

Analysis of Changes Induced In Human Periodontal Ligament, Dental Pulp, Bone Marrow and Adipose Stem Cells by Low Level Laser Therapy: A Review and New Perspectives



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Abstract

The biomodulation and the biostimulation of Low Level Laser Therapy (LLLT) promote wound healing, dentine repairing processes and stimulate the biological activity of human Periodontal Ligament Stem Cells (HPDLSCs), human Dental Pulp Stem Cells (HDPSCs), human Bone Marrow Stem Cells (HBMSCs) and human Adipose Stem Cells (HADSCs). The aim of the study was to review the literature on the LLLT effects on HPDLSCs, HDPSCs, HBMSCs and HADSCs. The electronic search was performed collecting articles in the PubMed, Medline, Scopus, Lilacs and Google Scholar databases from January 1990 to January 2018. LLLT was able to significantly increase HPDLSCs, HDPSCs, HBMSCs and HADSCs proliferation rate, stimulating osteogenic differentiation and opening new possibilities in the tissue regeneration. However, the research background on this topic showed high heterogeneity and the *in vitro* studies cannot always mimic the *in vivo* conditions. Thus, further clinical studies should be performed to determine the appropriate dose of irradiation in different patients.

Abbreviations: LLLT: Low Level Laser Therapy; HPDLSCs: Human Periodontal Ligament Stem Cells; HDPSCs: Human Dental Pulp Stem Cells; HBMSCs: Human Bone Marrow Stem Cells; HADSCs: Human Adipose Stem Cells; OXPHOS: Oxidative Phosphorylation; ETC: Electron Transport Chain; ATP: Adenosine Triphosphate; PDL: Periodontal Ligament

Introduction

In 1967, Endre Mester, a Hungarian physician, after applying low-power laser light to shaved mice noticed a faster hair growth compared to the control group [1,2]. This was a new non-surgical way of use the laser: instead of incise and coagulate tissues many researchers started to investigate the enhancing and stimulating effects of light. Currently the Low-Level Laser Therapy (LLLT), also called "cold laser therapy" is known for biostimulatory and biomodulatory effects *in vivo* and *in vitro*. The LLLT shows not a thermal but photochemical effect by triggering biochemical changes within cells after the application of a light ranging between 10mW-500mW. The result of Low-Level Laser irradiance on human tissues is a reduction of inflammation, pain relief and accelerated tissue regeneration. In dentistry, the use of LLLT is increasing in the last years because it promotes wound-healing, dentine repairing processes and stimulates the biological activity of mesenchymal

stem cells (MSCs) and human periodontal ligament stem cells (HPDLSCs) [3-26]. MSCs can differentiate into different specialized cell types and they can be identified and collected in humans from dental pulp stem cells (HDPSCs) [11,27-38], adipose tissue [39-45] and cancellous portions of bones [46,47]. The LLLT effects on cell proliferation have been investigated by several authors but the main part of the papers do not focus properly on HPDLSCs and HDPSCs, which could open new possibilities in regenerative medicine and dentistry. Therefore, the objective of the present study was to review the literature about the LLLT effects on the HPDLSCs and HDPSCs, but also on HBMSCs and HADSCs.

Methods

The electronic databases searched for eligible relevant scientific papers from January 1990 to January 2018 were Medline via

PubMed, Scopus, Cochrane Central Register of Controlled Trials via Cochrane Library, Lilac and Google Scholar databases. There was no language restriction set. Inclusion criteria were studies evaluating effects of LLLT on HPDLSCs, HDPSCs, HBMSCs and HADSCs. Papers that did not provide specifically data about HPDLSCs HDPSCs, HBMSCs and HADSCs were excluded. Reference lists of the selected articles were also hand-searched for other relevant papers that may have been missed by the search engines. The titles and abstracts of all studies resulting from the search were independently assessed by two reviewers. Full copies of all apparently relevant studies or those for which there were insufficient data in the title and abstract to make decision, were obtained. Any disagreement between the two reviewers on the eligibility of included studies was resolved through oral discussion and consensus. Studies that did not match the inclusion criteria in this second selection phase were excluded.

Mechanism of LLLT Action

It has been shown that LLLT can augment the oxidative phosphorylation (OXPHOS) modifying the redox basal-status of the whole cell and in particular of mitochondria [6,48]. During OXPHOS, thanks to electron transport chain (ETC), electrons are shifted from a reducing agent (even called electron donors) to oxidizing agent (even called electron acceptors), which in biological reduction-oxidation (redox) reactions is the oxygen (O₂) [49]. These redox reactions free energy that is mainly spent to synthesize chemical energy: the adenosine triphosphate (ATP) [50-52]. The mechanism of LLLT is based on the absorption of a specific visible red and near-infrared wavelengths by biological photoreceptors located inside human cells, augmenting the production of a trans-membrane electric and mechanical proton-H⁺ gradient in mitochondria necessary for OXPHOS [53-57], and enhancing the activity of mitochondrial complexes IV in an exposure-response relationship [58,59]. In addition, there is evidence that LLLT affects the mastocytes cells localized into endothelium in mucous membranes and dental pulp [4,60,61].

a) Laser stimulation can induce mast cells degranulation: although they show a key role in endothelial-leukocyte adhesion molecules and anaphylaxis, the labrocytes have a great defensive role too, being engaged in wound healing, angiogenesis, protecting from infectious agents and getting involved in blood-brain barrier action [62-64]. In conclusion, LLLT influences the biological function of a variety of cell types by stimulating mitochondrial OXPHOS and modulating inflammatory responses, exerting a range of several beneficial effects upon cell proliferation and healing.

Effects on HPDLSCs

The periodontium (from περί: peri- “around” and -odont “tooth”) is a specialized tissue surrounding the teeth composed by cementum, periodontal ligament (PDL), gingiva and alveolar cortex [65]. The PDL is a membrane-like connective tissue interposed between the tooth root and the alveolar bone of which the main component is represented by collagen fibers. It grants mechanical resistance during masticatory forces and control alveolar bone turnover maintaining tissue homeostasis and dissipating forces

during physiological or orthodontic tooth movement [21,66,67]. hPDLSCs has the faculty for self-renewal and the capacity to differentiate into different cell pools like cement oblasts and osteoblasts, which contribute to the repair of affected cementum and alveolar bone leading to a partial or complete periodontal regeneration [68-71].

For this reason, it is meaningful the possibility to stimulate HPDLSCs proliferation and differentiation to improve periodontal tissue regeneration [72]. Moreover LLLT helps pain reliefs through an increased synthesis of prostaglandin E₂, interleukin-1b and osteocalcin during tooth movement [73,74], and the decreasing levels of plasminogen activator under mechanical stress [70,75-80]. Kreisle [81,82] reported that the irradiated test group revealed a highly significant proliferation rate 24h after diode laser exposure at a power output of 10 mW in continuous wave modality at energy fluencies of 1.96-7.84 J/cm² compared to control group. Similarly Hakki [4] that observed a significant increase of collagen I mRNA expression only in the LLLT bio-stimulated group. Wu [21] observed an augmented proliferation and osteogenic differentiation of hPDLSCs via cAMP regulation with a low-power GaAlAs 660-nm at 2 J/cm², highlighting possible osteogenic inducibility of LLLT during periodontal tissue regeneration procedures [76]. Soares [83] showed that a power of 30 mW at 1.0 J/cm² has stimulating effects while under that parameters he noticed just a small changing on the proliferation rate of hPDLSC. In addition, it was observed an accumulative effect between repeated irradiation. According to the growth curve, the effect was greater when the test-group cells were irradiated with the dose of 1.0 J/cm² compared to 0.5 J/cm², in particular at 48h and 72h after the second laser stimulation. Huang [73] noticed higher viability of hPDLSCs at both 5 and 10J/cm² than the control group at day 7.

Table 1: Main papers of LLLT on HPDLSCs.

Authors (Year)	Laser (Wavelength)	Cell/Tissue Examined	Conclusion
Kreisler et al. (2002)	diode (809nm)	human gingival fibroblasts	Highly significant proliferation activity after irradiation
Hakki et al. (2010)	diode (940nm)	human gingival fibroblasts	Significant increase of collagen I mRNA expression in LLLT biostimulated group
Wu et al. (2013)	GaAlAs (660nm)	human periodontal ligament cells	Enhancing of the proliferation and osteogenic differentiation of hPDL cells
Huang et al. (2013)	diode (670nm)	human periodontal ligament cells	Positive variation in irradiated hPDLSCs compared to non-irradiated ones.
Soares et al. (2013)	InGaAIP (660nm)	human periodontal ligament cells	Small changing on the proliferation rate of hPDLSC

The flogosis markers expression like iNOS, COX-2, MMP-3, IL-1 and OC activity showed a remarkable positive variation in irradiated HPDLSCs at days 1 and 5 in the -100kPa incubator compared to non-irradiated ones. LLLT irradiation seems to improve periodontal parameters [84] and HPDLSCs showed good response grown onto 3D scaffold in the osteogenic differentiation [85]. These results suggested that LLLT and HPDLSCs have a role in the maintenance of the alveolar bone [23] and they are helpful in healing inflammation and may, in the future, augment regeneration procedures such as the tooth movement rate even if it is not yet showed definitively by other papers [86-91]. The most relevant papers focusing on LLLT and HPDLSCs are reported in Table 1.

Effects on HDPSCs

The hDPSCs can be collected from the pulp of all permanent teeth (in particular from third molars) and exfoliated deciduous teeth [92]. They can be detached and augmented showing multipotential plasticity [11,27-30,32-38,93] and immunosuppressive activity, that could be considered an added value during healing, reconstructive and transplantation procedures [31]. In particular, their most feasible and promising application is related to bone regeneration [36]. Ginani [94] founded pulp stem cells from permanent teeth exhibited higher proliferation analyzed at two times (72h and 96h after irradiation) when irradiated with wavelength of 660 nm and the dose of 1.0 J/cm² compared to the non-irradiated control group.

Table 2: Main papers of LLLT on HDPSCs.

Authors (Year)	Laser Wavelength	Cell/Tissue Examined	Conclusion
Ginami (2017)	InGaAlP (660nm)	human exfoliated deciduous teeth	LLL promote the proliferation of SHEDs and the maintenance of cell viability.
Arany (2014)	GaAlAs (810nm)	human dental pulp stem cells	LLL promote the activity of TGF-β1 that differentiates stem cells promoting dentin.
Pinheiro (2017)	InGaAlP (660nm)	human deciduous pulp stem cells	LLL on hDPSCs enhance regeneration in bone tissue in cleft and non-cleft patients

In a recent investigation Arany [95] demonstrated that low-power laser irradiation (810-nm GaAlAs diode laser) can be used as a minimally invasive tool promote the activity of an endogenous latent growth factor complex in the dental pulp, transforming growth factor-β1 (TGF-β1), that subsequently differentiate human dental stem cells to promote dentin regeneration. Other authors like Pinheiro [96] who stimulated for three weeks the hDPSCs with a low-power red 660 nm laser at 5, 10, and 20 J observed their potential in bone tissue regeneration in cleft and non-cleft patients. In particular the best pool of hDPSCs seems to be collected from the exfoliated deciduous teeth as showed by Ginani who irradiated these cells with a 660 nm laser at 30 mW with a dose of 1.0 J/cm² [97]. Recently Staffoli [98], Ching [99], Morsczech [100,101], Diomede [92] and Bressel [102] highlighted once again the encouraging data available in literature, which will lead soon to personalized therapies, and regenerative approaches dental stem

cells based. The most relevant papers focusing on LLLT and HDPSCs are reported in Table 2.

Effects on HBMSCs and HADSCs

Other sources of human mesenchymal stem cells investigated in time for bone regeneration are represented by human bone marrow-derived stem cells (HBMSCs) and adult adipose-derived stem cells (HADSCs) from adults. HBMSCs are easily and safely obtained by means of percutaneous withdrawal from the patient's bone marrow, and due to their multilineage potential, they can be stimulated to generate non-hematopoietic tissue, including bone, cartilage, tendons, and ligaments [26]. Particularly, bone marrow-derived MSCs differentiate into the osteogenic lineage, if cultured in presence of dexamethasone, ascorbic acid, and α-glycerophosphate (osteogenic medium). Soleimani [15] investigated effects of LLLT on HBMSCs proliferation and differentiation into neuron and osteoblast using different energy densities.

He found that LLLT promoted hBMSCs proliferation significantly at all energy densities except for 6 J/cm² in comparison to control groups on the seventh day of differentiation. LLLT at energy densities of 3 and 6 J/cm² dramatically facilitated the differentiation of HBMSCs into neurons and also, alkaline phosphatase activity was significantly enhanced in irradiated hBMSCs differentiated to osteoblast on the second, fifth, seventh, and tenth day of differentiation. He concluded that using LLLT at 810 nm wavelength enhances HBMSCs differentiation into neuron and osteoblast in the range of 2–6 J/cm², and at the same time increases BMSCs proliferation (except for 6 J/cm²).

Leonida [26] reported a significantly increased proliferation of HBMSCs seeded on a three dimensional scaffold of collagen compared to control group in the first week of LLLT but no further effects in the second week. There were no differences concerning HBMSCs differentiation toward the osteoblastic lineage in the first week but an exponential increase was observed after 14 days of laser irradiation, with respect to the control group. HADSCs were primarily described in 2001 as a population of cells derived from adipose tissue with the potential of differentiation into a number of mesenchymal cell types, including osteoblasts, chondrocytes and adipocytes [17]. Mvula [103] reported that LLLT at 5 J/cm² using 636 nm diode laser in combination with EGF increased the viability and proliferation of HADSCs, assessed using adenosine triphosphate (ATP) luminescence and optical density at 0, 24 and 48 hours after irradiation. De Villiers [19] investigated effects of LLLT on HADSCs, differentiated into smooth muscle cells using retinoic acid, exposed to a 636 nm diode laser at a 5 J/cm².

He found that, morphologically, HADSCs did not show any differences but there was an increase in viability and proliferation post-irradiation. In another research Mvula [17] investigated the effect of low level laser irradiation on primary cultures of hADSCs using a 635-nm diode laser, at 5 J/cm² with a power output of 50.2 mW and a power density of 5.5 mW/cm². He reported that cellular morphology did not appear to change after irradiation, there was an increase of cellular viability, measured by ATP luminescence statistically significant at 48 hours, and of proliferation of irradiated

cells, measured by optical density, at both time points. He also reported that Western blot analysis and immunocytochemical labeling indicated an increase in the expression of stem cell marker $\beta 1$ -integrin after irradiation. The most relevant papers focusing on LLLT and HBMSCs and HADSCs are reported in Table 3.

Table 3: Main papers of LLLT on HBMSCs and HADSCs.

Authors (Year)	Laser (Wavelength)	Cell/Tissue Examined	Conclusion
Soleimani et al. (2010)	GaAlAs (810nm)	human bone marrow stem cells	Increased differentiation into neuron and osteoblast in the range of 2–6 J/cm ² and proliferation except for 6 J/cm ²
Leonida et al. (2010)	NdYag (1064nm)	human bone marrow stem cells	Significant increase of proliferation in the first week and differentiation during the second week
Mvula et al. (2008)	diode (635nm)	human adipose stem cells	Increasing cellular viability, proliferation, and expression of $\beta 1$ -integrin
Mvula et al. (2010)	diode (636nm)	human adipose stem cells	Increased cell viability and proliferation
De Villier et al. (2011)	diode (636nm)	human adipose stem cells	No differences in morphology, increased cell viability and proliferation

Discussion

The biological outcome of laser irradiation is influenced by many variables, like: wavelength, spot diameter, energy and power density, duration and rate of irradiation, medium or plate variables, nutritional conditions and the pools of cell irradiated. All the studies analyzed showed qualitative and quantitative different parameters and for this reason it is very difficult to compare them and to identify a univocal protocol. Nearly all papers showed that LLLT had a positive effect on HPDLSCs, hDPSCs, hBMSCs and hADSCs proliferation with doses used between 0.5 and 10 J/cm², while doses higher than 10 J/cm² exert or no effects [7] or seems to be antiproliferative [93] and similar outcomes were found for LED [104]. In addition, no study showed deleterious effects of LLLT on these cells [105]. The majority of studies about LLLT focus on hPDLSCs probably due to the major interest in periodontal regeneration and speeding up orthodontic treatments [14,66,71].

At the best of our knowledge there is no studies performed on hPDLSCs and hDPSCs in-vivo and for this reason they cannot always mimic clinical conditions, so the limitations of these *in vitro* studies should be considered but there are some animal studies highlighting possible indications in the regeneration of smooth, skeletal muscle cells and infarcted myocardium [106-111].

Conclusion

LLLT seems to be effective in stimulating HPDLSCs, HDPSCs, hBMSCs and HADSCs proliferation but there is no unique protocol due to the very high heterogeneity of studies. The synergy between

LLLT and stem cells can open new possibilities in the tissue regeneration, but until now there are no reliable studies performed *in vivo* on humans. For this reason further studies, especially *in vivo* on human stem cells, should be performed to validate this promising therapy and to establish an easy and appropriate standardized protocol to provide the best clinical advantage for the patients.

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