin. It is composed of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale (Figure 1).

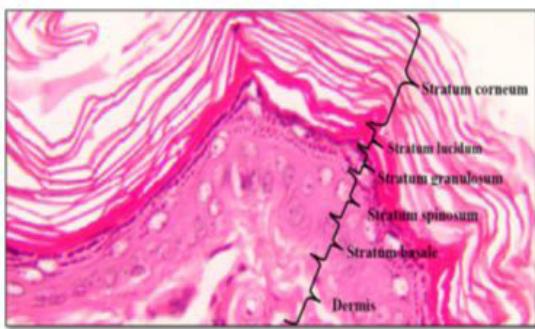


Figure 1: The epidermis of rat skin is composed of stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum and stratum basale.

PBMT that uses low level or low power to stimulate the cellular, it is involved non-thermal optical absorption. Thus, the knowledge of penetration depth as a function of wavelength provides an insight to treatment efficacy. The ability of laser to penetrate and absorbed by tissue is wavelength dependent such as shown in Figure 2. The shorter wavelength known as Ultraviolet (UV) radiation with wavelength < 400 nm, it has low penetrating power and could not penetrate more than a few micrometers beneath the skin [36]. In PBMT, UV therapy does not significantly promote the healing process but exhibits bactericide properties on the target [37]. Most previous studies have indicated that the skin has well response to red and near infrared wavelengths [38,39]. The absorption of light on skin tissues softens toward the region of red and near infrared in the so-called “Therapeutic window”, which allows absorbed by mitochondrial chromophores in skin cells for photo-biological treatments [40]. Although, longer the wavelength is significant deeper the penetration of light into the skin while as the wavelength increases into the far infrared regime, it begin to be heavily absorbed by water thus limits its penetration [41]. In this review, the effects of PBMT have been discussed within visible red and near infrared region on diabetic model.

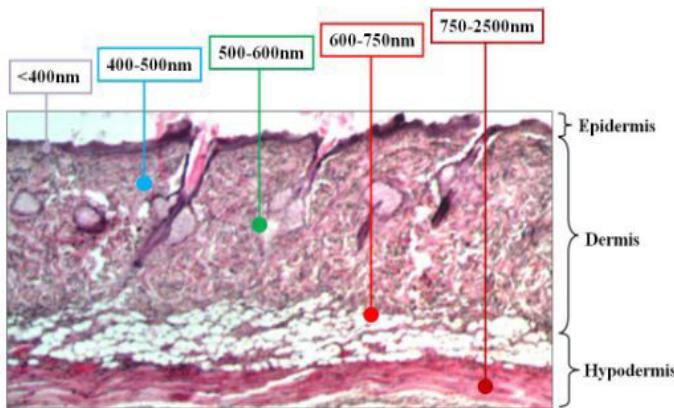


Figure 2: Penetration of various wavelengths into rat's skin.

Photobiomodulation Therapy with Visible Red Laser

Most studies have indicated that the optimal effects of PBMT in the visible red to near infrared range, there were shown high absorption by biological tissue [42,43]. We first define the visible red light corresponds to wavelength range of 600 nm to 750 nm. Few laser lines are commercially available within this range, 632.8 nm helium-neon (HeNe) laser is being the most common light source used in PBMT [44,45]. High blood glucose level are causing stiffens arteries, narrows blood vessels and decline growth of fibroblast. Esmaeelinejad et al. [46] had evaluated the stimulatory effects on human skin fibroblast in high glucose concentration medium by using 632.8 nm HeNe laser. Growth of human skin fibroblast showed significant inhibition of cellular viability and proliferation in high glucose concentrations media. The laser treated human skin fibroblast was causes morphological changes and turn into activated cells at low dose of 0.5 and 1.0 J/cm², whereas the inhibitory effects was shown in high dose of 2 J/cm². This indicated that the laser irradiation capable to accelerate collagen production in high blood glucose condition. A study accomplish by Ayuk et al. [47] to determine the effects of laser on collagen production and related cellular responses in diabetic wounded fibroblast model. PBMT has been shown to produce stimulatory effects on cell migration, viability, proliferation, and collagen content. Besides, high level of oxidative stress was often notice in diabetic patients or drug induction animal models, which causes inhibit healing process as well as reduced activity of antioxidant enzyme due to high production of free radical in the body. Denadai et al. [48] reveals the uses of laser irradiation was decreased levels of Malondiadehyde (MDA) that indicates a decrease in the levels of oxidative stress.

The primary roles of inflammation in wound healing are to prevent the infection and to control many gene products that are essential for restoration of tissue architecture [49]. Matrix Metalloproteinases (MMPs) used to remove the damaged Extracellular Matrix (ECM) for degradation and breakdown the cell membrane for angiogenesis and cells migration. Typically, diabetic patients have high level of MMPs as compared to ordinary individuals, it indicated that they have high risk to evolve into chronic wound [50]. Aparecida Da Silva et al. [51] studied the modulation of laser therapy on expression of matrix metalloproteinases (MMP-2 and MMP-9) in diabetic rats. The inversely relationship between MMP and rate of healing that indicated high level of MMP that reflects serve inflammation and inhibit the healing process. They found that laser irradiation at 660 nm was significant decrease expression of MMP 2 and MMP 9, there was no statistical difference between the laser-treated diabetic rat and healthy rats. They concluded that the use of laser therapy was able to normalize the expression of matrix metalloproteinase.

Photobiomodulation Therapy with Infrared Laser

The interaction of light with bimolecular obviously dictates the mechanism involved in PBMT. Kim et al. [52] stated that the longer wavelength light (infrared) have greater effects in cell stimulation than shorter wavelength (visible). Danca'kova et al. [53] reported that infrared 810 nm laser with an output of 30 mW that able to restores the similar healing response in diabetic wound as non-diabetic wound. The treated group exhibit significantly mature granulation tissue than in the control group. In cell culture, Khoo et al. [54] studied the effect of infrared laser to skin fibroblast of diabetic and non-diabetic rats in term of secretion of Fibroblast Growth Factor (FGF), Platelet Derived Growth Factor (PDGF) and Vascular Endothelial Growth Factor (VEGF), which were important growth factors in wound healing. In post-treatment, only FGF have significant increase in diabetic irradiated group than non-diabetic rat, although PDGF increased and VEGF decreased in both diabetic and nondiabetic irradiated groups. This finding suggests that PBMT able to promote formation of FGF, which is involved in angiogenesis on diabetic wound, but these variations were not statistically significant.

Other study on fibroblast culture was conduct by Chen's group [55] they were investigated the inflammation signaling pathway based on NF- κ B activation response. 810 nm laser irradiation has significant activated NF- κ B at earlier 1 hour and activates the redox-sensitive NF- κ B signaling via generation of Reactive Oxygen Species (ROS). A similar study by Aimbire et al. [56] reports that infrared laser irradiation (904 nm) with low dose of 5 J/cm² can deactivate of TNF α and NF- κ B response via decrease the ROS release in acute injury in order to lower the inflammatory response [57]. According to these results, laser therapy has stimulation effects to enhance mitochondria respiration, it also able to trigger inflammation response in earlier and minimize the inflammation release that can shorter the healing time.

Nevertheless, high penetrating power of infrared light are require low energy density for PBMT. The energy of radiation higher than cellular absorption, the excess energy is transferred to heat effects that are gain heat shock to damage or induce apoptosis on cellular. Some of report have been discussed that the high energy will cause inhibit healing process. Kawalec et al. [58] have suggests that 980 nm laser treatment at 18 J/cm² every other days enhances wound healing on diabetic group than control, while the energy density was increase to 36 J/cm², the reduction of healing process was observed. Lau et al. [59,60] also indicated that laser therapy was complex energy dependent. It is not only energy dependence but also depends on power density. They revealed that diabetic wounds have achieved optimum healing rate at low power density (0.1 W/cm²) and inhibit healing at 0.3 W/cm², whereas both of group have same total output energy (5 J/cm²).

Conclusion and Future Trend

Diabetic wound has brought socioeconomic burdens to patients, and significant cause of morbidity, mortality, and financial burden. PBMT provide improvement in wound healing via activating the cellular signaling and function. Visible red and infrared light have been experimentally found to induce positive biological response particularly in triggering mitochondrial components to release NF- κ B, ATP respiration, ROS and fibroblast. The actions of PBMT are wavelength dependent manner and dependent upon the absorption of cellular. The conclusive evidence of PBMT on diabetic wound encourage a further investigations, more details in term of energy absorption and optical properties of cellular are required to understanding of energy absorption of cellular and enhance the effectiveness of therapy. The technologies of PBMT have the potential applied to reduce the rate of amputation and death in diabetic patients.

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