

**REVIEW ARTICLE**

**Low Level Laser (LED- Ga-Al- As 660) Therapy On soft Tissue Healing: A Review Update**

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**Abstract**

The normal process of soft tissue repair involves the following steps: homeostasis, inflammation ("cleaning"), demolition, proliferation, and maturing<sup>10</sup>. The homeostatic phase occurs immediately after the appearance of the lesion and depends on platelet activity and on blood coagulation process, which includes a complex release of vasoactive substances, adhesive proteins, and growth factors for the development of other stages. Later on, the inflammatory process sets in with the presence of numerous chemical mediators and inflammatory cells polymorphonuclear leukocytes, macrophages, and lymphocytes. This phase is responsible for removing necrosis tissue and combating aggressive agents installed in the wound. Next, tissue proliferation, which is responsible for "closing" the wound, sets in, with re-epithelization, fibroplasia (matrix formation), and angiogenesis, essential for the supply of oxygen and nutrients needed for healing. Finally, there is wound contraction followed by remodeling, which takes place in the collagen of the region and has the objective of increasing tensile force and diminishing the scar size. [*Journal of Science Foundation, 2015;13(2):46-51*]

**Keywords:** Low Level Laser; soft Tissue; Healing

**Introduction**

Some of the most common cutaneous wounds include excoriations, burns, surgical incisions, and acute or chronic ulcerations (Snyder et al., 2005). Diabetes mellitus is one of the primary predisposing factors for skin lesion development and one of the most common reasons for patients to seek health care, as it represents an important cause of disability and premature death (Sugrue et al., 1990). Serious cutaneous foot lesions in diabetic patients are the cause for hospital admission in 51% of patients in endocrinology wards of Brazilian university hospitals (Chromey et al., 1992). When not properly healed, these lesions represent the main cause of morbidity, immobility and limb amputation, according to data from the American Diabetes Association.

Burn injuries, a clinical condition resulting from direct or indirect action of heat on the human body that causes different degrees of skin lesions, are a significant cause of mortality, primarily due to the infections that can evolve to septicemia. According to the Brazilian Society of Burn Injuries, there are 1 million cases each year in Brazil (Nussbaum et al., 1999). Skin lesions have a great morbidity potential primarily because of complications in the normal healing process. To prevent these complications and promote cure, one needs to understand the normal process of soft tissue repair, as well as the factors that determine its normal

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healing. Tissue healing highlighted as one of the main effects of LLLT is characterized by three main factors (Rocha et al., 2006). First, there is an increment of ATP production, as laser is considered to raise the production of ATP, leading to a boost in mitotic activity and to an increase in protein synthesis by mitochondria, resulting in greater tissue regeneration in the repair process (Ramos-e-Silva et al., 2002). Second, there is a stimulus to microcirculation, which increases the delivery of nutritional elements associated with increased speed of mitosis, facilitating cell multiplication. Finally, new vessels are formed from preexisting vessels. Several factors have a direct influence on tissue healing, altering this process, making it slower, thus allowing complications associated with wound exposure to the external environment. The table below displays the key local and systemic factors that affect tissue wound healing. Tissue lesions become a route for the installation of problems resulting from exposure to external agents, and therefore there is a need to accelerate the healing process by methods that shorten its duration. Laser therapy has become an important treatment for patients with cutaneous lesions, and there are ongoing studies aimed at understanding and confirming the known effects of laser application in tissue repair (Rocha et al., 2006).

**Low-level Laser**

The origin of low-intensity laser is attributed to Albert Einstein, who in his article entitled "Zur Quantum Theories der Strahlung" exposed the main physical principles of stimulated emission (laser phenomenon). This emission was later classified as "high- potency" with destructive potential and "low-potency" without destructive potential (Sheridan and Thompkins 2004). In order to be produced, laser light needs atoms, constituted by a central nucleus, that are positively charged balanced by negatively charged electrons that move around the nucleus in well-defined circular trajectories; in this rotational movement, there is no emission of energy. When the electron passes from one orbit to another, there is a release or absorption of energy called a photon. The devices that produce this beam of light are comprised of three parts like an active laser medium (gain medium), an external energy source, and a resonant optical cavity. The gain medium is a gas, solid or liquid containing the atoms that enable photons to leap electron levels emitting photons and constituting a laser light beam.

**Table 1: Parameters involved in determining the LLLT Irradiation parameters irradiation time or energy delivered (the dose)**

Irradiation parameter	Unit of measurement	Comment
Wavelength	nm	Light is electromagnetic energy which travels in discrete Packets that also have a wave-like property. Wavelength is measure in nanometers (nm) and is visible in the 400-700 nm range.
Irradiance	W/cm <sup>2</sup>	Often called Intensity, or Power Density and is calculated as Irradiance = Power (W)/Area (cm <sup>2</sup> )
Pulse structure	Peak Power (W) Pulse freq (Hz) Pulse Width (s) Duty cycle (%)	If the beam is pulsed then the Power should be the Average Power and calculated as follows: Average Power (W) = Peak Power (W) □ □ pulse width (s) pulse frequency (Hz)
Coherence	Coherence length	Coherent light produces laser speckle, which has been depends on postulated to play a role in the photobiomodulation Spectral band-width interaction with cells and subcellular organelles.
Polarization	Linear polarized or circular identical non-polarized	Light may have different effects than otherwise light (or even 90-degree rotated polarized polarized light). However, it is Known that polarized light is rapidly scrambled in highly scattering media such as tissue (probably in the first few hundred μm).

The external energy source furnishes the necessary energy to the system, so that electrons leap levels releasing, and not absorbing energy. This energy source should be able to produce high-energy or excited

states. The optical or resonator cavity makes the emerging photons return to the system, producing additional stimulated emissions; this phenomenon occurs by mirrors positioned at the cavity extremities, provoking a reflection of photons back to the sample (Contran et al., 2001). The differences between the various types of laser beams produced are determined by wavelengths: the shorter the wavelength, the greater its action and power of penetration. Additionally, lasers may be continuous or pulsed, and their potency is expressed in Watts (W), varying from deciwatts to megawatts. Energy is expressed in Joules per square centimeter ( $J/cm^2$ ), and therefore is equal to the potency multiplied by the duration of application. Knowledge of these parameters is vital for appropriate indication and therapeutic utilization of this method (Tanaka et al., 2004).

**Table 2: Parameters involved in determining the LLLT “dose”**

<u>Irradiation</u>	<u>Unit of Parameter measurement</u>	<u>Comment</u>
<b>Energy</b>	<b>(Joules) J</b>	<u>Calculated as:</u> Energy (J) = Power (W) x time (s). This mixes medicine and dose into a single expression and ignores Irradiance. Using Joules as an expression of dose is potentially unreliable as it assumes reciprocity (the inverse relationship between power and time).
<b>Energy Density</b>	<b>J/cm2</b>	Common expression of LLLT “dose” is Energy density. This expression of dose again mixes medicine and dose into a single expression and is potentially unreliable as it assumes a reciprocity relationship between irradiance and time.
<b>Irradiation Time</b>	<b>s</b>	In our view the safest way to record and prescribe LLLT is to define the four parameters of the medicine (see table 1.) and then define the irradiation time as “dose”.
<b>Treatment Interval</b>	<b>Hours, days or weeks</b>	The effects of different treatment interval are underexplored <b>at</b> this time though there is sufficient evidence to suggest that this is an important parameter.

### A. Action of Laser on Tissues and its role in the Healing Process

Based on the understanding of the mechanism of laser light origin, we observe that when low-intensity light is used, there is no thermal effect, i.e., the energy from the photons absorbed is not transformed into heat, but into photochemical, photophysical, and photobiological effects. This is an important principle of the interaction between laser light and cell or tissue specimens. When it is applied at an appropriate dose, laser can stimulate cell functions that are vital for the progress and resolution of the healing process via tissue biostimulation, such as increased mitochondrial ATP production, lymphocyte and mast cell activation, and proliferation of fibroblasts and other cells, besides promoting analgesia and anti-inflammatory effects (Contran et al., 2001). As previously stated, the action of laser on tissues depends on the duration of emission of the different energy densities, and on the application area. Therefore, if these parameters are not duly verified and/or calibrated, treatment may be ineffective, compromising therapeutic success. According to previously established parameters, in cutaneous lesions the tissue layer to be targeted depends on type of laser, potency used and duration of application. Using high potencies or application of light for fractions of a second, the power of penetration of HeNe radiation with a wavelength of 632 nm could reach up to 19 mm of depth in the dermis (Contran et al., 2001). Since the energy produced by the laser is only absorbed by a thin layer of adjacent tissue in addition to the spot targeted by the radiation, current recommendation is to use low-intensity laser that has a low power of penetration, with wavelengths between 640 and 940 nm in a punctiform application to the lesion.

## B. Mechanism of Action of Laser and Action on soft Tissue Wound Healing

**Laser Tissue Interactions:** The primary (physical) mechanisms relate to the interaction between photons and molecules in the tissue, while the secondary mechanisms relate to the effect of the chemical (Bio-chemical) changes induced by primary effects.

1. The first and commonest pathway that occurs when light is absorbed by living tissue is called internal conversion. This happens when the first excited singlet state of the chromophore undergoes a transition from a higher to a lower electronic state. It is sometimes called "radiation less de-excitation", because no photons are emitted. It differs from intersystem crossing in that, while both are radiationless methods of de-excitation, the molecular spin state for internal conversion remains the same, whereas it changes for intersystem crossing. The energy of the electronically excited state is given off to vibration modes of the molecule, in other words, the excitation energy is transformed into heat (Contran et al., 2001).

2. The second pathway that can occur is fluorescence. Fluorescence is a luminescence or re-emission of light, in which the molecular absorption of a photon triggers the emission of another photon with a longer wavelength. The energy difference between the absorbed and emitted photons ends up as molecular vibrations or heat. The wavelengths involved depend on the absorbance curve and Stokes shift of the particular fluorophore.

3. The third pathway that can occur after the absorption of light by a tissue chromophore (Biochemical) represents a number of processes broadly grouped under an umbrella category of photochemistry. Among the above three, internal conversion & fluorescence are the mechanisms those are involved in Physical Mechanism of laser tissue interaction, and third one is recognized as Bio-chemical (Contran et al., 2001).

**Physical Mechanisms:** There are two primary forms of physical effects generated by laser irradiation of biological tissues:

1. Photon-absorption (the basis of photo-biological action, and generated by all forms of light).

2. Internal conversion & fluorescence of light also generates Speckle formation, which is unique to laser therapy. The speckle field is created when coherent laser radiation is reflected, refracted and scattered. The speckle field is not simply a phenomenon created at and limited to the tissue surface, but is generated within a volume of tissue, persisting to the total extent of the depth of penetration of the laser beam. Laser speckles formed deep in the tissue create temperature and pressure gradients across cell membranes, increasing the rate of diffusion across those membranes (Contran et al., 2001).

**Biochemical Mechanisms:** The third pathway that can occur after the absorption of light by a tissue chromophore (Biochemical) represents a number of processes broadly grouped under an umbrella category of photochemistry. This is the basic mechanism by which way laser works in animal/ human cell/tissue. It has been established by thousands of research/application, and it is recognized by World Laser Association as well as American /European associations of Laser/photo-biology. Mitochondrial respiratory chain contains five complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), cytochrome c oxidase (Complex IV), and ATP synthase (Complex V). The first law of photobiology states that for low power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular photoacceptors, or chromophores- (Sutherland 2002). A chromophore is a molecule (or part of a molecule) which imparts some decided color to the compound of which it is an ingredient. Chromophores almost always occur in one of two forms: conjugated pi electron systems and metal complexes. Examples of such chromophores can be seen in chlorophyll (used by plants for photosynthesis), hemoglobin, cytochrome c oxidase (Cox), myoglobin, flavins, flavoproteins and porphyrins (Karu 1999).

## Tissue response & healing by LLLT

**A. Tissue response:** LLLT can provide the following beneficial impacts in both open surface wounds and closed connective or soft tissue injuries as follows:

**1. Enhanced leukocyte infiltration:** LLLT stimulates activity involving neutrophils, monocytes and lymphocytes.

**2. Increased macrophage activity:** LLLT accelerates macrophage activity in phagocytosis, growth factor secretion and stimulation of collagen synthesis.

**3. Increased neovascularization:** The significant angiogenesis that occurs with laser therapy promotes revascularization with subsequent improvement in perfusion and oxygenation. Endothelial cell regeneration is accelerated.

**4. Increased fibroblast proliferation:** LLLT stimulation increases fibroblast numbers and fibroblast-mediated collagen production.

**5. Keratinocyte proliferation:** The beneficial synthesis activities and growth factor ability of keratinocytes are enhanced by proliferation secondary to LLLT.

**6. Early epithelialization:** Laser-stimulated acceleration of epithelial cell regeneration speeds up wound healing, minimizes scarring, and reduces infection opportunities.

**7. Growth factor increases:** Two to five fold increases in growth-phase-specific DNA synthesis in normal fibroblasts, muscle cells, osteoblasts and mucosal epithelial cells irradiated with IR light are reported. Increases in vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF-2) secondary to IR light irradiation have also been reported.

**8. Enhanced cell proliferation and differentiation.** Laser-induced increases in NO, ATP and other compounds that stimulate higher activity in cell proliferation and differentiation into mature cells. Increased numbers of myofibroblasts, myofibrils, myotubes etc., as well as bone cell proliferation, have been clinically documented after- LLLT. Satellite cells, the precursor cells in the process of muscle regeneration, show significant increase in proliferation when irradiated with LLLT (Parizotto et al., 1998).

**9. Greater healed wound tensile strength.** In both soft tissue and connective tissue injuries, LLLT can increase the final tensile strength of the healed tissue. By increasing the amount of collagen production/synthesis and by increasing the intra and inter-molecular hydrogen bonding in the collagen molecules, laser therapy contributes to improved tensile strength (Hopkins et al., 2004). The preceding effects combine to achieve an accelerated healing rate. The time from onset of injury to mature healed wound is reduced (Kolárová et al., 1999). The cumulative effects of (physical & Bio-chemical) laser on tissue enhances physiological activities by ion-exchange, speckle formation, singlet oxygen, redox formation, ATP production & nitric oxide formation and exerts

- Enhances chemiosmosis,
- Enzyme & hormone regulation
- Stimulates the redox activity in the mitochondria,
- RNA synthesis and DNA production - causing mitosis and cell proliferation
- Calcium-ion influx into the cytoplasm,

So, Laser bio-stimulation may be an invaluable therapeutic modality for treating most wounds. Wound healing entails a) the process of inflammation during which the hematoma formed in and around the wound site is resolved; b) cellularity and protein synthesis, i.e., two processes that culminate in the formation of granulation tissue; and c) wound remodeling, a process that may continue long after the wound may be said to be well healed.

**B. Tissue Healing:** One of the truly unique characteristics of LLLT is that it has the ability to actually promote and enhance healing, not just treat symptoms. The irradiation by low-level laser light accelerates and enhances healing activities carried out by the body. Several of the unique characteristics of LLLT that work to alleviate pain and inflammation also play an important role in accelerating the healing process; the LLLT-mediated reduction in inflammation and pain frees the body's natural ability to repair and heal itself. The effects of LLLT can vary considerably. Cells being initially at a more reduced state (Lucas et al., 2002) have high potential to respond to LLLT, while cells at the optimal redox state respond weakly or do not respond to treatment with light. As wound healing progresses through the stages of inflammation, proliferation, remodeling and maturation, laser therapy presents the opportunity to impact each of these phases in positive and beneficial ways (Mester and Mester 1989).

### **Beneficial effect of LLLT on wound healing**

The beneficial effect of LLLT on wound healing can be explained by considering several basic biological mechanisms including the induction of expression cytokines and growth factors known to be responsible for the many phases of wound healing. Firstly there is a report that laser increases both protein and mRNA levels of IL-1 $\alpha$  and IL-8 in keratinocytes. These are cytokines responsible for the initial inflammatory phase of wound healing. Secondly there are reports that LLLT can upregulate cytokines responsible for fibroblast proliferation, and migration such as bFGF, HGF and SCF. Thirdly it has been reported that LLLT can increase growth factors such as VEGF responsible for the neovascularization necessary for wound healing.

Fourthly TGF- $\beta$  is a growth factor responsible for inducing collagen synthesis from fibroblasts and has been reported to be up regulated by LLLT. Fifthly there are reports that LLLT can induce fibroblasts to undergo the transformation into myofibroblasts, a cell type that expresses smooth muscle  $\alpha$ -actin and desmin and has the phenotype of contractile cells that hasten wound contraction.

## Conclusion

Several research studies have used superficial wounds to assess the effects of low-intensity laser on healing. Some have used clinical wounds such as ulcers of different sizes and depths and others have developed models of superficial wounds in animals. These diverse methods have produced a variety of results and conclusions on the effects of LLLT. Cells in the wound respond to light induced reactive oxygen species (ROS) leading to the expression of growth factors, such as transforming growth factor beta (TGF), and platelet derived growth factor (PDGF), which encourage synthesis of more collagen, increased formation of blood vessels, and less inflammation, all of which increase wound healing.

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