

## THE INFLUENCE OF LOW-INTENSITY LASER THERAPY ON BONE HEALING

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### CASE REPORT

#### ABSTRACT

**Objective:** Low-intensity laser therapy (LILT) is defined to supply direct biostimulative light energy to the cells. While several studies have demonstrated that LILT has stimulating effects on bone cells and can accelerate the repair process of the bone, others reported delayed fracture healing or no effects after LILT. The aim of this article was to review the studies evaluating the biomodulation effects of LILT on bone-derived stem cells.

#### MATERIALS AND METHODS:

To access relevant articles, searching in three electronic databases including PubMed, Google Scholar and Science Direct was conducted until April 2012. The key words used were low-level laser, low-intensity laser, low-power laser therapy, stem cell, bone marrow stem cell, bone and osteoblast. The articles that met the eligibility criteria were included in this review of literature.

#### RESULTS:

Twenty-five relevant articles (13 in vitro and 12 animal studies) were included. Eleven in vitro studies showed positive results with regard to acceleration of cell proliferation and differentiation. All animal studies showed improved bone healing in sites irradiated with low-intensity laser.

#### CONCLUSION:

Based on the results of the reviewed articles, low

intensity laser therapy can accelerate bone healing in extraction sites, bone fracture defects and distraction osteogenesis, provided proper parameters were applied.

#### KEYWORDS:

Stem Cells, Osteoblast, Low-Level Laser Therapy, Laser Phototherapy, Laser Biostimulation, stem cells, Bone Marrow Cell

#### INTRODUCTION

The principle of using low-intensity laser therapy (LILT) is to supply direct biostimulative light energy to body cells. Absorbed laser energy causes stimulation of molecules and atoms of cells. Using low-intensity laser radiation on the tissues does not cause rapid and significant increase in tissue temperature.

On the other hand, it has biochemical stimulation effects on cells, which creates multiple biological changes. These types of radiation affect the photoreceptor of cells and by stimulating the electron transport chain, modulate the cellular action<sup>1</sup>.

Various biostimulatory effects of LILT have been reported on wound healing and collagen synthesis via in vitro and in vivo studies<sup>1-2</sup>. With respect to the bone, LILT has been shown to modulate inflammation, accelerate cell proliferation<sup>3</sup> and enhance healing<sup>3-5</sup>.

While several studies<sup>1, 6-10</sup> have demonstrated that

LILT has stimulating effects on stem cells of the bone and accelerates the repair process of the bone, others reported delayed fracture healing or no effects after low-intensity laser irradiation<sup>11-12</sup>. This study was designed to review articles concerning application of low-intensity laser on bone tissue cells.

## **MATERIALS AND METHODS**

**Search strategy:** To access relevant articles, searching in three electronic databases including PubMed, Google Scholar and Science Direct was conducted and 25 articles were found till April 2012. The key words used in this search were: (low-level laser OR low-intensity laser OR low-power laser therapy OR laser phototherapy OR laser therapy) AND (osteoblast OR stem cell OR bone-marrow stem cell OR bone) (Table 1).

**TABLE 1**

### **KEY WORDS USED IN SEARCH STRATEGY**

After excluding duplicates, the remaining publications were retrieved. Of the 45791 publications, which were collected by the literature search through keyword association, 45722 were excluded due to having an irrelevant title or content to laser therapy and bone healing. Then, the reference lists of the remaining articles were checked to find any other studies relevant to the topic.

Finally, 25 articles met the eligibility criteria and were included in our review.

**Eligibility Criteria:** The selection criteria were the following: 1) original articles, 2) use of statistical methods; 3) intervention (the influence of low-intensity laser therapy on the bone healing process). Applications of various lasers were accepted. The bone healing process was characterized by proliferation and/or differentiation of human or animal bone marrow stem cells /osteoblasts, formation of bone matrix and/or trabecular osteoid tissue and/or bone and maximum load bearing.

### **RESULT:**

**In vitro studies:** A detailed description of the methods (laser parameters) and results of relevant studies are presented in Table 2. A brief report of the studies is presented in Table 2.

**TABLE 2**

### **IN VITRO STUDIES ON LOW-INTENSITY LASER THERAPY AND BONE-DERIVED CELLS**

The first in vitro study in the field of LILT on bone cells was published in 1998. Ozawa et al. showed that low-energy laser irradiation caused bone nodule formation in rats. In that study, osteoblast-like cells of the rat were irradiated with a diode laser. The authors suggested that laser irradiation may stimulate cellular proliferation and differentiation and this stimulation may only be exhibited in immature cells<sup>13</sup>.

In 2000, Dörtbudak et al. investigated the effect of diode laser irradiation on osteoblasts derived from mesenchymal cells. They showed that irradiation with a pulsed diode soft laser has a biostimulating effect on osteoblasts<sup>7</sup>.

In 2001, Coombe et al. investigated the effects of low-intensity laser irradiation on osteoblastic cells. Laser irradiation did not affect human osteosarcoma cell viability, proliferation or activation.

However, low-intensity laser irradiation at the energy level of 2 J resulted in a heat shock response. The authors concluded that low intensity laser irradiation was unable to stimulate the osteosarcoma cells utilized at a gross cell population level. The heat shock response and increased intracellular calcium demonstrated that the cells are affected by low-power laser<sup>14</sup>. Guzzardella et al. in 2002 evaluated the effects of laser on bone defect healing. Experimental defects of rat's femora were cultured and then irradiated with diode laser.

The amount of ALP/total protein and nitric oxide was significantly higher in the laser group. The results showed that LILT stimulation could accelerate bone healing<sup>15</sup>.

In 2005, Khadra et al. investigated the effect of LILT on the attachment, proliferation and differentiation of human osteoblast-like cells. Laser was irradiated on cultured human mandibular bone cells. LILT significantly enhanced cellular attachment and proliferation. Cells which were radiated by energy density of 3J/cm<sup>2</sup> showed more osteocalcin synthesis and transforming growth factor-b1 (TGF-b1) production.

However, ALP activity did not differ significantly among the lased and control groups. These results showed that LILT could modulate the activity of these cells<sup>16</sup>.

In 2005, Gottlib et al. evaluated the consequent phenotype modulation and development of

mesenchymal stem cells (MSCs) towards ossified tissue in a combined 3D biomatrix/LILT system and compared it with a control group. In that study He-Ne laser was applied. The authors concluded that this system biostimulates the proliferation and differentiation of MSCs into osteoblasts at early stages of culture and subsequently enhances ex-vivo ossification<sup>17</sup>.

In 2006, Arisu et al. investigated the effects of Nd:YAG laser irradiation on osteoblast cell cultures. The following results were obtained from this study:

Nd:YAG laser irradiation (20 mJ, 10 Hz, 10s) had a stimulatory effect on the cell viability and proliferation of human osteoblast-like cell culture.

Increase in pulse energy, pulse repetition rate and power output has an inhibitory effect on the cell viability and proliferation of human osteoblast-like cell culture.

The lowest parameters should be chosen if the pulse energy and power output were appropriate for the suggested therapy<sup>18</sup>.

In 2008, Stein et al. evaluated the effects of low-level laser therapy on growth and differentiation of human osteoblast-like cells. The results of this study indicated that diode laser has a biostimulatory effect on human osteoblast-like cells during the first 72 h after irradiation. The expression of osteopontin and collagen type I mRNA slightly decreased with time in controls and cells irradiated with 1 J/cm<sup>2</sup>, but their expression was increased by treatment with 2 J/cm<sup>2</sup> after 72 h<sup>19</sup>.

In 2008, Hou et al. investigated the effects of low-intensity laser irradiation on bone marrow mesenchymal stem cells (BMSCs). LILT significantly stimulated BMSCs proliferation. Noteworthy, an energy density of 0.5 J/cm<sup>2</sup> was found to be optimal in this regard. On the other hand, laser irradiation at an energy density of 5 J/cm<sup>2</sup> significantly stimulated proliferation, increased growth factor secretion and facilitated the myogenic differentiation of BMSCs. The authors concluded that LILT might provide a novel approach for the preconditioning of BMSCs prior to transplantation<sup>20</sup>.

In 2009, Gerbettaz et al. evaluated the effects of LILT on proliferation and differentiation of murine bone marrow cells. Diode laser exposure was administered three times a week on murine bone

marrow cells containing osteoblast progenitors. Laser-irradiated and non-irradiated groups were similar with regard to proliferation of bone marrow mesenchymal stem cell, and its differentiation into osteoblasts. They concluded that 808 nm wavelength infrared LILT does not alter murine bone progenitor cell proliferation and differentiation<sup>21</sup>.

In 2010, Petri et al. investigated the effects of LILT on human osteoblastic cells grown on titanium. The results of this study showed that LILT affected cell responses in a complex way. The authors suggested that LILT might have possible benefits on implant osseointegration despite a transient deleterious effect immediately after laser irradiation<sup>22</sup>.

In 2012, Soleimani et al. evaluated the effects of low-level laser irradiation on proliferation and differentiation of human BMSCs into osteoblasts. BMSCs were cultured and diode laser was applied at energy densities of 2 or 4 J/cm<sup>2</sup> for BMSCs being induced to osteoblasts. At both energy densities, LILT significantly promoted BMSCs proliferation in comparison to the control group.

Significant increase of ALP activity in irradiated cells indicated that BMSCs differentiated to osteoblast. It was concluded that using LILT with the mentioned parameters (Table 2) enhances BMSCs proliferation and differentiation into osteoblasts<sup>23</sup>.

In 2012, Saygun et al. evaluated the effects of LILT on the release of basic fibroblast growth factor (bFGF), insulin-like growth factor-I (IGF-I) and the receptor of IGF-I (IGFBP3) from osteoblasts.

The authors concluded that LILT increases the proliferation of osteoblast cells and stimulates the release of bFGF, IGF-I and IGFBP3 from these cells<sup>24</sup>.

**Animal studies:** A detailed description of the methods (laser parameters) and results of relevant studies are presented in Table 3. A brief report of the studies is presented in Table 3.

### **TABLE 3** **IN VIVO STUDIES REGARDING EFFECTS** **OF LILT ON BONE STRUCTURE**

In 1988, Takeda et al. evaluated effects of low-energy laser on extraction socket healing. The extraction wounds in the experimental group of rats were irradiated with diode laser 5 min once a day.

Histopathological examination showed that

proliferation of fibroblasts and formation of trabecular osteoid tissue was more prominent in the irradiated group<sup>25</sup>.

In 1998, Luger et al. evaluated the effect of low-power laser irradiation on the mechanical properties of tibia fracture healing in rats. Four weeks after LILT, the tibia was removed and tested at tension up to failure.

The maximal load at failure and the structural stiffness of the tibia were significantly increased in the lased group; whereas, the extension maximal load was reduced<sup>26</sup>. In 2003, Nicolau et al. investigated the effect of low-power diode laser on the bone structure and cells. The femurs of 48 rats were perforated and irradiated with a diode laser. The results showed that LILT increases the activity of bone cells (resorption and formation) around the site of the repair without changing the bone structure<sup>27</sup>. In 2003, Freitas et al. investigated the influence of He-Ne laser irradiation on the repair of surgically created damage in the tibia of rats. The results of this study showed that low-level laser therapy stimulated the growth of the trabecular area and the simultaneous invasion of osteoclasts and accelerated the organization of matrix tibiae<sup>8</sup>.

In 2004, Khadra et al. evaluated the effect of LILT with a diode laser on bone healing around titanium implants installed in rabbits. LILT resulted in a more tensile attachment of the bone to implants. In addition, the irradiated group had more bone-to-implant contact and more weight percentages of calcium and phosphorus<sup>5</sup>. In 2004, Khadra et al. evaluated the enhancement of bone formation in rat calvarial bone defects by low-level laser therapy. Diode laser was applied immediately after surgery and then daily for 6 consecutive days on osseous defects on the parietal bone of rats. The tissue samples from the experimental animals contained significantly more calcium, phosphorus and protein than the controls. Histological analyses disclosed more pronounced angiogenesis and connective tissue formation and more advanced bone formation in the experimental group than in the controls<sup>28</sup>.

In 2006, Nissan et al. investigated the effect of LILT on surgically created bony defects in rats. Diode laser was applied after surgically created bony cavities on both sides of the mandible of rats. Investigations in the newly formed callus showed that low power density (4 mW/cm<sup>2</sup>) significantly increased radiocalcium accumulation, but high power density (22.4 mW/

cm<sup>2</sup>) was not effective in this regard. On the other hand, no changes were noted in the activity of ALP with the laser treatment. It was concluded that laser therapy with low power density is effective on the bone healing process in experimentally created osseous cavities<sup>29</sup>.

Weber et al. used LILT in conjunction with autogenous bone graft and barrier membrane for the treatment of intrabony defects. It was found out that the quantity and quality of bone remodeling was more evident in irradiated animals than in nonirradiated animals<sup>30</sup>. In 2007, Pretel et al. investigated the effect of LILT on bone repair by a histological study in the mandible of rats. LILT resulted in a shorter period of the initial inflammatory phase of healing and earlier formation of new bone matrix. However, there were no significant differences between the groups at 60 days<sup>31</sup>. In 2007, Miloro et al. investigated the effect of LILT on mandibular distraction osteogenesis in rabbits. Histologically, the area of new bone trabeculation and ossification was more advanced for the lased group. The complete formation of the inferior border of mandible occurred sooner in the laser group than in the controls<sup>32</sup>. In 2008, Ribeiro et al. evaluated the effects of LILT on bone repair in rats treated with anti-inflammatory drugs. Results suggested that low-level laser therapy is able to improve bone repair in the tibia of rats because of an up-regulation for cyclooxygenase-2 expression in bone cells<sup>33</sup>. In 2009, Kreisner et al. evaluated the histological effect of low-level laser on distraction osteogenesis in rabbit mandibles. The percentage of newly formed bone was greater in the LILT group than in the control group<sup>34</sup>.

## DISCUSSION:

Since there is a wide variation in the method of studies evaluating the efficacy of LILT on bone healing, it is difficult to compare the results.

Most in vitro studies showed that LILT was effective in the proliferation of bone marrow stem cells, osteoblasts and osteoclasts. Lasers used in studies with positive results were diode (635nm, 685nm, 810nm, 830nm) and Nd:YAG laser<sup>13, 16, 18, 20, 24</sup>. On the other hand, Gerbettaz et al. showed no changes in the proliferation of osteoblasts and osteoclasts. The parameters of the laser (808 nm) used in that study was a power of 520 mW and an energy density of 4 J/cm<sup>2</sup>, repeated three times a week<sup>21</sup>. The authors suggested using a power meter as a crucial element in the studies

to set-up the different parameters of LILT protocols, since the energy density of “therapeutic window” seems very narrow. LILT in human osteosarcoma cell culture did not result in more cellular proliferation<sup>14</sup>. It was reported that LILT may be ineffective when applied to fresh wounds. In these conditions, cellular proliferation is active and the regeneration of tissue occurs at a normal rate; thus, additional application of laser may not provide further benefits. However, trophic ulcers and indolent wounds are accompanied with low oxygen concentration and insufficient nutrients that prevent cellular proliferation. In these situations, application of LILT serves as a signal to increase the proliferation of the cell. In a culture of tumor cells like the study of Coombe et al.<sup>14</sup>, all cells were at their most ability of proliferation in a way that LILT had a few or no effect on proliferation or activation of these cells. It is important to emphasize that variations in physical parameters may be another reason for the different results among studies.

Some studies focus on osteoblastic differentiation using LILT. The results of three studies showed that LILT was effective in the stimulation of differentiation of osteoblasts<sup>22-24</sup>. However, two other studies reported that low-power laser was not effective in the differentiation of cells to osteoblasts<sup>14, 21</sup>.

The results of in vitro studies showed that in both wavelengths of 670 nm and 830 nm, LILT resulted in a higher ALP activity and the expression of osteocalcin, osteopontin and collagen type I genes when irradiated to osteoblasts<sup>13, 19</sup>. It was noted that higher energy density (2 J/cm<sup>2</sup>) had no effect on cellular activity<sup>21</sup>.

There were a number of animal studies evaluating LILT on bone healing. The results of these studies showed that low-level laser accelerated the process of regeneration in extraction sites<sup>25</sup>, bone fracture defects<sup>26</sup>, experimentally induced bone defects<sup>15, 27-29, 31</sup> and distraction osteogenesis<sup>32, 34</sup>. Lasers used in these studies included He-Ne and diode (range of wavelength: 633 to 904 nm).

### **MECHANISM OF ACTION:**

The exact mechanism of action of LILT in biomodulation of bone healing is not known. However, previous studies have proposed number mechanisms. The results of an animal study in rabbits showed an increased mechanical strength of the interface between the implants and bone by

LILT. The mechanism of action was attributed to an increased metabolic speed and consequently a more rapid healing process<sup>5</sup>.

Another animal study in rats showed more bone matrix organization in sites irradiated with low-intensity laser. It was assumed that LILT could stimulate the collagen fibers to arrange in a lamellar structure<sup>27</sup>. Another study showed that LILT could stimulate the mineralization in the process of new bone formation in surgically created bony defects<sup>29</sup>. On the other hand, it was stated that the biostimulating effect of LILT on bone remodeling in surgically induced bony defects might be due to stimulating the modulation of the initial inflammatory response<sup>31</sup>. A study in rabbits showed that the efficacy of LILT in accelerating the process of distraction osteogenesis was related to its effect on bone turnover and consolidation<sup>32</sup>. Another study in the tibia of rats stated that the improvement of bone repair by LILT was due to its role in upregulation of cyclooxygenase-2 expression in bone cells<sup>33</sup>.

This study is subjected to some limitations; the hand search was not conducted in this review. Therefore, possible un-published or unindexed studies were not included.

### **CONCLUSION**

Based on the results of reviewed articles, low intensity laser therapy can accelerate bone healing in extraction sites, bone fracture defects and distraction osteogenesis in animal models. The mechanism of action might be through stimulation of cellular proliferation and differentiation and acceleration of the healing process. In spite of promising results obtained from in vitro and animal studies, no human studies were found with regard to the effectiveness of LILT in bone healing. Therefore, further clinical studies are suggested to evaluate the efficacy of LILT in bone healing. Improving the senior dental students' attitudes towards preventive dentistry is a challenge for dental education in Iran. In order to create more positive attitudes for future dental professionals, there should be an early and sufficient exposure to preventive aspects of dentistry in the dental curricula.

### **CLINICAL STUDIES CONCLUSION:**

Based on the results of the reviewed articles, low-intensity laser therapy can accelerate bone healing in extraction sites, bone fracture defects, and distraction osteogenesis, provided proper parameters were applied.

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