Photobiomodulation (PBM) / Low Level laser Therapy (LLLT)

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Potential Therapeutic Strategies for Skeletal Muscle Atrophy.

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The maintenance of muscle homeostasis is vital for life and health. Skeletal muscle atrophy not only seriously reduces people's quality of life and increases morbidity and mortality, but also causes a huge socioeconomic burden. To date, no effective treatment has been developed for skeletal muscle atrophy owing to an incomplete understanding of its molecular mechanisms. Exercise therapy is the most effective treatment for skeletal muscle atrophy. Unfortunately, it is not suitable for all patients, such as fractured patients and bedridden patients with nerve damage. Therefore, understanding the molecular mechanism of skeletal muscle atrophy is crucial for developing new therapies for skeletal muscle atrophy. In this review, PubMed was systematically screened for articles that appeared in the past 5 years about potential therapeutic strategies for skeletal muscle atrophy. Herein, we summarize the roles of inflammation, oxidative stress, ubiquitin-proteasome system, autophagic-lysosomal pathway, caspases, and calpains in skeletal muscle atrophy and systematically expound the potential drug targets and therapeutic progress against skeletal muscle atrophy. This review focuses on current treatments and strategies for skeletal muscle atrophy, including drug treatment (active substances of traditional Chinese medicine, chemical drugs, antioxidants, enzyme and enzyme inhibitors, hormone drugs, etc.), gene therapy, stem cell and exosome therapy (muscle-derived stem cells, non-myogenic stem cells, and exosomes), cytokine therapy, physical therapy (electroacupuncture, electrical stimulation, optogenetic technology, heat therapy, and low-level laser therapy), nutrition support (protein, essential amino acids, creatine, β-hydroxy-β-methylbutyrate, and vitamin D), and other therapies (biomaterial adjuvant therapy, intestinal microbial regulation, and oxygen supplementation). Considering many treatments have been developed for skeletal muscle atrophy, we propose a combination of proper treatments for individual needs, which may yield better treatment outcomes.

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Combination of Dental-Capping Agents with Low Level Laser Therapy Promotes Proliferation of Stem Cells from Apical Papilla.

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ABSTRACT

Background: Direct pulp capping is a vital pulp therapy, which stimulates differentiation of stem cells from apical papilla (SCAPs). SCAPs have multipotential capacity to differentiate into types of cells, contributing to the regeneration of tissues.

Objective: Considering the promising effects of dental-capping materials, we aim to investigate the effect of dental dressing materials combined with laser therapy on the percentage of SCAP viability and the consequent dental regeneration capacity.

Methods: We collected two immature third molar teeth and isolated SCAPs through collagenase type I enzymatic activity. Isolated SCAPs were then cultured with Dulbecco's modified Eagle's medium and α-minimum essential medium enriched with 15% and 10% fetal bovine serum, respectively. After reaching 70-80% confluency, cells were seeded in a 96-well plate and then treated with mineral trioxide aggregate (MTA), enamel matrix derivative (EMD), biodentine, and low level laser therapy (LLLT) alone and in combination for 24, 48, and 168 h. After that, cell survival rate was assessed using (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (MTT) assay.

Results: We found that combination of MTA, EMD, and LLLT as well as that of biodentine, EMD, and LLLT could lead to significant increase of SCAP viability as compared with other treatment groups. Combination of MTA and biodentine with EMD could also show increased level of SCAP proliferation and viability. However, MTA and biodentine alone reduced SCAP survival rate in all time points.

Conclusions: Our conclusion is that LLLT can serve as an enhancer of SCAP proliferation and differentiation rate when added to dental-capping agents such as MTA, EMD, and biodentine. Thus, LLLT combination with effective capping materials will serve as a promising option for dental tissue repair.

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Photobiomodulation therapy at red and near-infrared wavelengths for osteogenic differentiation in the scaffold-free microtissues.

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ABSTRACT

One of the novel strategies for bone tissue regeneration is photobiomodulation (PBM) which depends on the red and near-infrared light absorption by mitochondria and may trigger bone tissue regeneration via the production of intracellular ROS and ATP, NO release, etc. It is also important to identify the changes in those signal molecule levels in an in vivo mimicking platform such as 3-Dimensional (3D) Scaffold Free Microtissues (SFMs) that may serve more natural osteogenic differentiation responses to PBM. Herein, we aimed to increase the osteogenic differentiation capability of the co-culture of Human Bone Marrow Stem Cells (hBMSC) and Human Umbilical Vein Endothelial Cells (HUVECs) on 3D SFMs by triple light treatment at 655 and 808-nm of wavelengths with the energy densities of 1, 3, and 5 J/cm2. We performed the analysis of cell viability, diameter measurements of SFMs, intracellular ROS production, NO release, ATP activity, temperature measurements, DNA content, ALPase activity, calcium content, and relative gene expressions of ALP, Collagen, and Osteopontin by qRT-PCR. It was found that both wavelengths were effective in terms of the viability of SFMs. 1 and 5 J/cm2 energy densities of both wavelengths increased the SFM diameter with significant changes in intracellular ROS, ATP, and NO levels compared to the control group. We concluded that PBM therapy was successful to induce osteogenesis. 1 J/cm2 at 655 nm of wavelength and 5 J/cm2 at 808 nm of wavelength were the most effective energy densities for osteogenic differentiation on SFMs with triple light treatment.

Effect of red and near-infrared irradiation on periodontal ligament stem cells: ROS generation and cell cycle analysis.

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ABSTRACT
Reconstruction of lost tooth structures and the periodontium with the help of tissue engineering has found a special place in dentistry in recent years with reports of great therapeutic success. Stem cells from the periodontal ligament have the potential for high differentiation into the bone and periodontal ligament cells and are therefore a suit candidate for regenerative therapies of the periodontium and other tissues. In this regard, the use of photobiomodulation on these cells by light irradiation can be effective in increasing the efficiency of these regenerative methods. The effect of red and near-infrared lasers was investigated in pulsed and continuous modes on the cell viability, ROS production and the cell cycle of Periodontal Ligament Stem cells (PDLSCs) using MTT assay and flowcytometry techniques. The result shows that both red and near-infra-red (NIR) irradiations at 3 J/cm2 maintain cell viability. ROS generation assay indicated that in PDL stem cells irradiated with NIR laser (940 nm), ROS production was greater than in the red (660 nm) irradiated groups. Cell cycle analysis revealed that NIR irradiation can enhance the proportion of S-phase cells and declinedecline the proportion of G1-phase cells compared to the red laser irradiation groups. Moreover, this enhancement was greater in the pulsed group compared to the continuous mode group. Overall, the current study results showed that photobiomodulation can support the cell viability of PDLSCs and could affect the ROS production and cell cycle. This effect was more with 940 nm (NIR) irradiation pulsed mode compared to 660 nm (red).Communicated by Ramaswamy H. Sarma.

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980nm Photobiomodulation Promotes Osteo/odontogenic Differentiation of the Stem Cells from Human Exfoliated Deciduous Teeth via the Cross-talk between BMP/Smad and Wnt/β-catenin Signaling Pathways.

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ABSTRACT

evidence: Increasing evidence suggests stem cells from human exfoliated deciduous teeth (SHEDs) serve as desirable sources of dentin regeneration. Photobiomodulation (PBM) has shown great potential in enhancing the proliferation and osteogenesis of human bone marrow mesenchymal stem cells (hBMMSCs). However, the specific role of PBM in odontogenic differentiation of SHEDs is little know, and we further investigated potential mechanism of PBM osteo/odontogenisis. A 980 nm diode laser with different energy densities of (0.5, 5, 10 J/cm2) in a 100-mW continuous wave was used for irradiation every 24h. Osteo/odontogenic differentiation of SHEDs was achieved by performing alkaline phosphatase (ALP) and alizarin red staining (ARS) and osteo/odontogenic markers were also evaluated by qRT-PCR and western blotting. Additionally, western blot and immunohistochemical staining were performed to evaluate the levels of BMP/Smad and Wnt/β-catenin signaling-related proteins. We found that PBM at 5 J/cm2 increased mineral deposition, and upregulated the expression of related osteo/odontogenic markers along with the elevated expression of β-catenin and phosphorylation level of Smad1/5/9. Furthermore, Wnt signaling inhibition using DKK1 and BMP signaling inhibition using noggin inhibited PBM-induced osteo/odontogenic marker expression when used individually or jointly. In conclusion, PBM induces the osteo/odontogenic differentiation of SHEDs through cross-talk between BMP/Smad and Wnt/β-catenin signaling pathways.

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Effect of diode low level laser and red light emitting diode irradiation on cell proliferation and osteogenic/odontogenic differentiation of stem cells from the apical papilla.

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ABSTRACT
Background: This experimental study aimed to assess the effect of irradiation of red light-emitting diode (LED) and Diode low-level laser (LLL) on osteogenic/odontogenic differentiation of stem cells from the apical papilla (SCAPs).
Materials and methods: SCAPs were isolated from the human tooth root. The experimental groups were subjected to 4 J/cm2 diode low level laser and red LED irradiation in osteogenic medium. The control group did not receive any irradiation. Cell viability/proliferation of SCAPs was assessed by the methyl thiazolyl tetrazolium (MTT) assay on days 1 and 2 (n = 9). Osteogenic differentiation was evaluated by alizarin red staining (ARS) (n = 3), and expression of osteogenic genes by real-time polymerase chain reaction (RT-PCR) (n = 12) on days 1 and 2. SPSS version 18 was used for data evaluation. The Kruskal-Wallis and Mann-Whitney tests were used to compare the groups at each time point.
Results: The MTT assay showed no significant difference in cell viability/proliferation of SCAPs in the low level laser, red LED, and control groups at 24 or 48 h ($P < 0.001$). The ARS assessment showed that low level laser and red LED irradiation enhanced osteogenic differentiation of SCAPs. low level laser and red LED irradiation both induced over-expression of osteogenic/dentinogenic genes including alkaline phosphatase (ALP), dentin sialophosphoprotein (DSPP), dentin matrix protein 1 (DMP-1), and bone sialoprotein (BSP) in SCAPs. Up-regulation of genes was significantly greater in low level laser irradiation group than red LED group ($P < 0.001$).
Conclusion: Diode low level laser irradiation with 4 J/cm2 energy density and red LED irradiation enhanced osteogenic differentiation of SCAPs without adversely affecting cell viability.

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Anti-inflammatory effect of green photobiomodulation in human adipose-derived mesenchymal stem cells.

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ABSTRACT

biomodulation: Photo biomodulation (PBM) as a non-invasive and safe treatment has been demonstrated the anti-inflammatory potential in a variety of cell types, including stem cells. However, further investigations using different laser parameters combined with more accurate methods such as quantitative measurement of inflammatory gene expression at the mRNA level are still necessary. The aim of this study was to evaluate the effect of 532 nm green laser on cell proliferation as well as expression of inflammatory genes in human adipose-derived mesenchymal stem cells (hADMSCs) using RNA sequencing (RNA-seq) technique and confirmatory RT-PCR. hADMSCs were cultured in DMEM low glocuse medium with 10% fetal bovine serum until the fourth passage. Cultured cells were divided in two groups: control group (no laser irradiation) and laser group, irradiated with 532 nm laser at 44 m J/cm2 with an output power of 50 mW and a density of 6 mW/cm2, every other day, 7 s each time. The cell viability was assessed using MTT assay 24 h after each irradiation on days 3, 5, and 7 after cell seeding, followed by performing RNA-seq and RT-PCR. The MTT assay showed that PBM increased cell proliferation on day 5 after irradiation compared to day 3 and decreased on day 7 compared to day 5. In addition, gene expression analysis in hADMSCs using RNA-seq revealed down-regulation of inflammatory genes including CSF2, CXCL2, 3, 5, 6, 8, and CCL2, 7. These results indicate that 532 nm PBM with the parameters used in this study has a time-dependent effect on hADMSCs proliferation as well as anti-inflammatory potential.

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NIR irradiation of human buccal fat pad adipose stem cells and its effect on TRP ion channels.

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ABSTRACT

effect: The effect of near infrared (NIR) laser irradiation on proliferation and osteogenic differentiation of buccal fat pad-derived stem cells and the role of transient receptor potential (TRP) channels was investigated in the current research. After stem cell isolation, a 940 nm laser with 0.1 W, 3 J/cm2 was used in pulsed and continuous mode for irradiation in 3 sessions once every 48 h. The cells were cultured in the following groups: non-osteogenic differentiation medium/primary medium (PM) and osteogenic medium (OM) groups with laser-irradiated (L+), without irradiation (L-), laser treated + Capsazepine inhibitor (L + Cap), and laser treated + Skf96365 inhibitor (L + Skf). Alizarin Red staining and RT-PCR were used to assess osteogenic differentiation and evaluate RUNX2, Osterix, and ALP gene expression levels. The pulsed setting showed the best viability results (P <; 0.05) and was used for osteogenic differentiation evaluations. The results of Alizarin red staining were not statistically different between the four groups. Osterix and ALP expression increased in the (L+) group. This upregulation abrogated in the presence of Capsazepine, TRPV1 inhibitor (L + Cap); however, no significant effect was observed with Skf96365 (L + Skf.

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Promoted CD4 + T cell-derived IFN-γ/IL-10 by photobiomodulation therapy modulates neurogenesis to ameliorate cognitive deficits in APP/PS1 and 3xTg-AD mice.

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ABSTRACT

BACKGROUND: The immune system has been implicated in synaptic plasticity, inflammation, and the progression of Alzheimer's disease (AD). However, there were few studies on improving the niche microenvironment of neural stem cells (NSCs) in the brain of AD to promote adult hippocampal neurogenesis (AHN) by regulating the function of non-parenchymal immune cells.

METHODS: The lymph nodes of amyloid precursor protein/presenilin 1 (APP/PS1) and 3xTg (APP/PS1/tau) mouse models of AD were treated with photobiomodulation therapy (PBMT) for 10 J/cm2 per day for 1 month (10 min for each day), T lymphocytes isolated from these two AD models were treated with PBMT for 2 J/cm2 (5 min for each time). The NSCs isolated from hippocampus of these two AD models at E14, and the cells were co-cultivated with PBMT-treated T lymphocyte conditioned medium for NSCs differentiation.

RESULTS: Our results showed that PBMT treatment could promote AHN and reverse cognitive deficits in AD mouse model. The expression of interferon-γ (IFN-γ) and interleukin-10 (IL-10) was upregulated in the brain of these two AD models after PBMT treated, which was induced by the activation of Janus kinase 2 (JAK2)-mediated signal transducer and activator of transcription 4 (STAT4)/STAT5 signaling pathway in CD4+ T cells. In addition, elevated CD4+ T cell levels and upregulated transforming growth factor-β1 (TGFβ1)/insulin-like growth factors-1 (IGF-1)/brain-derived neurotrophic factor (BDNF) protein expression levels were also detected in the brain. More importantly, co-cultivated the PBMT-treated T lymphocyte conditioned medium with NSCs derived from these two AD models was shown to promote NSCs differentiation, which was reflected in the upregulation of both neuronal class-III β-tubulin (Tuj1) and postsynaptic density protein 95 (PSD95), but the effects of PBMT was blocked by reactive oxygen species (ROS) scavenger or JAK2 inhibitor.

CONCLUSION: Our research suggests that PBMT exerts a beneficial neurogenesis modulatory effect through activating the JAK2/STAT4/STAT5 signaling pathway to promote the expression of IFN-γ/IL-10 in non-parenchymal CD4+ T cells, induction of improvement of brain microenvironmental conditions and alleviation of cognitive

Effects of photobiomodulation on mitochondrial function in diabetic adipose-derived stem cells in vitro.

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ABSTRACT

are: Herein are reported the effects of photobiomodulation (PBM) on adenosine triphosphate (ATP) and reactive oxygen species (ROS) quantification and mitochondria membrane potential (MMP) of the mitochondria of diabetic adipose-derived stem cells (ADSCs) in vitro. Additionally, the expression of PTEN-induced kinase 1 (PINK1) and RBR E3 ubiquitin-protein ligase (PARKIN) genes, which are involved in mitochondrial quality, were quantified. First, type one diabetes was induced in 10 rats. The rats were then kept for 1 month, after which fat tissue was excised from subcutaneous regions, and stem cells were selected from the fat, characterized as ADSC, and cultivated and increased in elevated sugar conditions in vitro; these samples were considered diabetic-ADSC. Two groups were formed, namely, diabetic-control-ADSC and PBM-diabetic-ADSC. ATP, ROS quantification, and MMP of mitochondria of diabetic ADSCs in vitro were measured, and the expression of PINK1 and Parkin genes was quantified in vitro. The results revealed that PBM significantly increased ATP quantification ($p = 0.05$) and MMP activity ($p = 0.000$) in diabetic-ADSCs in vitro compared to the control diabetic-ADSCs; however, it significantly decreased ROS quantification ($p = 0.002$) and PINK1($p = 0.003$) and PARKIN gene expression ($p = 0.046$) in diabetic-ADSCs. The current findings indicate for the first time that PBM has the potential to maintain the function and quality of mitochondrial diabetic-ADSCs by significantly increasing ATP quantification and MMP activity in diabetic-ADSCs in vitro while significantly decreasing ROS quantification and PINK1 and PARKIN gene expression, making PBM an attractive candidate for use in improving the efficacy of autologous stem cell remedies for diabetic patients with infected diabetic foot ulcers.

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Low-level laser therapy with different irradiation methods modulated the response of bone marrow mesenchymal stem cells in vitro.

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ABSTRACT

Aim: Low-level laser therapy (LLLT) also known as photobiomodulation is a treatment to change cellular biological activity. The exact effects of LLLT remain unclear due to the different irradiation protocols. The purpose of this study was to investigate the effects of LLLT by three different irradiation methods on the proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) in vitro. BMSCs were inoculated in 24-well plates and then irradiated or not (control) with a laser using three different irradiation methods. The irradiation methods were spot irradiation, covering irradiation, and scanning irradiation according to different spot areas (0.07 cm2 or 1.96 cm2) and irradiation areas (0.35 cm2 or 1.96 cm2), respectively. The laser was applied three times at energy densities of 4 J/cm2. The cell proliferation by CCK-8. ALP activity assay, alizarin red, and quantitative real-time polymerase chain reaction (RT-PCR) were performed to assess osteogenic differentiation and mineralization. Increases in cell proliferation was obvious following irradiation, especially for covering irradiation. The ALP activity was significantly increased in irradiated groups compared with non-irradiated control. The level of mineralization was obviously improved following irradiation, particularly for covering irradiation. RT-PCR detected significantly higher expression of ALP, OPN, OCN, and RUNX-2 in the group covering than in the others, and control is the lowest. The presented results indicate that the biostimulative effects of LLLT on BMSCs was influenced by t he irradiation method, and the covering irradiation is more favorable method to promote the proliferation and osteogenic differentiation of BMSCs.

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940 nm diode laser induced differentiation of human adipose derived stem cells to temporomandibular joint disc cells.

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ABSTRACT

BACKGROUND: Temporomandibular disorder (TMD) refers to a group of disorders that affect temporomandibular joint (TMJ) and its associated muscles with very limited treatment options. Stem cell research is emerging as one of the promising fields in the treatment of degenerative diseases. The ability of human adipose derived stem cells to differentiate into many cell types is driving special interest in several disease management strategies. Photobiomodulation has enhanced the role of these stem cells through their ability to promote cell proliferation and differentiation. Hence, this study examined the differentiation potential of human adipose derived stem cells (ADSCs) into fibroblasts and chondrocytes using a 940 nm diode laser for possible TMD therapy.

MATERIALS: ADSCs were cultured at different seeding densities and for different time intervals. After irradiation at 24, 48, 72 h, 1, 2 and 3 weeks, ADSC viability and morphological changes were assessed in groups with and without basic fibroblast growth factor. Additionally, the level of adenosine triphosphate (ATP) in the cells was also recorded. The differentiated fibroblasts and chondrocytes were characterized with flow cytometry and immunofluorescence techniques, at 1- and 2-weeks post-irradiation.

RESULTS: Increased ATP proliferation and cell viability above 90% were observed in all post-irradiation experimental groups. Post irradiation results from flow cytometry and immunofluorescence at 1- and 2-weeks confirmed the expression of chondrogenic and fibroblastic cell surface markers.

CONCLUSION: This study describes stimulatory techniques utilized to differentiate ADSCs into fibroblastic and chondrogenic phenotypes using diode lasers at 940 nm. The study proposes a new treatment model for patients with degenerative disc diseases of the TMJ. The study will offer new possibilities in tissue engineering and TMJ disc management through photobiomodulation of ADSCs using a 940 nm diode laser.

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Repair effect of photobiomodulation combined with human umbilical cord mesenchymal stem cells on rats with acute lung injury.

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ABSTRACT

Aim: Acute lung injury (ALI) impaired the function of blood oxygen exchange function, resulting in tissue hypoxia and patient death. Recently, human umbilical cord mesenchymal stem cells (hUCMSCs) are thought to mitigate the effects of ALI, which boosts researchers' interest in employing stem cell-based therapies to manage ALI. However, as a novel therapy, hUCMSCs still face various limitations such as migrating weakly and insufficient proliferation in vivo. Photobiomodulation (PBM) effciently promotes cell proliferation, migration and homing, which presents a promising strategy for overcoming above limitations. In this study, PBM was emerged to intervene hUCMSCs through detecting cell proliferation, oxidative stress-related factors and inflammatory factors. These results assuredly confirmed that PBM enhanced the antioxidant capacity of cells and improved cell survival in vitro experiments. In vivo, PBM-intervened hUCMSCs intuitively reduce thickness of alveolar septum, excessive secretion of inflammatory factors, relieves bleeding, edema and fibrosis. As a physical intervention, PBM further strengthens the therapeutic effect of hUCMSCs and depicted a hopeful therapy in ALI treatment.

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Potential of stem cells for treating infected Diabetic Foot Wounds and Ulcers: a systematic review.

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ABSTRACT

Aim: Infected diabetic foot ulcers (iDFUs) cause great concern, as they generally heal poorly and are precursive of diabetic-related foot amputation and even death. Scientists have tested various techniques in attempts to ascertain the best treatment for iDFUs; however, the results have remained inconclusive. Stem cell therapy (SCT) appears to improve iDFU through its antimicrobial impacts, yet cogent information regarding the repair of iDFUs with SCT is lacking. Herein, published articles are evaluated to report coherent information about the antimicrobial effects of SCT on the repair of iDFUs in diabetic animals and humans. In this systematic review, we searched the Scopus, Medline, Google Scholar, and Web of Science databases for relevant full-text English language articles published from 2000 to 2022 that described stem cell antimicrobial treatments, infected diabetic wounds, or ulcers. Ultimately, six preclinical and five clinical studies pertaining to the effectiveness of SCT on healing infected diabetic wounds or ulcers were selected. Some of the human studies confirmed that SCT is a promising therapy for diabetic wounds and ulcers. Notably, more controlled studies performed on animal models revealed that stem cells combined with a biostimulator such as photobiomodulation decreased colony forming units and hastened healing in infected diabetic wounds. Moreover, stem cells alone had lower therapeutic impact than when combined with a biostimulant.

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Photobiomodulation isolated or associated with adipose-derived stem cells allograft improves inflammatory and oxidative parameters in the delayed-healing wound in streptozotocin-induced diabetic rats.

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ABSTRACT

Aim: The single and associated impressions of photobiomodulation (PBM) and adipose-derived stem cells (ADS) on stereological parameters (SP), and gene expression (GE) of some antioxidant and oxidative stressors of repairing injured skin at inflammation and proliferation steps (days 4 and 8) of a delayed healing, ischemic, and infected wound model (DHIIWM) were examined in type one diabetic (DM1) rats. DM1 was induced by administration of streptozotocin (40 mg/kg) in 48 rats. The DHIIWM was infected by methicillin-resistant Staphylococcus aureus (MRSA). The study comprised 4 groups (each, n = 6): Group 1 was the control group (CG). Group 2 received allograft human (h) ADSs transplanted into the wound. In group 3, PBM (890 nm, 80 Hz, 0.2 J/cm2) was emitted, and in group 4, a combination of PBM+ADS was used. At both studied time points, PBM+ADS, PBM, and ADS significantly decreased inflammatory cell count ($p <; 0.05$) and increased granulation tissue formation compared to CG ($p <; 0.05$). Similarly, there were lower inflammatory cells, as well as higher granulation tissue in the PBM +ADS compared to those of alone PBM and ADS (all, $p <; 0.001$). At both studied time points, the GE of catalase (CAT) and superoxide dismutase (SOD) was remarkably higher in all treatment groups than in CG ($p <; 0.05$). Concomitantly, the outcomes of the PBM+ADS group were higher than the single effects of PBM and ADS ($p <; 0.05$). On day 8, the GE of NADPH oxidase (NOX) 1 and NOX4 was substantially less in the PBM+ADS than in the other groups ($p <; 0.05$). PBM+ADS, PBM, and ADS treatments significantly accelerated the inflammatory and proliferative stages of wound healing in a DIIWHM with MRSA in DM1 rats by decreasing the inflammatory response, and NOX1 and 4 as well; and also increasing granulation tissue formation and SOD and CAT. The associated treatment of PBM+ADS was more effective than the individual impacts of alone PBM and ADS because of the additive anti-inflammatory and proliferative effects of PBM plus ADS treatments.

Different Protocols of Combined Application of Photobiomodulation In Vitro and In Vivo Plus Adipose-Derived Stem Cells Improve the Healing of Bones in Critical Size Defects in Rat Models.

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ABSTRACT

Aim: Introduction: Long bone segmental deficiencies are challenging complications to treat. Hereby, the effects of the scaffold derived from the human demineralized bone matrix (hDBMS) plus human adipose stem cells (hADSs) plus photobiomodulation (PBM) (in vitro and or in vivo) on the catabolic step of femoral bone repair in rats with critical size femoral defects (CDFDs) were evaluated with stereology and high stress load (HSL) assessment methods. Methods: hADSs were exposed to PBM in vitro; then, the mixed influences of hDBMS+hADS+PBM on CSFDs were evaluated. CSFDs were made on both femurs; then hDBMSs were engrafted into both CSFDs of all rats. There were 6 groups (G)s: G1 was the control; in G2 (hADS), hADSs only were engrafted into hDBMS of CSFD; in G3 (PBM) only PBM therapy for CSFD was provided; in G4 (hADS+PBM in vivo), seeded hADSs on hDBMS of CSFDs were radiated with a laser in vivo; in G5 (hADSs+PBM under in vitro condition), hADSs in a culture system were radiated with a laser, then transferred on hDBMS of CSFDs; and in G6 (hADS+PBM in conditions of in vivo and in vitro), laser-exposed hADSs were transplanted on hDBMS of CSFDs, and then CSFDs were exposed to a laser in vivo. Results: Groups 4, 5, and 6 meaningfully improved HSLs of CSFD in comparison with groups 3, 1, and 2 (all, P=0.001). HSL of G5 was significantly more than G4 and G6 (both, P=0.000). Gs 6 and 4 significantly increased new bone volumes of CSFD compared to Gs 2 (all, P=0.000) and 1 (P=0.001 & P=0.003 respectively). HSL of G 1 was significantly lower than G5 (P=0.026). Conclusion: HSLs of CSFD in rats that received treatments of hDBMS plus hADS plus PBM were significantly higher than treatments with hADS and PBM alone and control groups.

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The Effect of bisphenol A and Photobiomodulation Therapy on Autophagy-Related Genes Induction in Adipose Tissue-Derived Stem Cells.

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ABSTRACT

Aim: Introduction: As adipose tissue-derived stem cells (ADSCs) can divide rapidly and be prepared non-invasively, they have extensively been used in regenerative medicine. On the other hand, a new method of therapy, known as photobiomodulation (PHT), has been used to treat many diseases, such as inflammatory conditions, wound healing and pain. Besides, exposure to chemical substances such as bisphenol A (BPA), at low levels, can lead to autophagy. This study investigated the effects of BPA and PHT on the expression of autophagy-related genes, including LC3, NRF2, P62, in rat ADSCs as a model. Methods: ADSCs isolation and purification were confirmed by immunocytochemistry (ICC). The cells were then treated with different concentrations of BPA and also subjected to PHT. Reverse transcription polymerase chain reaction (RT-PCR) was used for the evaluation of LC3, NRF2 and P62 gene expressions. Oil red O staining was used for adipogenic vacuole formation. Result: ICC showed that the isolated cells were CD 49-positive but CD 31 and CD 34-negative. The viability test indicated that the number of live cells after 24 hours in the BPA groups at concentrations of 0, 1, 50, 100 and 200 µM was 100%, 93%, 81%, 72%, and 43% respectively. The difference in cell viability between groups 50, 100 and 200 µM was significant as compared with the control groups (P <; 0.05). Moreover, in the group with 1 µM concentration of BPA, the expressions of LC3, NRF2 and P62 genes were upregulated. However, in the treatment group at the concentration of 200 µM of BPA, the LC3 gene was expressed, but NRF2 and P62 genes were downregulated. Conclusion: BPA and PHT induce autophagy and adiposeness in ADSCs in a dose-dependent manner.

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Application of Fibrin Associated with Photobiomodulation as a Promising Strategy to Improve Regeneration in Tissue Engineering: A Systematic Review.

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Fibrin, derived from proteins involved in blood clotting (fibrinogen and thrombin), is a biopolymer with different applications in the health area since it has hemostasis, biocompatible and three-dimensional physical structure properties, and can be used as scaffolds in tissue regeneration or drug delivery system for cells and/or growth factors. Fibrin alone or together with other biomaterials, has been indicated for use as a biological support to promote the regeneration of stem cells, bone, peripheral nerves, and other injured tissues. In its diversity of forms of application and constitution, there are platelet-rich fibrin (PRF), Leukocyte- and platelet-rich fibrin (L-PRF), fibrin glue or fibrin sealant, and hydrogels. In order to increase fibrin properties, adjuvant therapies can be combined to favor tissue repair, such as photobiomodulation (PBM), by low-level laser therapy (LLLT) or LEDs (Light Emitting Diode). Therefore, this systematic review aimed to evaluate the relationship between PBM and the use of fibrin compounds, referring to the results of previous studies published in PubMed/MEDLINE, Scopus and Web of Science databases. The descriptors "fibrin AND low-level laser therapy" and "fibrin AND photobiomodulation" were used, without restriction on publication time. The bibliographic search found 44 articles in PubMed/MEDLINE, of which 26 were excluded due to duplicity or being outside the eligibility criteria. We also found 40 articles in Web of Science and selected 1 article, 152 articles in Scopus and no article selected, totaling 19 articles for qualitative analysis. The fibrin type most used in combination with PBM was fibrin sealant, mainly heterologous, followed by PRF or L-PRF. In PBM, the gallium-aluminum-arsenide (GaAlAs) laser prevailed, with a wavelength of 830 nm, followed by 810 nm. Among the preclinical studies, the most researched association of fibrin and PBM was the use of fibrin sealants in bone or nerve injuries; in clinical studies, the association of PBM with medication-related treatments osteonecrosis of the jaw (MRONJ). Therefore, there is scientific evidence of the contribution of PBM on fibrin composites, constituting a supporting therapy that acts by stimulating cell activity, angiogenesis, osteoblast activation, axonal growth, anti-inflammatory and anti-edema action, increased collagen synthesis and its maturation, as well as biomolecules.

The Role of Photobiomodulation on Dental-Derived Mesenchymal Stem Cells in Regenerative Dentistry: A Comprehensive Systematic Review.

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ABSTRACT

Aim: Photobiomodulation therapy involves exposing tissues to light sources, including light-emitting diodes or low-level lasers, which results in cellular function modulation. The molecular mechanism of this treatment is revealed, demonstrating that depending on the light settings utilized, it has the potential to elicit both stimulatory and inhibitory reactions.

Objectives: The current systematic review aimed to evaluate the impact of photobiomodulation therapy on dental stem cells and provide an evidence-based conclusion in this regard.

Methods: This systematic review was performed and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) revised guidelines. PICO(S) components were employed to define the inclusion criteria. Web of Science, Scopus, Medline as well as grey literature, and google scholar were searched up to September 2021 to retrieve relevant papers.

Results: Photobiomodulation therapy showed promising effects on the proliferation, viability, and differentiation of dental stem cells. This finding was based on reviewing related articles with a low risk of bias.

Conclusion: Despite the positive benefits of photobiomodulation therapy on dental stem cells, the current data do not provide a definitive conclusion on the best physical parameters for enhancing cell viability, proliferation, and differentiation.

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The 532 nm Laser Treatment Promotes the Proliferation of Tendon-Derived Stem Cells and Upregulates Nr4a1 to Stimulate Tenogenic Differentiation.

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ABSTRACT

Aim: Objective: This study aimed to verify the effect of photobiomodulation therapy (PBMT) with a wavelength of 532 nm on the proliferation and differentiation of tendon-derived stem cells (TDSCs) of Sprague-Dawley (SD) rats. Background: The combination of PBMT and stem cell transplantation with TDSCs provides a new treatment strategy for tendon injury. Nevertheless, the effect of PBMT on the biological behavior of TDSCs and its internal mechanisms remain unclear. Methods: TDSCs were isolated from Achilles tendons of SD rats and identified by cell morphology and flow cytometric analysis. Energy density gradient experiment was performed to determine the ideal energy. Then, TDSCs were treated with PBMT using a wavelength of 532 nm at a fluence of 15 J/cm2 in 532 nm laser group, and the TDSC in control group were not treated with 532 nm laser. Cell response after irradiation was observed to ascertain cell morphology and cell proliferation in the 532 nm laser group and the control group. The RNA expression levels of the key genes of TDSC differentiation, including scleraxis (Scx), tenomodulin (Tnmd), Mohawk homeobox (Mkx), Decorin (Dcn), peroxisome proliferator-activated receptor gamma (PPARγ), SRY-box transcription factor 9 (Sox9), and RUNX family transcription factor 2 (Runx2), were detected by reverse transcription-polymerase chain reaction. Then, gene chip microarray was used to detect the expression of differential genes after 532 nm laser intervention in TDSCs, and the target genes were screened out to verify the role in this process in vitro and in vivo. Results: When the 532 nm laser energy density was 15 J/cm2, the proliferation capacity of TDSCs was improved (2.73 ± 0.24 vs. 1.81 ± 0.71, $p <; 0.05$), and the expression of genes related to tenogenic differentiation of TDSCs was significantly increased ($p <; 0.01$). After RNA sequencing and bioinformatics analyses, we speculated that nuclear receptor subfamily 4 group A member 1 (Nr4a1) was involved in the tenogenic differentiation process of TDSCs regulated by 532 nm laser treatment. Subsequent experiments confirmed that Nr4a1 regulated the expression of the tenogenic differentiation genes Scx and Tnmd in TDSCs. Conclusions: A 532 nm laser with 15 J/cm2 regulated the process of TDSC proliferation and upregulated Nr4a1 to stimulate tenogenic differentiation.

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Low-level controllable blue LEDs irradiation enhances human dental pulp stem cells osteogenic differentiation via transient receptor potential vanilloid 1.

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ABSTRACT

Aim: Human dental pulp stem cells (hDPSCs) have attracted tremendous attention in tissue regeneration engineering due to their excellent multidirectional differentiation potential. Photobiomodulation (PBM) using low-level light-emitting diodes (LEDs) or lasers has been proved to promote the osteogenesis of mesenchymal stem cells. However, the effect of LEDs on osteogenic differentiation of hDPSCs has little published data. In this work, the effect of blue LEDs with different energy densities of 2, 4, 6, 8, 10 J/cm2 on osteogenic differentiation of hDPSCs was examined by using in vitro ALP staining, ALP activity, mineralization, and real-time PCR. The results showed that compared with the control group, osteogenic differentiation was significantly enhanced in blue LEDs treated groups. As the energy density increased, the level of osteogenesis initially increased and then decreased reaching the highest level at 6 J/cm2. Transient receptor potential vanilloid 1 (TRPV1), a Ca2+ ion channel, was believed to be a potential player in osteogenesis by photobiomodulation. By immunofluorescence assay, calcium influx assay, PCR, and ALP staining, it was shown that blue LEDs irradiation can increase the activity of TRPV1 and intracellular calcium levels similarly to the agonist of TRPV1 capsaicin. Additionally, pretreatment with capsazepine, a selective TRPV1 inhibitor, was able to abrogate the osteogenic effect of blue LEDs. In conclusion, these findings proposed that blue LEDs can promote the osteogenesis of hDPSCs within the appropriate range (4 -8 J/cm2) during culture of osteogenic medium, and TRPV1/Ca2+ may be an essential signaling pathway involved in blue LEDs-induced osteogenesis, providing new insights for the use of hDPSCs in tissue regeneration engineering.

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Photobiomodulation effects on periodontal ligament stem cells: A systematic review of in-vitro studies.

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ABSTRACT

Aim: Stem cell therapy has been considered to play a paramount role in the treatment modalities available for regenerative dentistry. The established beneficial effects of photobiomodulation (PBM) at the cellular level have led to the combined use of these two factors (PBM and stem cells). The main goal of this study was firstly to critically appraise the effects of PBM on periodontal ligament stem cells (PDLSCs), and secondly to explore the most effective PBM protocols applied.

Objectives: Pubmed, Cochrane, Scopus, Science Direct, and Google Scholar search engines were used to identify experimental in vitro studies in which PBM was applied to cultured PDLSCs. After applying specific keywords, additional filters, and inclusion/exclusion criteria, a preliminary number of 245 articles was narrowed down to 11 in which lasers and LEDs were used within the 630 - 1064 nm wavelength range. Selected articles were further assessed by three independent reviewers for strict compliance with PRISMA guidelines, and a modified Cochrane Risk of Bias to determine eligibility.

Methods: The dataset analysed was extracted from the studies with sufficient and clearly presented PBM protocols. Simple univariate regression analysis was performed to explore the significance of contributions of potential quantitative predictor variables towards study outcomes, and a one-way ANOVA model was employed for testing differences between the laser or LED sources of the treatments. The significance level for testing was set at $\alpha = 0.05$.

Results: The proliferation rate, osteogenic differentiation, and expression of different indicative genes for osteogenesis and inflammation suppression were found to be positively affected by the application of various types of lasers and LEDs. With regard to the PBM protocol, only the wavelength variable appeared to affect the treatment outcome; indeed, the 940 nm wavelength parameter was found not to exert a favourable effect.

Conclusion: Photobiomodulation can enhance the stemness and differentiation capacities of periodontal ligament stem cells. Therefore, for PBM protocols, there remains no consensus amongst the scientific community. Statistical analyses performed here indicated that the employment of a near-infrared (NIR) wavelength of 940 nm may not yield a significant

Impact of photobiomodulation on macrophages and their polarization during diabetic wound healing: a systematic review.

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ABSTRACT

Aim: This review aims to providing essential information and the current knowledge about the potential role of macrophages, especially their M2 subtypes in different diabetic wounds both in clinical and pre-clinical models under the influence of photobiomodulation (PBM). The long-term goal is to advance the macrophage-based therapies to accelerate healing of diabetic foot ulcers. We reviewed all databases provided by PubMed, Google Scholar, Scopus, Web of Science, and Cochrane precisely from their dates of inception to 25/10/2021. The keywords of Diabetes mellitus diseases, wound healing, macrophage, and photobiomodulation or low-level laser therapy were used in this systematic review.A total of 438 articles were initially identified in pubmed.ncbi.nlm.nih.gov (15 articles), Google scholar (398 articles), Scopus (18 articles), and Web of Science (7 articles). Four hundred sixteen articles that remained after duplicate studies (22 articles) were excluded. After screening abstracts and full texts, 14 articles were included in our analysis. Among them, 4 articles were about the effect of PBM on macrophages in type 2 diabetes and also found 10 articles about the impact of PBM on macrophages in type 1 diabetes. The obtained data from most of the reviewed studies affirmed that the PBM alone or combined with other agents (e.g., stem cells) could moderate the inflammatory response and accelerate the wound healing process in pre-clinical diabetic wound models. However, only very few studies conducted the detailed functions of polarized macrophages and M2 subtypes in wound healing of diabetic models under the influence of PBM. Further pre-clinical and clinical investigations are still needed to investigate the role of M2 macrophages, especially its M2c subtype, in the healing processes of diabetic foot ulcers in clinical and preclinical settings.

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High-Intensity Red Light-Emitting Diode Irradiation Suppresses the Inflammatory Response of Human Periodontal Ligament Stem Cells by Promoting Intracellular ATP Synthesis.

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ABSTRACT
Aim: Periodontitis is an inflammatory lesion in the periodontal tissue. The behavior of human periodontal ligament stem cells (hPDLSCs), which play an important role in periodontal tissue regeneration, is restricted by the influence of inflammatory mediators. Photobiomodulation therapy exerts anti-inflammatory effects. The purpose of this study was to investigate the effects of light-emitting diode (LED) irradiation on the inflammatory responses of hPDLSCs. The light source was a red LED (peak wavelength: 650 nm), and the total absolute irradiance was 400 mW/cm2. The inflammatory response in hPDLSCs is induced by tumor necrosis factor (TNF)-α. Adenosine triphosphate (ATP) levels and pro-inflammatory cytokine (interleukin [IL]-6 and IL-8) production were measured 24 h after LED irradiation, and the effects of potassium cyanide (KCN) were investigated. LED irradiation at 6 J/cm2 significantly increased the ATP levels and reduced TNF-α-induced IL-6 and IL-8 production. Furthermore, the inhibitory effect of LED irradiation on the production of pro-inflammatory cytokines was inhibited by KCN treatment. The results of this study showed that high-intensity red LED irradiation suppressed the TNF-α-stimulated pro-inflammatory cytokine production in hPDLSCs by promoting ATP synthesis. These results suggest that high-intensity red LED is a useful tool for periodontal tissue regeneration in chronically inflamed tissues.

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Enhancing therapeutic efficacy of human adipose-derived stem cells by modulating photoreceptor expression for advanced wound healing.

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ABSTRACT

BACKGROUND: Human adipose-derived stem cells (hADSCs) have been widely used for regenerative medicine because of their therapeutic efficacy and differentiation capacity. However, there are still limitations to use them intactly due to some difficulties such as poor cell engraftment and viability after cell transplantation. Therefore, techniques such as photobiomodulation (PBM) are required to overcome these limitations. This study probed improved preclinical efficacy of irradiated hADSCs and its underlying molecular mechanism.

METHODS: hADSCs were irradiated with green organic light-emitting diodes (OLEDs). Treated cells were analyzed for mechanism identification and tissue regeneration ability verification. Expression levels of genes and proteins associated with photoreceptor, cell proliferation, migration, adhesion, and wound healing were evaluated by performing multiple assays and immunostaining. Excision wound models were employed to test in vivo therapeutic effects.

RESULTS: In vitro assessments showed that Opsin3 (OPN3) and OPN4 are both expressed in hADSCs. However, only OPN4 was stimulated by green OLED irradiation. Cell proliferation, migration, adhesion, and growth factor expression in treated hADSCs were enhanced compared to control group. Conditioned medium containing paracrine factors secreted from irradiated hADSCs increased proliferation of human dermal fibroblasts and normal human epidermal keratinocytes. Irradiated hADSCs exerted better wound healing efficacy in vivo than hADSCs without OLED irradiation.

CONCLUSIONS: Our study introduces an intracellular mechanism of PBM in hADSCs. Our results revealed that photoreceptor OPN4 known to activate Gq-protein and consequently lead to reactive oxygen species production responded to OLED irradiation with a wavelength peak of 532 nm. In conclusion, green OLED irradiation can promote wound healing capability of hADSCs, suggesting that green OLED has potential preclinical applications.

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A Comparative Analysis of Photobiomodulation-Mediated Biological Effects of Single Versus Double Irradiation on Dental Pulp Stem Cells: An In Vitro Study.

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ABSTRACT

Aim: Objective: In recent years, fractionated irradiation protocols, rather than a simple plan of exposure, have been proposed as a more effective method in the field of tissue regeneration. Thus, this study aimed at a comparative analysis of single versus double irradiation of an 808-nm diode laser, in terms of dental pulp stem cells' (DPSCs) viability and proliferation in vitro. Methods: Subcultured DPSCs were either irradiated, or not (control group), with energy densities of 3, 7, and 12 J·cm-2 in a single- or double-session manner (24 h apart). On 0, 12, 24, 48, and 72 h postirradiation, cell viability and proliferation were evaluated through Trypan Blue and alamarBlue assays, respectively. Results: During the first 48 h postirradiation, the highest rates of DPSC proliferation were assigned to double irradiation at 3 or single exposure to 7 J·cm-2, with no cytotoxic effects on cell viability. Inversely, single irradiation at 12, or a double session of exposure to 7 or 12 J·cm-2, led to a significant descent in the rates of proliferation and cell viability. Conclusions: Within the limitations of this study, evidence suggests a positive impact on the biological responses of DPSCs following double session of exposure to lower energy densities as well as a single irradiation at a higher energy dosage.

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Neuronal differentiation potential of primary and immortalized adipose stem cells by photobiomodulation.

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ABSTRACT

Aim: Adipose Stem Cells (ASCs) are capable of neuronal differentiation, which makes them an ideal choice for therapies in nerve injuries. Principally, the differentiation of autologous ASCs to neurons offers solutions for the replacement therapies of nervous system with patient's own genetic background. On the contrary, the use of genetically modified (immortalized) ASCs has the benefit of accessibility by surpassing ethical concerns and ease for propagation as a continuous cell culture. Photobiomodulation (PBM) is a therapeutic modality with laser or light, which is widely been used for modulating stem cell bioprocesses viz. proliferation and differentiation. A comparative analysis was performed to evaluate the neuronal differentiation potential of primary ASCs isolated from a healthy human subject with commercially obtained immortalized ASCs with PBM. The outcome of this analysis will help us to know either primary or immortalized ASCs are most suitable for biomedical applications. Both primary and immortalized ASCs were characterized using their surface protein markers CD44/90/133/166 and induced to differentiate into neuronal cells using Fibroblast Growth Factor, basic (bFGF) and forskolin following PBM using Near Infra-Red (NIR) lasers. Based on the expression of nestin, an early neuronal marker an exposure to 5, 10 and 15 J/cm2 of NIR and growth inducers for 14 days the primary ASCs demonstrated a higher neuronal differentiation potential compared to the immortalized ASCs. However, newly differentiated cells from either of these ASCs did not reveal βIII-tubulin, an intermediate neuronal marker even by 21 days of differentiation. This study gives an indication that immortalized ASCs have a phenotype and differentiation potential slightly less but comparable to the freshly isolated ASCs. We suggest that PBM along with growth inducers offer a better solution of differentiating ASCs to neurons.

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Photobiomodulation and Stem Cell on Repair of Osteoporotic Bones.

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ABSTRACT

Aim: Objective: This study examined the use of photobiomodulation (PBM) plus adipose-derived stem cells (ASCs) to enhance the osteogenic properties of demineralized bone matrix (DBM) scaffold in a critical size femoral defect (CSFD) of ovariectomy-induced osteoporotic (OVX) rats. Background: PBM could be used as a unique strategy to enhance the osteogenic potential of DBMs seeded with ASCs. Materials and methods: The OVX rats with a CSFD were divided into six groups: (1) Control (C); (2) DBM scaffold alone (S); (3) S+PBM; (4) S+alendronate; (5) S+ASC; (6) S+PBM+ASC. Stereological analysis, real-time polymerase chain reaction (RT-PCR), and cone-beam computed tomography (CBCT) were performed after euthanization at 4 and 8 weeks postimplantation surgery. Results: In the 8th week, Groups 4 and 6 showed a greatly high new trabecular bone volume than the scaffold group (all, $p = 0.009$). The CBCT data demonstrated that the CSFD was significantly smaller in the two, three, and six groups relative to the control group ($p = 0.01$, $p = 0.000$, and $p = 0.000$, respectively). RT-PCR revealed that Groups 3 and 6 had higher messenger RNA levels of osteocalcin (OC) and osteoprotegerin (OPG) compared with the control group ($p = 0.05$). Group 6 had significantly lower expression of receptor activator of nuclear factor-κB ligand (RANKL) compared with the control group ($p = 0.02$). Conclusions: The combination of DBM plus PBM plus ASC, as well as DBM plus PBM significantly improved the healing of CSFD in OVX rats, and affected the expression of OPG, OC, and RANKL genes.

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Effect of Photobiomodulation on Structure and Function of Extracellular Vesicle Secreted from Mesenchymal Stem Cells.

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ABSTRACT

Aim: The current study intended to evaluate the effect of photobiomodulation on the morphology and function of EVs secreted from mesenchymal stem cells (MSCs) derived from periodontal ligament (PDL) and the buccal fat pad (BFP) in vitro.These cells were irradiated at 660 nm or kept in dark as control. EVs were then isolated from each group using ultracentrifugation. EVs were defined by Flow cytometry and Western blot tests. Electron microscopy (SEM) was used to study the morphology of EVs. Then MTT and wound healing scratch assays were applied to compare the cell survival and migration of human dermal fibroblast (HDF) cells treated with the EVs obtained from the four groups. According to SEM images, isolated EV were round and cup-shaped in all groups showing no destructive effects of laser irradiation on EV morphology. MTT test results revealed statistically significant difference between the HDF cells treated with different EV groups from hPDLSCs-Dark in compared to control (0 µg/mL) ($p <;0.05$) and treated with exosome from hPDLSCs-Irradiation cells compared to dark group ($p <;0.05$). However, scratch wound healing assay did not show significant different between various groups ($p >0.05$). Further studies with different irradiation protocols are recommended to find an optimal strategy.

Photochem Photobiol, 2022 04

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Photobiomodulation Therapy Affects the Elastic Modulus, Cytoskeletal Rearrangement and Migration Capability of Human Osteosarcoma Cells.

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ABSTRACT

Aim: Photobiomodulation (PBM) therapy utilizes low-power lasers to modulate the viability of living human cells and leads to changes in proliferation, differentiation, adhesion and gene expression, even though the rearrangement of cytoskeleton was not previously studied. The present study aims to evaluate the photobiological effects on the elastic behavior of human osteosarcoma cells (MG-63) and their morphological changes. Fluorescence staining, confocal imaging and atomic force microscopy (AFM) topography were performed to study the effects of PBM therapy with the exposure of 532 nm-25mW, 650 nm-3mW, 650 nm-150mW and 780 nm -70mW beams following the 5-min continuous irradiation. The area of each beam was 3.14cm2 with a source-surface distance of 20 cm. Besides the cell proliferation assessment, the migratory potential of MG-63 was determined with the wound healing technique. The results indicated an increase in stiffness and shape index of radiation-induced cells 24 h after exposure along with the obvious F-actins changes. But, cell stiffening was not observed 72 h after 532 nm laser irradiation. Also, a decrease in the migration rate was seen in all of the groups after 72 h of irradiation except cells treated with 532 nm wavelength. However, 532 nm laser beams increase the migratory potential 24 h after exposure. Within 72 h after irradiation, the cell proliferation was only affected by applying 532 nm and 650 nm-150mW laser beams. It was concluded that applying photobiomodulation with wavelengths of 650 nm (at both utilized powers) and 780 nm alters the migration capability and provides a quantitative description of cytoskeletal changes. Moreover, membrane stiffening can be considered as the biological marker of PBM treatments.

Lasers Med Sci, 2022 04

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Photobiomodulation treatments drive osteogenic versus adipocytic fate of bone marrow mesenchymal stem cells reversing the effects of hyperglycemia in diabetes.

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ABSTRACT

Aim: Diabetes mellitus (DM) is a chronic metabolic disease that affects bone metabolism, which can be related to a reduced osteogenic potential of bone marrow mesenchymal stem cells (BM-MSCs). MSCs from diabetic rats (dBM-MSC) have shown a tendency to differentiate towards adipocytes (AD) instead of osteoblasts (OB). Since photobiomodulation (PBM) therapy is a non-invasive treatment capable of recovering the osteogenic potential of dBM-MSCs, we aimed to evaluate whether PBM can modulate MSC's differentiation under hyperglycemic conditions. BM-MSCs of healthy and diabetic rats were isolated and differentiated into osteoblasts (OB and dOB) and adipocytes (AD and dAD). dOB and dAD were treated with PBM every 3 days (660 nm; 5 J/cm2; 0.14 J; 20 mW; 0.714 W/cm2) for 17 days. Cell morphology and viability were evaluated, and cell differentiation was confirmed by gene expression (RT-PCR) of bone (Runx2, Alp, and Opn) and adipocyte markers (Pparγ, C/Ebpα, and C/Ebpβ), production of extracellular mineralized matrix (Alizarin Red), and lipid accumulation (Oil Red). Despite no differences on cell morphology, the effect of DM on cells was confirmed by a decreased gene expression of bone markers and matrix production of dOB, and an increased expression of adipocyte and lipid accumulation of dAD, compared to heatlhy cells. On the other hand, PBM reversed the effects of dOB and dAD. The negative effect of DM on cells was confirmed, and PBM improved OB differentiation while decreasing AD differentiation, driving the fate of dBM-MSCs. These results may contribute to optimizing bone regeneration in diabetic patients.

Lasers Med Sci, 2022 04

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Effect of Photobiomodulation Therapy on Differentiation of Mesenchymal Stem Cells Derived from Impacted Third Molar Tooth into Neuron-like Cells.

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ABSTRACT

Aim: Peripheral nerve damages are among the most important consequences of dental and maxillofacial procedures. Tissue engineering using mesenchymal stem cells (MSCs) is a promising method to manage such injuries. Moreover, photobiomodulation therapy (PBMT) can enhance this treatment. The present study aimed to investigate the effect of PBMT on differentiation of MSCs derived from dental follicle (DF) into neurons. MSCs were isolated from an impacted tooth follicle by digestion method. The stem cells were cultured, and differentiated into neurons. The cells received two sessions of PBMT with 810 or 980nm diode laser (100 mW, 4 J/cm2) in either DMEM or neural inductive medium . Phenotypic characterization of the cells was determined using Flow cytometry. In addition, β-tubulin and MAP2 genes expression level changes were analyzed using RT-PCR and western blot technique. After 14 days, Flow cytometry analysis confirmed the mesenchymal nature of cells. RT-PCR and western blot affirmed the expression of β-tubulin and MAP2 genes and proteins, respectively. PBMT with both wavelengths significantly increased β-tubulin and MAP2 expression in neural inductive medium with highest expression mean in 980-nm group. PBMT with 810 and 980-nm lasers could be a promising adjunctive method in differentiation of DF-originated MSCs into neural cells.

Photochem Photobiol, 2022 04

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Single Cell Effects of Photobiomodulation on Mitochondrial Membrane Potential and Reactive Oxygen Species Production in Human Adipose Mesenchymal Stem Cells.

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ABSTRACT

Aim: Photobiomodulation (PBM) has recently emerged in cellular therapy as a potent alternative in promoting cell proliferation, migration, and differentiation during tissue regeneration. Herein, a single-cell near-infrared (NIR) laser irradiation system (830 nm) and the image-based approaches were proposed for the investigation of the modulatory effects in mitochondrial membrane potential (ΔΨm), reactive oxygen species (ROS), and vesicle transport in single living human adipose mesenchymal stem cells (hADSCs). The irradiated-hADSCs were then stained with 2',7'-dichlorodihydrofluorescein diacetate (H₂DCFDA) and Rhodamine 123 (Rh123) to represent the ΔΨm and ROS production, respectively, with irradiation in the range of 2.5-10 (J/cm²), where time series of bright-field images were obtained to determine the vesicle transport phenomena. Present results showed that a fluence of 5 J/cm² of PBM significantly enhanced the ΔΨm, ROS, and vesicle transport phenomena compared to the control group (0 J/cm²) after 30 min PBM treatment. These findings demonstrate the efficacy and use of PBM in regulating ΔΨm, ROS, and vesicle transport, which have potential in cell proliferation, migration, and differentiation in cell-based therapy.

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Near Infrared Laser Photobiomodulation of Periodontal Ligament Stem Cells.

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ABSTRACT

OBJECTIVE: To determine the effect of different energy densities of near infrared diode lasers with wavelengths of 810 or 940 nm on the proliferation and survival of periodontal ligament derived stem cells (PDLSCs).

METHODS: After isolation and characterisation, PDLSCs were cultured in clear 96-well plates. Each well was irradiated by either 810 nm (L1) or 940 nm (L2) lasers, with energy densities of 0.5, 1.5 and 2.5 J/cm2 and an output power of 100 mW. A non-irradiated well was used as a control. Cellular viability was measured 24 hours after irradiation using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay and proliferation was measured 24, 48 and 72 hours after irradiation using trypan blue staining and counting. Propidium iodide (PI) staining was used to identify any pyknotic nuclei or nuclear fragmentation 72 hours after irradiation.

RESULTS: An increase in viability was observed only in the group with the 940 nm laser irradiation at energy density of 2.5 J/cm2 (P <; 0.001). The proliferation of cells was significantly increased in the group with 940 nm laser irradiation at energy density of 2.5 J/cm2 at all the time points examined in comparison to other groups (P <; 0.001). PI staining showed no change in cell nuclei in any of the groups.

CONCLUSION: Irradiation of PDLSCs with a 940 nm laser at an energy density of 2.5 J/cm2 could promote efficient cell proliferation.

Chin J Dent Res, 2022 03 25(1) 57-65

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Activation of the AKT/GSK-3β/β-catenin pathway via photobiomodulation therapy promotes neural stem cell proliferation in neonatal rat models of hypoxic-ischemic brain damage.

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ABSTRACT

Background: Hypoxic-ischemic brain damage (HIBD) significantly affects neurodevelopment in infants and is a leading cause of severe neurological morbidity and mortality in neonates. Our previous study found that photobiomodulation therapy (PBMT) improves the impaired spatial learning and memory of HIBD rat models. However, the neuroprotective mechanism conferred by PBMT in HIBD is unclear.

Methods: In the present study, HIBD model rats were treated with PBMT at 5 mW/cm2 per day in the dark for 14 days (10 min each day), and primary neural stem cells (NSCs) after oxygen-glucose deprivation (OGD) were treated with PBMT for 10 min at 1, 5, 10, and 20 mW/cm2 in the dark. PBMT promoted hippocampal neural stem cell (NSC) proliferation in vivo and in vitro.

Results: Mechanistically, PBMT upregulated phosphatidylinositol 3 kinase (PI3K), phosphorylated protein kinase B (p-AKT), phosphorylated glycogen synthase kinase 3 beta (p-GSK-3β), β-catenin, and cyclin D1 expression in vivo and in vitro, promoting NSC proliferation. Furthermore, both LY294002 (a PI3K inhibitor) and IWR-1 (a Wnt/β-catenin inhibitor) inhibited the PBMT promotion of NSC proliferation after OGD and suppressed β-catenin and cyclin D1 expression in vitro.

Conclusions: PBMT improved the spatial learning and memory of HIBD rats and promoted hippocampal NSC proliferation through the AKT/GSK-3β/β-catenin pathway.

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Enhancing health span: muscle stem cells and hormesis.

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ABSTRACT

Aim: Sarcopenia is a significant public health and medical concern confronting the elderly. Considerable research is being directed to identify ways in which the onset and severity of sarcopenia may be delayed/minimized. This paper provides a detailed identification and assessment of hormetic dose responses in animal model muscle stem cells, with particular emphasis on cell proliferation, differentiation, and enhancing resilience to inflammatory stresses and how this information may be useful in preventing sarcopenia. Hormetic dose responses were observed following administration of a broad range of agents, including dietary supplements (e.g., resveratrol), pharmaceuticals (e.g., dexamethasone), endogenous ligands (e.g., tumor necrosis factor α), environmental contaminants (e.g., cadmium) and physical agents (e.g., low level laser). The paper assesses both putative mechanisms of hormetic responses in muscle stem cells, and potential therapeutic implications and application(s) of hormetic frameworks for slowing muscle loss and reduced functionality during the aging process.

Biogerontology, 2022 03

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Photobiomodulation Therapy to Autologous Bone Marrow in Humans Significantly Increases the Concentration of Circulating Stem Cells and Macrophages: A Pilot Study.

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ABSTRACT

Aim: Objective: The aim of this study was to examine the effect of photobiomodulation therapy (PBMT) of the bone marrow (BM) on the concentration of stem cells and other cells in the circulating blood (CB) in humans. Background: Circulating stem cells have received increasing attention in recent years due to their potential role in regenerative medicine. Various biological processes have been shown to be affected by PBMT. Methods: The study was conducted on 15 volunteers. Ga-Al-As diode laser 808 nm wavelength was applied to both tibias of each volunteer for PBMT to the BM. The kinetics of concentration of various cells in the CB was followed by comparing blood samples relative to their baseline levels prior to application of PBMT to the BM. CD-34+ cells and macrophages were identified in CB samples using flow cytometry technology. Results: PBMT to the BM caused a significant ($p <; 0.01$) increase in the concentration of CD-34+ cells in the CB from $7.8 \pm 3.0\%$ (mean ± SD) of total mononucleated cell to $29.5 \pm 10.1\%$ of total commencing at about 2 h post-PBMT. The levels of CD-34+ cells peaked at 2-4 days post-PBMT and then gradually returned to baseline levels. Macrophages in the CB were also significantly ($p <; 0.01$) elevated following PBMT to the BM from $7.8 \pm 6.0\%$ (mean ± SD) of the total mononucleated cells to $52.1 \pm 7.9\%$ of total. Conclusions: Application of PBMT to the BM in humans can significantly increase the concentration of CD-34+ cells and macrophages in the CB. These cells may consequently home in on the impaired target organs and improve their function, as has been previously shown in experimental animal models. Furthermore, the results may also have clinical relevance in respect to enrichment of CB in cells that may be consequently isolated for cell therapy. Clinical Trial Registration No. is .

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Low-Level Laser Irradiation Promotes Proliferation and Differentiation on Apical Papilla Stem Cells.

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ABSTRACT

Aim: Introduction: Low-level laser therapy (LLLT) has been reported to improve cell proliferation and differentiation. The stem cells derived from dental apical papilla (SCAPs) are a promising therapy because they are easily obtained from immature human teeth. The effect of LLLT over SCAPs is still unknown. This study aimed to evaluate the proliferation and osteogenic potential of the SCAPs stimulated with LLLT. Methods: SCAPs were isolated from the third molars of a healthy donor and characterized according to the minimum established criteria. SCAPs were cultured for 24 hours before being exposed to LLLT. Cells were exposed to different doses, energy, and wavelengths for selecting the irradiation parameters. SCAPs proliferation was evaluated with the MTT assay at 24 hours and 7-day post-laser exposure. VEGF and TGFβ2 expression were assessed with a specific enzyme-linked immunosorbent assay (ELISA). The osteogenic differentiation potential was analyzed with alizarin red staining, and the nodule quantification was performed by the relative optical density (ROD) analysis using ImageJ software. Results: The cells isolated from the apical papilla showed phenotype and stem cell properties. SCAPs irradiated with one dose at 6 J/m2 and 650 nm exhibited significantly higher proliferation (P>0.05) than the controls nonirradiated. LLLT stimulated SCAPs' expression of factors VEGF and TGFβ2. Also, SCAPs irradiated showed higher osteogenic activity (P<;0.05). Conclusion: LLLT promotes proliferation, osteogenic differentiation, and VEGF and TGFβ2 expression on SCAPs. LLLT is a practical approach for the preconditioning of SCAPs in vitro for future regenerative therapies. More studies are needed to determine the underlying molecular processes that determine the mechanism of the LLLT.

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Laser Photobiomodulation 808 nm: Effects on Gene Expression in Inflammatory and Osteogenic Biomarkers in Human Dental Pulp Stem Cells.

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ABSTRACT

Aim: The tissue engineering of dental oral tissue is tackling significant advances and the use of stem cells promises to boost the therapeutical approaches of regenerative dentistry. Despite advances in this field, the literature is still scarce regarding the modulatory effect of laser photobiomodulation (PBM) on genes related to inflammation and osteogenesis in Postnatal Human Dental Pulp Stem cells (DPSCs). This study pointedly investigated the effect of PBM treatment in proliferation, growth and differentiation factors, mineralization, and extracellular matrix remodeling genes in DPSCs. Freshly extracted human third molars were used as a source for DPSCs isolation. The isolated DPSCs were stimulated to an inflammatory state, using a lipopolysaccharide (LPS) model, and then subjected or not to laser PBM. Each experiment was statistically evaluated according to the sample distribution. A total of 85 genes related to inflammation and osteogenesis were evaluated regarding their expression by RT-PCR. Laser PBM therapy has shown to modulate several genes expression in DPSCs. PBM suppressed the expression of inflammatory gene TNF and RANKL and downregulated the gene expression for VDR and proteolytic enzymes cathepsin K, MMP-8 and MMP-9. Modulation of gene expression for proteinase-activated receptors (PARs) following PBM varied among different PARs. As expected, PBM blocked the odontoblastic differentiation of DPSCs when subjected to LPS model. Conversely, PBM has preserved the odontogenic potential of DPSCs by increasing the expression of TWIST-1/RUNEX-2/ALP signaling axis. PBM therapy notably played a role in the DPSCs genes expression that mediate inflammation process and tissue mineralization. The present data opens a new perspective for PBM therapy in mineralized dental tissue physiology.

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Control of stem cell differentiation by using extrinsic photobiomodulation in conjunction with cell adhesion pattern.

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ABSTRACT

Aim: The induction and direction of stem cell differentiation into needed cell phenotypes is the central pillar of tissue engineering for repairing damaged tissues or organs. Conventionally, a special recipe of chemical factors is formulated to achieve this purpose for each specific target cell type. In this work, it is demonstrated that the combination of extrinsic photobiomodulation and collagen-covered microislands could be used to induce differentiation of Wharton's jelly mesenchymal stem cells (WJ-MSCs) with the differentiation direction dictated by the specific island topography without use of chemical factors. Both neurogenic differentiation and adipogenic differentiation could be attained with a rate surpassing that using chemical factors. Application of this method to other cell types is possible by utilizing microislands with a pattern tailored particularly for each specific cell type, rendering it a versatile modality for initiating and guiding stem cell differentiation.

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Area light source-triggered latent angiogenic molecular mechanisms intensify therapeutic efficacy of adult stem cells.

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ABSTRACT

Aim: Light-based therapy such as photobiomodulation (PBM) reportedly produces beneficial physiological effects in cells and tissues. However, most reports have focused on the immediate and instant effects of light. Considering the physiological effects of natural light exposure in living organisms, the latent reaction period after irradiation should be deliberated. In contrast to previous reports, we examined the latent reaction period after light exposure with optimized irradiating parameters and validated novel therapeutic molecular mechanisms for the first time. we demonstrated an organic light-emitting diode (OLED)-based PBM (OPBM) strategy that enhances the angiogenic efficacy of human adipose-derived stem cells (hADSCs) via direct irradiation with red OLEDs of optimized wavelength, voltage, current, luminance, and duration, and investigated the underlying molecular mechanisms. Our results revealed that the angiogenic paracrine effect, viability, and adhesion of hADSCs were significantly intensified by our OPBM strategy. Following OPBM treatment, significant changes were observed in HIF-1α expression, intracellular reactive oxygen species levels, activation of the receptor tyrosine kinase, and glycolytic pathways in hADSCs. In addition, transplantation of OLED-irradiated hADSCs resulted in significantly enhanced limb salvage ratio in a mouse model of hindlimb ischemia. Our OPBM might serve as a new paradigm for stem cell culture systems to develop cell-based therapies in the future.

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Evaluation of the effects of preconditioned human stem cells plus a scaffold and photobiomodulation administration on stereological parameters and gene expression levels in a critical size bone defect in rats.

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We assessed the impact of photobiomodulation (PBM) plus adipose-derived stem cells (ASCs) during the anabolic and catabolic stages of bone healing in a rat model of a critical size femoral defect (CSFD) that was filled with a decellularized bone matrix (DBM). Stereological analysis and gene expression levels of bone morphogenetic protein 4 (BMP4), Runt-related transcription factor 2 (RUNX2), and stromal cell-derived factor 1 (SDF1) were determined. There were six groups of rats. Group 1 was the untreated control or DBM. Study groups 2-6 were treated as follows: ASC (ASC transplanted into DBM, then implanted in the CSFD); PBM (CSFD treated with PBM); irradiated ASC (iASC) (ASCs preconditioned with PBM, then transplanted into DBM, and implanted in the CSFD); ASC + PBM (ASCs transplanted into DBM, then implanted in the CSFD, followed by PBM administration); and iASC + PBM (the same as iASC, except CSFDs were exposed to PBM). At the anabolic step, all treatment groups had significantly increased trabecular bone volume (TBV) (24.22%) and osteoblasts (83.2%) compared to the control group (all, $p = .000$). However, TBV in group iASC + PBM groups were superior to the other groups (97.48% for osteoblast and 58.8% for trabecular bone volume) (all, $p = .000$). The numbers of osteocytes in ASC (78.2%) and iASC + PBM (30%) groups were remarkably higher compared to group control (both, $p = .000$). There were significantly higher SDF (1.5-fold), RUNX2 (1.3-fold), and BMP4 (1.9-fold) mRNA levels in the iASC + PBM group compared to the control and some of the treatment groups. At the catabolic step of bone healing, TBV increased significantly in PBM (30.77%), ASC + PBM (32.27%), and iASC + PBM (35.93%) groups compared to the control group (all, $p = .000$). There were significantly more osteoblasts and osteocytes in ASC (71.7%, 62.02%) ($p = .002$, $p = .000$); PBM (82.54%, 156%), iASC (179%, 23%), and ASC + PBM (108%, 110%) (all, $p = .000$), and iASC + PBM (79%, 100.6%) ($p = .001$, $p = .000$) groups compared to control group. ASC preconditioned with PBM in vitro plus PBM in vivo significantly increased stereological parameters and SDF1, RUNX2, and BMP4 mRNA expressions during bone healing in a CSFD model in rats.

Irradiation with a red light-emitting diode enhances the proliferation of stem cells of apical papilla via the ERK5 signalling pathway.

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ABSTRACT
This Querystudy aimed to investigate the effects of low-energy red light-emitting diode (LED) irradiation on the proliferation of stem cells from apical papilla (SCAPs) and preliminarily elucidated the underlying molecular mechanisms. SCAPs were isolated and identified in vitro. The light source was a 10 W red LED with continuous output and a wavelength of 600-700 nm. SCAPs were irradiated with 0 (control group), 0.5 J/cm2, 1 J/cm2, 3 J/cm2, or 5 J/cm2. Cell Counting Kit-8 (CCK-8) assays were used to analyze cell proliferation rates and determine the most effective concentration of extracellular signal-regulated kinase 5 (ERK5) blocker, BIX02189. A real-time polymerase chain reaction (RT-PCR) was carried out to determine the involvement of the ERK5 signalling pathway and proliferation-associated genes (C-Jun, Jun B, and Cyclin D1). 5-Ethynyl-2'-deoxyuridine (EDU) was used to analyze cell cycle kinetic parameters. CCK-8 assay results suggested that SCAPs in red LED groups exhibited a higher proliferation rate than those in the control group, and 10 μmol/L BIX02189 was the most effective blocker. The RT-PCR results demonstrate that red LEDs upregulated the expression of the ERK5, C-Jun, Jun B, and Cyclin D1 genes, and BIX02189 successfully blocked the ERK5 signalling pathway. The results of EdU staining indicated that red LED promoted DNA synthesis activity and that BIX02189 suppressed cells into S phase. Red LEDs irradiation enhances the proliferation of SCAPs via the ERK5 signalling pathway by upregulating the expression of C-Jun, Jun B, and Cyclin D1.

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Lightwave-reinforced stem cells with enhanced wound healing efficacy.

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ABSTRACT

Aim: Comprehensive research has led to significant preclinical outcomes in modified human adipose-derived mesenchymal stem cells (hADSCs). Photobiomodulation (PBM), a technique to enhance the cellular capacity of stem cells, has attracted considerable attention owing to its effectiveness and safety. Here, we suggest a red organic light-emitting diode (OLED)-based PBM strategy to augment the therapeutic efficacy of hADSCs. In vitro assessments revealed that hADSCs basked in red OLED light exhibited enhanced angiogenesis, cell adhesion, and migration compared to naïve hADSCs. We demonstrated that the enhancement of cellular capacity was due to an increased level of intracellular reactive oxygen species. Furthermore, accelerated healing and regulated inflammatory response was observed in mice transplanted with red light-basked hADSCs. Overall, our findings suggest that OLED-based PBM may be an easily accessible and attractive approach for tissue regeneration that can be applied to various clinical stem cell therapies.

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Effects of Photobiomodulation Therapy with Various Laser Wavelengths on Proliferation of Human Periodontal Ligament Mesenchymal Stem Cells.

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Several methods have been proposed to enhance the regeneration and healing time in periodontal therapy. Photobiomodulation therapy (PBMT) is a recently suggested novel technique for this purpose. This study aimed to compare the efficacy of PBMT with various laser wavelengths and energy densities on proliferation of human periodontal ligament mesenchymal stem cells (PDLMSCs). The wells containing PDLMSCs were subjected to laser irradiation at 635, 660, 808 and 980 nm wavelengths with 1, 1.5, 2.5 and 4 J cm-2 energy densities. Cell proliferation and viability were evaluated after 1, 3 and 5 days with the methyl thiazolyl tetrazolium (MTT) assay and 4,6-diamidino-2-phenylindole (DAPI) staining. No significant difference was observed among the experimental and the control groups on day 1 ($P > 0.05$). On day 3, 808 nm laser at 4 J cm-2 energy density and 980 nm laser at all densities had significant differences with control group. On day 5, the control group had significant differences in cell proliferation with 808 nm laser at 2.5 and 4 J cm-2 energy densities, and 980 nm laser at all densities. PBMT with 635, 660, 808 and 980 nm wavelengths increased the proliferation of PDLMSCs but the maximum cell viability was prominent after irradiation by 980 nm laser with energy density of 4 J cm-2 on day 3.

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Photobiomodulation of inflamed dental pulp stem cells under different nutritional conditions.

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Aim: The present study aimed to investigate photobiomodulation's (PBM) effect on inflamed dental pulp stem cells (IDPSCs) under different nutritional conditions. Methods: Cell proliferation and odontogenic differentiation were evaluated using the MTT assay and real-time quantitative reverse transcription PCR, respectively after laser PBM of cells in 5 or 10% fetal bovine serum (FBS) culture conditions. Results: A significant positive effect of laser irradiation on cell proliferation under both nutritional conditions after 24 and 48 h was observed. DMP-1 gene expression increased in the groups with laser irradiation and 5% FBS. Comparison of gene expression levels in the four groups revealed no statistically significant stimulatory effect. The highest gene expression was observed in the non-laser group with 5% FBS. Conclusion: Further studies are required to obtain an irradiation setup to ideally improve inflamed dental pulp stem cells' proliferation and differentiation.

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Bioenergetics of photobiomodulated osteoblast mitochondrial cells derived from human pulp stem cells: systematic review.

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Dental pulp cells are a source of multipotent mesenchymal stem cells with a high proliferation rate and multilineage differentiation potential. This study investigated the photobiomodulated bioenergetic effects of mitochondria in osteoblasts that differentiated from human pulp stem cells. The systematic review followed PRISMA guidelines. The PICO question was formulated. Criteria for inclusion and exclusion were established prior to searches being performed on the PubMed/MEDLINE, Embase, and Scopus. Articles were identified and included if published in English within last 10 years; photobiomodulation or low-level laser therapy were discussed; the delivery parameters for dose and time were included and the studies focused on bioenergetics of osteoblast mitochondria. Studies excluded were non-human dental pulp tissue and in vivo studies. A total number of 110 articles were collated, 106 were excluded leaving a total of 4 articles. These studies demonstrated that in vitro use of photobiomodulation was performed using different laser and LED types; InGaAlP; InGaN; and InGaAsP with average wavelengths of 630 to 940 nm. Primary human osteoblastic STRO-1 and mesenchymal stem cell lineages were studied. Three out of four articles confirmed positive bioenergetic effects of photobiomodulation on mitochondria of osteoblasts derived from human pulp cells. This systematic review demonstrated a lack of adequate reporting of bioenergetics of osteoblast mitochondria after photobiomodulation treatment.

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Photobiomodulation therapy upregulates the growth kinetics and multilineage differentiation potential of human dental pulp stem cells-an in vitro Study.

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This study aims to evaluate the impact of red LED irradiation on the viability, proliferation, colonogenic potential, markers expression along with osteogenic and chondrogenic differentiation of dental pulp stem cells. DPSCs were isolated from sound human permanent teeth using enzymatic digestion method and seeded with regular culture media. Cells at P4 were irradiated using red LED Light (627 nm, 2 J/cm2) and examined for growth kinetics, and multilineage differentiation using the appropriate differentiation media. The irradiated groups showed an increase in cellular growth rates, cell viability, clonogenic potential, and decrease in population doubling time compared to the control group. Cells of the irradiated groups showed enhanced differentiation towards osteogenic and chondrogenic lineages as revealed by histochemical staining using alizarin red and alcian blue stains. Photobiomodulation is an emerging promising element of tissue engineering triad besides stem cells, scaffolds, and growth factors.

Lasers Med Sci, 2021 11

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Increased Anti-Allergic Effects of Secretome of Low-Level Light Treated Tonsil-Derived Mesenchymal Stem Cells in Allergic Rhinitis Mouse Model.

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Background: Low-level light therapy (LLLT) is widely used for the photobiomodulation of cell behavior. Recent studies have shown that LLLT affects the proliferation and migration of various types of mesenchymal stem cells (MSCs). However, there is a lack of studies investigating the effect of LLT on enhancing the immunomodulatory properties of tonsil-derived MSCs (T-MSCs).
Objective: The aim of this study was to investigate the immunomodulatory effects of conditioned media from T-MSCs (T-MSCs-CM) treated with LLLT in allergic inflammation.
Methods: We isolated T-MSCs from human palatine tonsils and evaluated the ingredients of T-MSCs-CM. The effect of T-MSCs-CM treated with LLLT was evaluated in a mouse model of allergic rhinitis (AR). We randomly divided the mice into four groups (negative control, positive control, T-MSCs-CM alone, and T-MSCs-CM treated with LLLT). To elucidate the therapeutic effect, we assessed rhinitis symptoms, serum immunoglobulin (Ig), the number of inflammatory cells, and cytokine expression.
Results: We identified increased expression of immunomodulatory factors, such as HGF, TGF-β, and PGE, in T-MSCs-CM treated with LLLT, compared to T-MSCs-CM without LLLT. Our animal study demonstrated reduced allergic symptoms and lower expression of total IgE and OVA-specific IgE in the LLLT-treated T-MSCs-CM group compared to the AR group and T-MSCs-CM alone. Moreover, we found that T-MSCs-CM treated with LLLT showed significantly decreased infiltration of eosinophils, neutrophils, and IL-17 cells in the nasal mucosa and reduced IL-4, IL-17, and IFN-γ expression in OVA-incubated splenocytes compared to the AR group.
Conclusions: The present study suggests that T-MSCs-CM treated with LLLT may provide an improved therapeutic effect against nasal allergic inflammation than T-MSCs-CM alone.

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Simultaneous Treatment of Photobiomodulation and Demineralized Bone Matrix With Adipose-Derived Stem Cells Improve Bone Healing in an osteoporotic bone defect.

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Introduction: The ability of simultaneous treatment of critical-sized femoral defects (CSFDs) with photobiomodulation (PBM) and demineralized bone matrix (DBM) with or without seeded adipose-derived stem cells (ASCs) to induce bone reconstruction in ovariectomized induced osteoporotic (OVX) rats was investigated. Methods: The OVX rats with CSFD were arbitrarily separated into 6 groups: control, scaffold (S, DBM), S + PBM, S + alendronate (ALN), S + ASCs, and S + PBM + ASCs. Each group was assessed by cone beam computed tomography (CBCT) and histological examinations. Results: In the fourth week, CBCT and histological analyses revealed that the largest volume of new bone formed in the S + PBM and S + PBM + ASC groups. The S + PBM treatment relative to the S and S + ALN treatments remarkably reduced the CSFD (Mann-Whitney test, P = 0.009 and P = 0.01). Furthermore, S + PBM + ASCs treatment compared to the S and S + ALN treatments significantly decreased CSFD (Mann Whitney test, P = 0.01). In the eighth week, CBCT analysis showed that extremely enhanced bone regeneration occurred in the CSFD of the S + PBM group. Moreover, the CSFD in the S + PBM group was substantially smaller than S, S + ALN and S + ASCs groups (Mann Whitney test, P = 0.01, P = 0.02 and P = 0.009). Histological observations showed more new bone formation in the treated CSFD of S + PBM + ASCs and S + PBM groups. Conclusion: The PBM plus DBM with or without ASCs significantly enhanced bone healing in the CSFD in OVX rats compared to control, DBM alone, and ALN plus DBM groups. The PBM plus DBM with or without ASCs significantly decreased the CSFD area compared to either the solo DBM or ALN plus DBM treatments.

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Efficacy of Photobiomodulation and Vitamin D on Odontogenic Activity of Human Dental Pulp Stem Cells.

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Introduction: The regeneration of dental pulp tissue using human dental pulp stem cells (HDPSCs) has attracted increasing attention in recent years. Recent studies have suggested that several factors such as photobiomodulation (PBM) and vitamin D affect the proliferation and differentiation of HDPSCs. Therefore, the present study evaluated the effects of PBM and vitamin D on odontogenic differentiation of HDPSCs for dentin -like tissue formation. Methods: HDPSCs were collected, isolated, and characterized and then divided into six groups: group I, control; group II, vitamin D (10-7 Mol); group III, irradiation at 1 J/cm2 of 810 nm diode laser; group IV, irradiation at 1 J/cm2 and culture with vitamin D; group V, irradiation at 2 J/cm2, and group VI, irradiation at 2 J/cm2 and culture with vitamin D, cell viability assay was measured through MTT. Alkaline phosphatase (ALP) enzyme activity and mRNA levels of vascular endothelial growth factor (VEGF), bone morphogenic protein-2 (BMP-2), and dentin sialophosphoprotein (DSPP) were also assessed. Results: PBM at 1 and 2 J/cm2 combined with vitamin D significantly promoted HDPSCs proliferation through MTT assay and odontogenic differentiation through gene expression of VEGF, BMP-2, and DSPP levels ($P < 0.0001$). Conclusion: PBM at 2 J/cm2 combined with vitamin D enhanced the HDPSCs proliferation and odontogenic differentiation and thus could be a novel strategy for dentin regeneration in dentistry.

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The effect of 805 nm near-infrared photobiomodulation on proliferation and differentiation of bone marrow stem cells in murine rats.

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ABSTRACT

Aim: To evaluate the effect of near infra-red gallium-aluminium-arsenide (GaAlAs) diode laser (805 nm) irradiation on proliferation and differentiation of rat femoral bone marrow-derived mesenchymal stem cells (BMSCs) cultured in osteogenic medium.

Objectives: BMSCs were obtained from femurs of 60 Sprague Dawley rats (200 gm). The control group comprised isolated BMSCs supplemented with an osteogenic differentiation medium. On the other hand, in the experimental group, the BMSCs were irradiated with a near-infrared laser in addition to an osteogenic differentiation medium. The experimental group was irradiated with a soft tissue laser comprising of allium-aluminium-arsenic (Ga-Al-Ar) Diode at a near-infrared wavelength of 805 nm in continuous mode. The different output powers applied were 0.5 W, 1.0 W, 1.5 W and 2.0 W respectively. Various energy levels of 1, 4, 7 and 10 J were used for irradiation. Alkaline phosphatase (ALP) assay and Alizarin staining were performed to confirm osteogenic differentiation. Statistical analysis was done using a one-way ANOVA and a p-value of <0.05 was considered significant.

Methods: According to our findings, 1.27 J/cm2 was the optimal energy density value that significantly increased the BMSC proliferation at the output of 1.5 W with the power density of 1.27 W/cm2. On 1.27 J/cm2, there was a significant difference compared to the control group on the first day, and the osteogenic differentiation increased significantly on the 4th day compared to the 1st day.

Results: According to our findings, 1.27 J/cm2 was the optimal energy density value that significantly increased the BMSC proliferation at the output of 1.5 W with the power density of 1.27 W/cm2.

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Effectiveness of preconditioned adipose-derived mesenchymal stem cells with photobiomodulation for the treatment of diabetic foot ulcers: a systematic review.

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The primary goal of this systematic review article was to provide an outline of the use of diabetic autologous adipose-derived mesenchymal stem cells (DAAD-MSCs) in the treatment of wounds and ulcers in animal models and patients with diabetes mellitus (DM). The secondary goal was to present the outcomes of pretreatment of diabetic adipose-derived mesenchymal stem cells (DAD-MSCs) with probable different agents in the treatment of diabetic foot ulcers (DFUs) and wounds. In view of possible clinical applications of AD-MSC-mediated cell therapy for DFUs, it is essential to evaluate the influence of DM on AD-MSC functions. Nevertheless, there are conflicting results about the effects of DAAD-MSCs on accelerating wound healing in animals and DM patients. Multistep research of the MEDLINE, PubMed, Embase, Clinicaltrials.gov, Scopus database, and Cochrane databases was conducted for abstracts and full-text scientific papers published between 2000 and 2020. Finally, 5 articles confirmed that the usage of allogeneic or autologous AD-MSCs had encouraging outcomes on diabetic wound healing. One study reported that DM changes AD-MSC function and therapeutic potential, and one article recommended that the pretreatment of diabetic allogeneic adipose-derived mesenchymal stem cells (DAlD-MSCs) was more effective in accelerating diabetic wound healing. Recently, much work has concentrated on evolving innovative healing tactics for hastening the repair of DFUs. While DM alters the intrinsic properties of AD-MSCs and impairs their function, one animal study showed that the pretreatment of DAlD-MSCs in vitro significantly increased the function of DAlD-MSCs compared with DAlD-MSCs without any treatment. Preconditioning diabetic AD-MSCs with pretreatment agents like photobiomodulation (PBM) significantly hastened healing in delayed-healing wounds. It is suggested that further animal and human studies be conducted in order to provide more documentation. Hopefully, these outcomes will help the use of DAAD-MSCs plus PBM as a routine treatment protocol for healing severe DFUs in DM patients.

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Cellular Signalling and Photobiomodulation in Chronic Wound Repair.

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Photobiomodulation (PBM) imparts therapeutically significant benefits in the healing of chronic wounds. Chronic wounds develop when the stages of wound healing fail to progress in a timely and orderly frame, and without an established functional and structural outcome. Therapeutic benefits associated with PBM include augmenting tissue regeneration and repair, mitigating inflammation, relieving pain, and reducing oxidative stress. PBM stimulates the mitochondria, resulting in an increase in adenosine triphosphate (ATP) production and the downstream release of growth factors. The binding of growth factors to cell surface receptors induces signalling pathways that transmit signals to the nucleus for the transcription of genes for increased cellular proliferation, viability, and migration in numerous cell types, including stem cells and fibroblasts. Over the past few years, significant advances have been made in understanding how PBM regulates numerous signalling pathways implicated in chronic wound repair. This review highlights the significant role of PBM in the activation of several cell signalling pathways involved in wound healing.

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Phototoxicity-free blue light for enhancing therapeutic angiogenic efficacy of stem cells.

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Low-level light therapy (LLLT) is a safe and noninvasive technique that has drawn attention as a new therapeutic method to treat various diseases. However, little is known so far about the effect of blue light for LLLT due to the generation of reactive oxygen species (ROS) that can cause cell damage. We introduced a blue organic light-emitting diode (bOLED) as a safe and effective light source that could generate a low amount of heat and luminance compared to conventional light sources (e.g., light-emitting diodes). We compared phototoxicity of bOLED light with different light fluences to human adipose-derived stem cells (hADSC). We further explored molecular mechanisms involved in the therapeutic efficacy of bOLED for enhancing angiogenic properties of hADSC, including intracellular ROS control in hADSCs. Using optimum conditions of bOLED light proposed in this study, photobiomodulation and angiogenic properties of hADSCs were enhanced. These findings might open new methods for using blue light in LLLT. Such methods can be implemented in future treatments for ischemic disease.

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Low-level laser treatment promotes skin wound healing by activating hair follicle stem cells in female mice.

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The aim of the study was to explore the effect and mechanism of a low-level laser on hair follicle stem cells in full-thickness skin wound healing in mice. Full-thickness skin defects were generated by a 5-mm punch biopsy tool on the backs of depilated C57/BL6N mice, which were randomly divided thereafter into a low-dose laser treatment group (LLLT-Low), a high-dose laser treatment group (LLLT-High), and a control group (control). From the day of modeling to the day before the skin samples were taken, the wound area and wound edge of the mice in the LLLT-Low and LLLT-High groups were irradiated with a laser comb every 24 h, and the energy density was 1 J/cm2 and 10 J/cm2, respectively. The control group was irradiated with an ordinary fluorescent lamp. At 0, 3, 5, 10, and 14 days after modeling, pictures of each wound were taken, and the percent wound closure was analyzed. At 3, 5, 10, and 14 days after modeling, the samples were observed by hematoxylin and eosin (HE) and immunofluorescence (IF) staining. Whole transcriptome sequencing (RNA-Seq) was performed on the samples on day 10. Gene Ontology (GO) analysis was performed, and the results were validated by Western blot analysis and enzyme-linked immunosorbent assay (ELISA). The analysis of the percent of wound closure showed that healing was accelerated (significantly from 5 to 10 days) in the LLLT-Low group, but there was no clear change in the LLLT-High group. HE staining showed that the LLLT-Low group had an increasing number of hair follicles and a tendency to migrate to the center of the wound. There was no significant increase in the number of hair follicles and no obvious migration in the LLLT-High group. Immunofluorescence staining showed that the total number of CK15 + hair follicle stem cells in the LLLT-Low group was higher than that in the control group and LLLT-High group at all time points. The number and farthest migration distance of CK15 + hair follicle stem cells increased significantly with time, and after 5 days, they were significantly higher than those in the control group and LLLT-High group. RNA-Seq and Western blot analysis showed that the expression of related genes in hair follicle stem cells, including CK15, in the LLLT-Low group was upregulated. GO analysis and ELISA showed that the expression of many cytokines,

Impact of preconditioned diabetic stem cells and photobiomodulation on quantity and degranulation of mast cells in a delayed healing wound simulation in type one diabetic rats.

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Herein, we report the influence of administering different protocols of preconditioned diabetic adipose-derived mesenchymal stem cells (ADSs) with photobiomodulation in vitro, and photobiomodulation in vivo on the number of mast cells (MCs), their degranulation, and wound strength in the maturation step of a Methicillin-resistant Staphylococcus aureus (MRSA)-infectious wound model in rats with type one diabetes. An MRSA-infectious wound model was generated on diabetic animals, and they were arbitrarily assigned into five groups (G). G1 were control rats. In G2, diabetic ADS were engrafted into the wounds. In G3, diabetic ADS were engrafted into the wound, and the wound was exposed to photobiomodulation (890 nm, 890 ± 10 nm, 80 Hz, 0.2 J/cm2) in vivo. In G4, preconditioned diabetic ADS with photobiomodulation (630 and 810 nm; each 3 times with 1.2 J/cm2) in vitro were engrafted into the wound. In G5, preconditioned diabetic ADS with photobiomodulation were engrafted into the wound, and the wound was exposed to photobiomodulation in vivo. The results showed that, the maximum force in all treatment groups was remarkably greater compared to the control group (all, p = 0.000). Maximum force in G4 and G5 were superior than that other treated groups (both p = 0.000). Moreover, G3, G4, and G5 showed remarkable decreases in completely released MC granules and total numbers of MC compared to G1 and G2 (all, p = 0.000). We concluded that diabetic rats in group 5 showed significantly better results in terms of accelerated wound healing and MC count of an ischemic infected delayed healing wound model.

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Photobiomodulation as an antioxidant substitute in post-thawing trauma of human stem cells from the apical papilla.

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ABSTRACT

Aim: Cryopreservation, the most common method of preserving stem cells, requires post-processing because it produces trauma to the cells. Post-thawing trauma typically induces cell death, elevates reactive oxygen species (ROS) concentration, and lowers mitochondrial membrane potential (MMP). Although this trauma has been solved using antioxidants, we attempted to use photobiomodulation (PBM) instead of chemical treatment. We used a 950-nm near-infrared LED to create a PBM device and chose a pulsed-wave mode of 30 Hz and a 30% duty cycle. Near-infrared radiation (NIR) at 950 nm was effective in reducing cell death caused by hydrogen peroxide induced-oxidative stress. Cryodamage also leads to apoptosis of cells, which can be avoided by irradiation at 950 nm NIR. Irradiation as post-processing for cryopreservation had an antioxidant effect that reduced both cellular and mitochondrial ROS. It also increased mitochondrial mass and activated mitochondrial activity, resulting in increased MMP, ATP generation, and increased cytochrome c oxidase activity. In addition, NIR increased alkaline phosphatase (ALP) activity, a biomarker of differentiation. As a result, we identified that 950 nm NIR PBM solves cryodamage in human stem cells from the apical papilla, indicating its potential as an alternative to antioxidants for treatment of post-thawing trauma, and further estimated its mechanism.

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Photobiomodulation with a 660-Nanometer Light-Emitting Diode Promotes Cell Proliferation in Astrocyte Culture.

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Astrocytes act as neural stem cells (NSCs) that have the potential to self-renew and differentiate into other neuronal cells. The protein expression of these astrocytes depends on the stage of differentiation, showing sequential expression of multiple proteins such as octamer-binding transcription factor 4 (Oct4), nestin, glial fibrillary acidic protein (GFAP), and aldehyde dehydrogenase 1 family member L1 (aldh1L1). Photobiomodulation (PBM) affects cell apoptosis, proliferation, migration, and adhesion. We hypothesized that astrocyte proliferation and differentiation would be modulated by PBM. We used an optimized astrocyte culture method and a 660-nanometer light-emitting diode (LED) to enhance the biological actions of many kinds of cells. We determined that the 660-nanometer LED promoted the biological actions of cultured astrocytes by increasing the reactive oxygen species levels. The overall viability of the cultured cells, which included various cells other than astrocytes, did not change after LED exposure; however, astrocyte-specific proliferation was observed by the increased co-expression of GFAP and bromodeoxyuridine (BrdU)/Ki67. Furthermore, the 660-nanometer LED provides evidence of differentiation, as shown by the decreased Oct4 and GFAP co-expression and increased nestin and aldh1L1 expression. These results demonstrate that a 660-nanometer LED can modify astrocyte proliferation, which suggests the efficacy of the therapeutic application of LED in various pathological states of the central nervous system.

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Low level laser therapy promotes bone regeneration by coupling angiogenesis and osteogenesis.

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Background: Bone tissue engineering is a new concept bringing hope for the repair of large bone defects, which remains a major clinical challenge. The formation of vascularized bone is key for bone tissue engineering. Growth of specialized blood vessels termed type H is associated with bone formation. In vivo and in vitro studies have shown that low level laser therapy (LLLT) promotes angiogenesis, fracture healing, and osteogenic differentiation of stem cells by increasing reactive oxygen species (ROS). However, whether LLLT can couple angiogenesis and osteogenesis, and the underlying mechanisms during bone formation, remains largely unknown.
Methods: Mouse bone marrow mesenchymal stem cells (BMSCs) combined with biphasic calcium phosphate (BCP) grafts were implanted into C57BL/6 mice to evaluate the effects of LLLT on the specialized vessel subtypes and bone regeneration in vivo. Furthermore, human BMSCs and human umbilical vein endothelial cells (HUVECs) were co-cultured in vitro. The effects of LLLT on cell proliferation, angiogenesis, and osteogenesis were assessed.
Results: LLLT promoted the formation of blood vessels, collagen fibers, and bone tissue and also increased CD31hiEMCNhi-expressing type H vessels in mBMSC/BCP grafts implanted in mice. LLLT significantly increased both osteogenesis and angiogenesis, as well as related gene expression (HIF-1α, VEGF, TGF-β) of grafts in vivo and of co-cultured BMSCs/HUVECs in vitro. An increase or decrease of ROS induced by H2O2 or Vitamin C, respectively, resulted in an increase or decrease of HIF-1α, and a subsequent increase and decrease of VEGF and TGF-β in the co-culture system. The ROS accumulation induced by LLLT in the co-culture system was significantly decreased when HIF-1α was inhibited with DMBPA and was followed by decreased expression of VEGF and TGF-β.
Conclusions: LLLT enhanced vascularized bone regeneration by coupling angiogenesis and osteogenesis. ROS/HIF-1α was necessary for these effects of LLLT. LLLT triggered a ROS-dependent increase of HIF-1α, VEGF, and TGF-β and resulted in subsequent formation of type H vessels and osteogenic differentiation of mesenchymal stem cells. As ROS also was a target of HIF-1α, there may be a positive feedback loop between ROS and HIF-1α, which further amplified HIF-1α induction via the LLLT-mediated ROS increase. This study provided new insight into the effects of LLLT on vascularization and bone regeneration in bone tissue engineering.

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Corticospinal Motor Circuit Plasticity After Spinal Cord Injury: Harnessing Neuroplasticity to Improve Functional Outcomes.

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Spinal cord injury (SCI) is a devastating condition that affects approximately 294,000 people in the USA and several millions worldwide. The corticospinal motor circuitry plays a major role in controlling skilled movements and in planning and coordinating movements in mammals and can be damaged by SCI. While axonal regeneration of injured fibers over long distances is scarce in the adult CNS, substantial spontaneous neural reorganization and plasticity in the spared corticospinal motor circuitry has been shown in experimental SCI models, associated with functional recovery. Beneficially harnessing this neuroplasticity of the corticospinal motor circuitry represents a highly promising therapeutic approach for improving locomotor outcomes after SCI. Several different strategies have been used to date for this purpose including neuromodulation (spinal cord/brain stimulation strategies and brain-machine interfaces), rehabilitative training (targeting activity-dependent plasticity), stem cells and biological scaffolds, neuroregenerative/neuroprotective pharmacotherapies, and light-based therapies like photodynamic therapy (PDT) and photobiomodulation (PMBT). This review provides an overview of the spontaneous reorganization and neuroplasticity in the corticospinal motor circuitry after SCI and summarizes the various therapeutic approaches used to beneficially harness this neuroplasticity for functional recovery after SCI in preclinical animal model and clinical human patients' studies.

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Efficacy of Photobiomodulation and Metformin on Diabetic Cell Line of Human Periodontal Ligament Stem Cells through Keap1/Nrf2/Ho-1 Pathway.

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Background: Diabetes mellitus (DM) is a metabolic disorder resulting from hyperglycemia. Hyperglycemia contributes to oxidative stress, and the release of advanced glycation end products (AGEs) further promotes disease pathogenesis. Uncontrolled diabetes reflects great oral complications and affects human oral health. So, the present study aimed to assess the effects of photobiomodulation therapy (PBMT) and Metformin on proliferation and viability of human periodontal ligament stem cells (HPDLSCs) cultured in high glucose medium.
Methods: HPDLSCs were collected, isolated, and characterized and then divided into eight groups. Addition of extra glucose to diabetic groups 24 hours before cell irradiations. Metformin was added to half of the diabetic groups. Cells were irradiated with 808 nm diode laser 24, 48 hours. Cell viability was analyzed with MTT assay 24 hours post-irradiation to detect cell viability in each group. Real-time (PCR) was used to evaluate gene expression of Nrf2, Keap1, PIK3, and HO-1 and the effect of PBMT on Keap1/Nrf2/Ho-1 Pathway. ELISA reader was used to evaluating cell viability through (ROS, TNF-α, IL-10) protein levels after cell irradiation.
Results: Photobiomodulation at 1, 2, and 3 J/cm2 combined with metformin significantly promoted diabetic cell lines of HPDLSCs viability (in MTT assay and ELISA reader of ROS, TNF-α, IL-10 results) and gene expression of Nrf2, Keap1, PIK3, and HO-1 levels ($p < 0.05$).
Conclusion: photobiomodulation with 3 J/cm2 combined with metformin enhanced proliferation and viability of diabetic cell lines of HPDLSCs and thus could improve differentiation and function of diabetic cell lines of HPDLSCs with minimum side effects.

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The effect of photobiomodulation therapy on antioxidants and oxidative stress profiles of adipose derived mesenchymal stem cells in diabetic rats.

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We studied the effects of photobiomodulation therapy (PBMT) on adipose-derived mesenchymal stem cells (ADSCs) which were extracted from streptozotocin (STZ) induced diabetic rats. Adipose tissue was extracted from the hypodermis of diabetic rats, and diabetic ADSCs were extracted, characterized, and cultured. There were two in vitro groups: control-diabetic ADSCs, and PBMT-diabeticADSCs. We used 630 nm and 810 nm laser at 1.2 J/cm 2 with 3 applications 48 h apart. We measured cell viability, apoptosis, population doubling time (PDT), and reactive oxygen species (ROS) by flow cytometry. Gene expression of antioxidants, including cytosolic copper-zinc superoxide dismutase (SOD1), catalase (CAT), total antioxidant capacity (TAC), and oxidative stress biomarkers (NADPH oxidase 1 and 4) by quantitative real time (qRT) - PCR. In this study, data were analyzed using t-test. Viability of PBMT-diabetic- ADSC group was higher than control- diabetic-ADSC ($p = 0.000$). PDT and apoptosis of PBMT- diabetic-ADSC group were lower than control-diabetic -ADSC ($p = 0.001$, $p = 0.02$). SOD1 expression and TAC of PBMT- diabetic-ADSC group were higher than control -diabetic -ADSC ($p = 0.018$, $p = 0.005$). CAT of PBMT -diabetic-ADSC group was higher than control-diabetic -ADSC. ROS, NOX1, and NOX4 of PBMT- diabetic -ADSC group were lower than control-diabetic-ADSC ($p = 0.002$, $p = 0.021$, $p = 0.017$). PBMT may improve diabetic- ADSC function in vitro by increasing levels of cell viability, and gene expression of antioxidant agents (SOD1, CAT, and TAC), and significantly decreasing of levels of PDT, apoptosis, ROS, and gene expression of oxidative stress biomarkers (NOX1 and NOX4).

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Low-level laser irradiation enhances the proliferation and osteogenic differentiation of PDLSCs via BMP signaling.

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The aim of this in vitro study was to evaluate the effects of low-level laser therapy (LLLT) at different energy intensities on proliferation and osteogenesis of periodontal ligament stem cells (PDLSCs). We designed one control group, without irradiation and four testing groups, treated with LLLT (Nd:YAG;1064 nm) at 2, 4, 6, and 8 J/cm2 for human PDLSCs. Cell proliferation was measured using colony-forming unit fibroblast assay and 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide assay. Osteogenic capacity of cells was determined by alkaline phosphatase (ALP) staining, ALP activity assay, Alizarin Red S staining, and the gene levels of runt-related transcription factor 2 (Runx2), ALP, osteocalcin, and bone morphogenetic protein 2 (BMP2). The effects of LLLT on secretion of TNF-α and IL-1β in PDLSCs were measured by enzyme-linked immunosorbent assay. BMP/Smad pathway was measured through the expression of Smad1/5/8 phosphorylation (P-Smad1/5/8). LDN-193189, an inhibitor of the BMP/Smad pathway, was used to explore the underlying effects of BMP/Smad signaling on the process of LLLT regulating the proliferation and osteogenesis of PDLSCs. Our results demonstrated LLLT could promote the proliferation and osteogenesis of PDLSCs at 2-6 J/cm2 and LLLT at 8 J/cm2 significantly suppress osteogenic differentiation of PDLSCs. Moreover, LLLT stimulated the secretion of TNFα and IL-β1. Finally, we found the irradiation positively modulates the P-Smad1/5/8 level. When the cells were treated with LDN-193189, the proliferation and osteogenic effects of LLLT on PDLSCs were attenuated. In conclusion, LLLT may upregulate the proliferation and bone formation ability of PDLSCs via the BMP/Smad signaling.

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Influence of photobiomodulation and vitamin D on osteoblastic differentiation of human periodontal ligament stem cells and bone-like tissue formation through enzymatic activity and gene expression.

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Background: (1)Human periodontal ligament stem cells (HPDLSCs) are a unique population of mesenchymal stem cells (MSCs). Recently, the positive effects of photobiomodulation on the regulation of MSCs proliferation and osteogenic differentiation have gained significant attention. This study aimed to assess the effects of photobiomodulation and vitamin D (as an anabolic factor) on HPDLSCs for bone regeneration.
Methods: (2)HPDLSCs were collected, isolated, and characterized and then divided into six groups: groups I and II, control and (10-7 Mol) vitamin D, respectively; group III, irradiation at 1 J/cm2 of 808-nm diode laser; group IV, irradiation at 1 J/cm2 and culture with vitamin D; group V, irradiation at 2 J/cm2, and group VI, irradiation at 2 J/cm2 and culture with vitamin D. Cell viability assay was measured through MTT assay and cell growth curve. Alkaline phosphatase (ALP) enzyme activity and mRNA levels of RUNX2, collagen 1 (Col-1), ALP, and osteonectin were also assessed.
Results: (3)Photobiomodulation at 1 and 2 J/cm2 combined with vitamin D significantly promoted HPDLSC proliferation (in MTT assay and cell growth curve results) and osteogenic differentiation (through the gene expression of RUNX2, Col-1, ALP, and osteonectin levels ($p < 0.05$).
Conclusion: (4)Laser irradiation at 2 J/cm2 combined with vitamin D3 enhanced osteoblast differentiation and proliferation of cultured HPDLSCs and thus could further substitute bone grafting.

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The impact of photobiomodulation on the chondrogenic potential of adipose-derived stromal/stem cells.

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Due to their capacity to differentiate into the chondrogenic lineage, adipose-derived stromal/stem cells (ASC) are a promising source of therapeutically relevant cells for cartilage tissue regeneration. Their differentiation potential, however, varies between patients. In our study, we aim to stimulate ASC towards a more reliable chondrogenic phenotype using photobiomodulation (PBM). LED devices of either blue (475 nm), green (516 nm) or red (635 nm) light were used to treat human ASC from donors of varying chondrogenic potential. The treatment was applied either once during the 2D expansion phase or repeatedly during the 3D differentiation phase. Chondrogenic differentiation was assessed via pellet size, GAG/DNA content, histology and gene expression analysis. Reactions to PBM were found to be wavelength-dependent and more pronounced when the treatment was applied during expansion. Donors were assigned to responder categories according to their response to the treatment during expansion, whereby good responders were mainly donors with low intrinsic chondrogenic potential. Exposed to light, they revealed a particularly high relative increase in pellet size (more than twice the size of untreated controls after red light PBM), intense collagen type II immunostaining (low/absent in untreated controls) and activation of otherwise absent COL2A1 expression. Conversely, on a donor with high intrinsic chondrogenic potential, light had adverse effects. When applied with shorter wavelengths (blue, green), it led to reduced pellet size, GAG/DNA content and collagen type II immunostaining. However, when PBM was applied in 3D, the same donor was the only one to react with increased differentiation to all three wavelengths. We were able to demonstrate that PBM can be used to enhance or hamper chondrogenesis of ASC, and that success depends on treatment parameters and intrinsic cellular potential. The improvement of chondrogenesis in donors with low intrinsic potential highlights PBM as potent tool for cell-based cartilage regeneration. Its cost-effectiveness and ease of use make for an attractive treatment option to enhance the performance of ASC in cartilage tissue engineering.

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Photobiomodulation has rejuvenating effects on aged bone marrow mesenchymal stem cells.

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The plasticity and proliferative capacity of stem cells decrease with aging, compromising their tissue regenerative potential and therapeutic applications. This decline is directly linked to mitochondrial dysfunction. Here, we present an effective strategy to reverse aging of mouse bone marrow mesenchymal stem cells (BM-MSCs) by restoring their mitochondrial functionality using photobiomodulation (PBM) therapy. Following the characterization of young and aged MSCs, our results show that a near-infrared PBM treatment delivering 3 J/cm 2 is the most effective modality for improving mitochondrial functionality and aging markers. Furthermore, our results unveil that young and aged MSCs respond differently to the same modality of PBM: whereas the beneficial effect of a single PBM treatment dissipates within 7 h in aged stem cells, it is lasting in young ones. Nevertheless, by applying three consecutive treatments at 24-h intervals, we were able to obtain a lasting rejuvenating effect on aged MSCs. Our findings are of particular significance for improving autologous stem cell transplantation in older individuals who need such therapies most.

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Photoactivation of TGFβ/SMAD signaling pathway ameliorates adult hippocampal neurogenesis in Alzheimer's disease model.

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Amyloid precursor protein/presenilin 1 (APP/PS1) mice were treated with photobiomodulation therapy (PBMT) for 0.1 mW/mm 2 per day in the dark for 1 month (10 min for each day). The neural stem cells (NSCs) were isolated from hippocampus of APP/PS1 transgenic mice at E14, and the cells were treated with PBMT for 0.667 mW/mm 2 in the dark (5 min for each time).

In this study, photobiomodulation therapy (PBMT) is found to promote AHN in APP/PS1 mice. The latent transforming growth factor-β1 (LTGFβ1) was activated in vitro and in vivo during PBMT-induced AHN, which promoted the differentiation of hippocampal APP/PS1 NSCs into newborn neurons. In particular, behavioral experiments showed that PBMT enhanced the spatial learning/memory ability of APP/PS1 mice. Mechanistically, PBMT-stimulated reactive oxygen species (ROS) activates TGFβ/Smad signaling pathway to increase the interaction of the transcription factors Smad2/3 with Smad4 and competitively reduce the association of Smad1/5/9 with Smad4, thereby significantly upregulating the expression of doublecortin (Dcx)/neuronal class-III β-tubulin (Tuj1) and downregulating the expression of glial fibrillary acidic protein (GFAP). These in vitro effects were abrogated when eliminating ROS. Furthermore, specific inhibition of TGFβ receptor I (TGFβR I) attenuates the DNA-binding efficiency of Smad2/3 to the Dcx promotor triggered by PBMT.

Our study demonstrates that PBMT, as a viable therapeutic strategy, directs the adult hippocampal APP/PS1 NSCs differentiate towards neurons, which has great potential value for ameliorating the drop of AHN in Alzheimer's disease mice.

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Photobiomodulation therapy for hair regeneration: A synergetic activation of β-CATENIN in hair follicle stem cells by ROS and paracrine WNTs.

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Photobiomodulation therapy (PBMT) has shown encouraging results in the treatment of hair loss. However, the mechanism by which PBMT controls cell behavior to coordinate hair cycle is unclear. Here, PBMT is found to drive quiescent hair follicle stem cell (HFSC) activation and alleviate hair follicle atrophy. Mechanistically, PBMT triggers a new hair cycle by upregulating β-CATENIN expression in HFSCs. Loss of β-Catenin (Ctnnb1) in HFSCs blocked PBMT-induced hair regeneration. Additionally, we show PBMT-induced reactive oxygen species (ROS) activate the PI3K/AKT/GSK-3β signaling pathway to inhibit proteasome degradation of β-CATENIN in HFSCs. Furthermore, PBMT promotes the expression and secretion of WNTs in skin-derived precursors (SKPs) to further activate the β-CATENIN signal in HFSCs. By contrast, eliminating ROS or inhibiting WNT secretion attenuates the activation of HFSCs triggered by PBMT. Collectively, our work suggests that PBMT promotes hair regeneration through synergetic activation of β-CATENIN in HFSCs by ROS and paracrine WNTs by SKPs.

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Photobiomodulation of mineralisation in mesenchymal stem cells.

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Mesenchymal stem cells (MSCs) and photobiomodulation (PBM) both offer significant therapeutic potential in regenerative medicine. MSCs have the ability to self-renew and differentiate; giving rise to multiple cellular and tissue lineages that are utilised in repair and regeneration of damaged tissues. PBM utilises light energy delivered at a range of wavelengths to promote wound healing. The positive effects of light on MSC proliferation are well documented; and recently, several studies have determined the outcomes of PBM on mineralised tissue differentiation in MSC populations. As PBM effects are biphasic, it is important to understand the underlying cellular regulatory mechanisms, as well as, provide accurate details of the irradiation conditions, to optimise and standardise outcomes. This review article focuses on the use of red, near-infra-red (R/NIR) and blue wavelengths to promote the mineralisation potential of MSCs; and also reports on the possible molecular mechanisms which underpin transduction of these effects. A variety of potential photon absorbers have been identified which are reported to mediate the signalling mechanisms, including respiratory chain enzymes, flavins, and cryptochromes. Studies report that R/NIR and blue light stimulate MSC differentiation by enhancing respiratory chain activity and increasing reactive oxygen species levels; however, currently, there are considerable variations between irradiation parameters reported. We conclude that due to its non-invasive properties, PBM may, following optimisation, provide an efficient therapeutic approach to clinically support MSC-mediated hard tissue repair. However, to optimise application, further studies are required to identify appropriate light delivery parameters, as well as elucidate the photo-signalling mechanisms involved.

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The effect of LED photobiomodulation on the proliferation and osteoblastic differentiation of periodontal ligament stem cells: in vitro.

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PDLSCs seeded on 96- and 24-well plates, for proliferation and osteoblastic differentiation, respectively, were irradiated daily by LED light with peak emission wavelengths of 630, 680, and 830 nm at constant energy densities of 3.5 J/cm 2. Cultures were grown for 8 days for the proliferation assay, 10 days for the alkaline phosphatase (ALP) assay, and 28 days for Alizarin red staining. Mitochondrial activity, ALP enzyme level, and the ability to form calcium phosphate deposits were measured and compared across cultures.

Results obtained from statistical analysis of the experimental data indicated that the rate of proliferation (P < 0.05) in 830-nm irradiated cultures were significantly higher than the control samples at day 6 and 8; whereas, for the 630- and 680-nm groups, test results showed lower proliferation rates at day 8. For osteoblastic differentiation, significantly greater mineralization than the control samples was detected in the red-light groups (630 and 680 nm) during the late differentiation period (P < 0.001), which was supported by a higher ALP activity of the 630- and 680-nm groups in the early stage (P < 0.01).

The results of this study demonstrate that the PDLSCs responded differently to specific LED wavelengths. For enhancing cellular proliferation, 830-nm LED irradiation was more effective. On the other hand, the wavelengths of 630 and 680 nm were better for stimulating osteoblastic differentiation.

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Photobiomodulation combined with adipose-derived stem cells encapsulated in methacrylated gelatin hydrogels enhances in vivo bone regeneration.

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Reconstruction of bone defects is still a significant challenge. The aim of this study was to evaluate the effect of application of photobiomodulation (PBM) to enhance in vivo bone regeneration and osteogenic differentiation potential of adipose-derived stem cells (ADSCs) encapsulated in methacrylated gelatin (GEL-MA) hydrogels. Thirty-six Sprague-Dawley rats were randomly separated into 3 experimental groups (n = 12 each). The groups were control/blank defect (I), GEL-MA hydrogel (II), and ADSC-loaded GEL-MA (GEL-MA+ADSC) hydrogel (III). Biparietal critical sized bone defects (6 mm in size) are created in each animal. Half of the animals from each group (n = 6 each) were randomly selected for PBM application using polychromatic light in the near infrared region, 600-1200 nm. PBM was administered from 10 cm distance cranially in 48 h interval. The calvaria were harvested at the 20th week, and macroscopic, microtomographic, and histologic evaluation were performed for further analysis. Microtomographic evaluation demonstrated the highest result for mineralized matrix formation (MMF) in group III. PBM receiving samples of group III showed mean MMF of 79.93±3.41%, whereas the non-PBM receiving samples revealed mean MMF of 60.62±6.34 % (p=0.002). In terms of histologic evaluation of bone defect repair, the higher scores were obtained in the groups II and III when compared to the control group (2.0 for both PBM receiving and non-receiving specimens; p;0.001). ADSC-loaded microwave-induced GEL-MA hydrogels and periodic application of photobiomodulation with polychromatic light appear to have beneficial effect on bone regeneration and can stimulate ADSCs for osteogenic differentiation.

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Photobiomodulation: An Effective Approach to Enhance Proliferation and Differentiation of Adipose-Derived Stem Cells into Osteoblasts.

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Osteoporosis is regarded as the most common chronic metabolic bone condition in humans. In osteoporosis, bone mesenchymal stem cells (MSCs) have reduced cellular function. Regenerative medicine using adipose-derived stem cell (ADSC) transplantation can promote the growth and strength of new bones, improve bone stability, and reduce the risk of fractures. Various methods have been attempted to differentiate ADSCs to functioning specialized cells for prospective clinical application. However, commonly used therapies have resulted in damage to the donor site and morbidity, immune reactions, carcinogenic generation, and postoperative difficulties. Photobiomodulation (PBM) improves ADSC differentiation and proliferation along with reducing clinical difficulties such as treatment failures to common drug therapies and late initiation of treatment. PBM is a noninvasive, nonthermal treatment that encourages cells to produce more energy and to undergo self-repair by using visible green and red and invisible near-infrared (NIR) radiation. The use of PBM for ADSC proliferation and differentiation has been widely studied with multiple outcomes observed due to laser fluence and wavelength dependence. In this article, the potential for differentiating ADSCs into osteoblasts and the various methods used, including biological induction, chemical induction, and PBM, will be addressed. Likewise, the optimal laser parameters that could improve the proliferation and differentiation of ADSC, translating into clinical success, will be commented on.

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470 nm LED Irradiation Inhibits the Invasiveness of CD133-positive Human Colorectal Cancer Stem Cells by Suppressing the Cyclooxygenase-2/prostaglandin E2 Pathway.

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The effects of blue LEDs on their viability, proliferation and invasion were analyzed using MTT and transwell methods. In addition, the anti-invasiveness effect of blue LED on them was evaluated by zymography, semi-quantitative RT-PCR and western blot analysis.

Irradiation with blue LED at 3 J/cm 2 resulted in inhibition of their viability, proliferation and invasiveness. Their matrix metalloproteinase 2 (MMP-2) and MMP-9 activities were reduced by blue LED irradiation. Semi-quantitative RT-PCR also showed similar results. In addition, western blotting analyses showed that cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) synthesis were significantly inhibited by LED irradiation in CD133 + colorectal CSCs.

Down-regulation of the COX-2/PGE2 signaling pathway by blue LED irradiation led to reduce expression of MMP -2 and MMP-9, inhibiting the invasiveness of CD133 + colorectal CSC.

Anticancer Res, 2021 Mar 41(3) 1407-1420

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Near-infrared 940-nm diode laser photobiomodulation of inflamed periodontal ligament stem cells.

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Photobiomodulation (PBM) is an acceptable method of stimulating stem cells through its non-invasive absorption by the cell photoreceptors and the induction of cellular response. The current research was aimed at evaluating the effect of near-infrared PBM on proliferation and osteogenic differentiation in inflamed periodontal ligament stem cells (I-PDLSCs). I-PDLSCs were isolated and characterized. Third passage cells were irradiated with 940-nm laser at an output power of 100 mW in a continuous wave. A fluence of 4 J/cm 2 in three sessions at 48-h intervals was applied and compared with non-irradiated controls. Cell viability and proliferation were evaluated by MTT assay. Alkaline phosphatase activity, quantitative Alizarin red staining test, and q-RT-PCR were used to evaluate the osteogenic properties of the I-PDLSCs in four groups of (a) osteogenic differentiation medium + laser (ODM + L), (b) osteogenic differentiation medium without laser (ODM), (c) non-osteogenic differentiation medium + laser (L), and (d) non-osteogenic differentiation medium (control). There was a non-significant increase in the viability of cells at 48- and 72-h post last laser irradiation. Alizarin red staining revealed no significant stimulatory effect of PBM at 14 and 21 days. However, alkaline phosphatase activity was significantly higher in the L + ODM group. Expression of osteogenic-related genes had a statistically significant increase at 21-day post irradiation. The irradiation used in the present study showed no significant increase in the proliferation of I-PDLSCs by PBM. However, expression levels of osteogenic-related genes and alkaline phosphatase activity were significantly increased in irradiated groups.

Lasers Med Sci, 2021 Mar

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Low-intensity photobiomodulation at 632.8 nm increases tgfβ3, col2a1, and sox9 gene expression in rat bone marrow mesenchymal stem cells in vitro.

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The high incidence of cartilage destructions, as well as the social and economic importance of this pathology attracted great interest to the problem. At the present time, some data are available about the 632.8 nm low-intensity laser photobiomodulation positive effect on the cartilage tissue proliferation. The effect of this wavelength laser irradiation on the mesenchimal stem cell (MSC) differentiation in the chondrogenic direction was studied. The main aim of this work was to assess the low-intensity photobiomodulation effect on chondrogenesis. In this experiment, the cell model was used to compare the photobiomodulation and cytokine Tgfβ3 (transforming growth factor β 3) effects. Bone marrow MSCs were isolated from Wistar rats and cultured for the third passage. Chondrogenic effects of low-intensity He-Ne laser photobiomodulation and cytokine Tgfβ3 (10 ng/μL) were analyzed and compared after 21 days. The radiation source was the standard LGN-208 helium-neon (He-Ne) laser (632.8 nm, 1.7 mWt). Irradiation was performed cyclically for 15 min with 45-min pauses. The increase of the responsible for chondrogenesis (col2a1, tgfβ3, and sox9) main gene expression under the photobiomodulation at 632.8 nm was evaluated in comparison with Tgfβ3 effect. The tgfβ3, col2a1, and sox9 gene expression increase was obtained in two experimental groups: using the laser photobiomodulation and cytokine Tgfβ3 effect. Gene expression levels of tgfβ3, col2a1, and sox9 were measured using real-time polymerase chain reaction (RT-PCR) according to the -ΔΔCt method. It was found that the responsible for chondrogenesis genes expression (tgfβ3, col2a1, sox9) increased under the action of specific laser photobiomodulation during the observation period (from 0 to 21 days). The chondrogenic differentiation effect under the laser irradiation is less significant than Tgfβ3 cytokine effect.

Lasers Med Sci, 2021 Feb

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Enhancement of Wound Healing by Conditioned Medium of Adipose-Derived Stromal Cell with Photobiomodulation in Skin Wound.

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ASC were split and seeded on chitosan-coated 24 well plate at a density of 7.5×10 4 cells/cm 2, and allowed to adhere at 37°C. Within 3 days of culture, ASC formed spheroids by PBM irradiation. Conditioned medium (CM) fractions were collected from the PBM-ASC to yield nor adipose-derived stromal cell spheroid (spheroid) and PBM-spheroid, respectively, centrifuged at 13,000 g at 4°C for 10 min, and stored prior to use for ELISA, protein assay, or in vivo wound-healing assays. Phosphate-buffered saline, cultured CM from ASCs, PBM irradiation prior to implanting conditioned medium from ASC, cultured CM from ASC spheroid, and PBM-spheroid-CM (PSC) were transplanted into a wound bed in athymic mice to evaluate therapeutic effects of PSC in vivo. PSC enhanced wound closure in a skin injury model compared to PBS, CM, PBM-CM, and spheroid-CM. The density of vascular formations increased as a result of angiogenic factors released by the wound bed and enhanced tissue regeneration at the lesion site.

These results indicate that implant of PSC can significantly improve functional recovery compared to PBS, CM, PBM-CM, or spheroid-CM treatment. Implant of PSC may be an effective form of paracrine mediated therapy for treating a wound bed.

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Enhancing the Therapeutic Potential of Mesenchymal Stem Cells with Light-Emitting Diode: Implications and Molecular Mechanisms.

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This study evaluated the effects of light-emitting diode (LED) on mesenchymal stem cells (MSCs). An electronic search was conducted in PubMed/MEDLINE, Scopus, and Web of Science database for articles published from 1980 to February 2020. Ten articles met the search criteria and were included in this review. The risk of bias was evaluated to report quality, safety, and environmental standards. MSCs were derived from adipose tissue, bone marrow, dental pulp, gingiva, and umbilical cord. Protocols for cellular irradiation used red and blue light spectrum with variations of the parameters. The LED has been shown to induce greater cellular viability, proliferation, differentiation, and secretion of growth factors. The set of information available leads to proposing a complex signaling cascade for the action of photobiomodulation, including angiogenic factors, singlet oxygen, mitogen-activated protein kinase/extracellular signal-regulated protein kinase, Janus kinase/signal transducer, and reactive oxygen species. In conclusion, although our results suggest that LED can boost MSCs, a nonuniformity in the experimental protocol, bias, and the limited number of studies reduces the power of systematic review. Further research is essential to find the optimal LED irradiation parameters to boost MSCs function and evaluate its impact in the clinical setting.

Oxid Med Cell Longev, 2021 2021 6663539

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Photobiomodulation with a wavelength > 800 nm induces morphological changes in stem cells within otic organoids and scala media of the cochlea.

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Photobiomodulation (PBM) is a therapeutic approach to certain diseases based on light energy. Currently, stem cells (SCs) are being considered as putative treatments for previously untreatable diseases. One medical condition that could be treated using SCs is sensorineural hearing loss. Theoretically, if properly delivered and differentiated, SCs could replace lost hair cells in the cochlea. However, this is not currently possible due to the structural complexity and limited survival of SCs within the cochlea. PBM facilitates SC differentiation into other target cells in multiple lineages. Using light with a wavelength > 800 nm, which can penetrate the inner ear through the tympanic membrane, we assessed morphological changes of mouse embryonic stem cells (mESCs) during "otic organoid" generation, and within the scala media (SM) of the cochlea, after light energy stimulation. We observed enhanced differentiation, which was confirmed by an increased number of otic vesicles and increased cell attachment inside the SM. These results suggest that > 800-nm light affected the morphology of mESCs within otic organoids and SM of the cochlea. Based on our results, light energy could be used to enhance otic sensory differentiation, despite the structural complexity of the inner ear and limited survival time of SCs within the cochleae. Additional studies to refine the light energy delivery technology and maximize the effect on otic differentiation are required.

Lasers Med Sci, 2021 Feb

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Physical and Biological Properties of a Chitosan Hydrogel Scaffold Associated to Photobiomodulation Therapy for Dental Pulp Regeneration: An In Vitro and In Vivo Study.

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For the in vitro analysis, stem cells from the apical papilla (SCAPs) were characterized by flow cytometry and applied in the chitosan scaffold for evaluating adhesion, migration, and proliferation. For the in vivo analysis, the chitosan scaffold was applied in a rodent orthotopic dental pulp regeneration model under the influence of PBMT (660 nm; power output of 20 mW, beam area of 0.028 cm 2, and energy density of 5 J/cm 2).

The scaffold tested in this study allowed significantly higher viability, proliferation, and migration of SCAPs in vitro when PBMT was applied, especially with the energy density of 5 J/cm 2. These results were in consonance to those of the in vivo data, where pulp-like tissue formation was observed inside the root canal.

Chitosan hydrogel when applied with a blood clot and PBMT could in the future improve previous results of dental pulp regeneration through cell homing approaches.

Biomed Res Int, 2021 2021 6684667

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In Vitro Wound Healing Potential of Photobiomodulation Is Possibly Mediated by Its Stimulatory Effect on AKT Expression in Adipose-Derived Stem Cells.

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Increasing evidence suggests that adipose-derived stem cells (ADSCs) serve as a therapeutic approach for wound healing. The aim of this study was to determine the effect of photobiomodulation (PBM) on antioxidant enzymes in ADSCs. Four ADSC cell models, namely, normal, wounded, diabetic, and diabetic wounded, were irradiated with 660 nm (fluence of 5 J/cm 2 and power density of 11.2 mW/cm 2) or 830 nm (fluence of 5 J/cm 2 and power density of 10.3 mW/cm 2). Nonirradiated cells served as controls. Cell morphology and wound migration were determined using light microscopy. Cell viability was determined by the trypan blue exclusion assay. The enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of antioxidants (superoxide dismutase (SOD), catalase (CAT), and heme oxygenase (HMOX1)). AKT activation and FOXO1 levels were determined by immunofluorescence and western blotting. The gaps (wound) in PBM-treated wounded and diabetic wounded cell models closed faster than the controls. PBM treatment significantly increased antioxidant levels in all cell models. This reflects that oxidative stress is reduced on the counterpart of increased antioxidant levels. This might be due to the activation of the AKT signaling pathway as evidenced by the increased AKT signals via western blotting and immunofluorescence. This data suggests that PBM promotes wound healing by increasing antioxidant levels by activating AKT signaling.

Oxid Med Cell Longev, 2021 2021 6664627

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Effect of mesenchymal stem cells injection and low-level laser therapy on bone formation after rapid maxillary expansion: an animal study.

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Total of 60 rats went under RPE treatment. After 7 days, retention period started and interventions (group A, Control (saline); group B, LLLT; group C, BMSCs; group D, LLLT + BMSCs) were performed in the sutural area. After 21 days, radiographic and histological analyses were done. Histological analyses were conducted to evaluate the following criteria of the newly formed bone: the number of osteoblasts, new bone formation, vascularization, connective tissue. Moreover, sutural width was assessed in histologic images. To evaluate bone density at suture area, gray scale and Hounsfield Unit values were measured based on the occlusal radiographic and Micro-Computed topography images respectively.

Only in group C and D, osteoblasts and new bone formation were observed in all of the samples. There were no significant differences among the study groups regarding the post-treatment sutural width (P > 0.05). In the radiographic analysis, only group D showed more bone density compared to the control group (P = 0.022). Similarly, in micro-CT analysis, the most bone density was observed in group D which was significantly more than the control group (P = 0.013).

Our findings suggest that the application of LLLT and BMSCs is the most beneficial approach in accelerating bone regeneration in the inter-maxillary suture.

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Synergistic effect of three-dimensional coculture and photobiomodulation therapy on vascularized liver spheroid formation by stem cells.

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Despite studies reporting functional differentiation of liver cells, a three-dimensional, vascularized liver organ has yet to be developed from mesenchymal stem cells. We investigated whether treatment with photobiomodulation (PBM) before three-dimensional liver spheroid transplantation improved the recovery of liver function via stimulation of angiogenesis and hepatocyte differentiation. Liver spheroids composed of hepatic, endothelial, and mesenchymal cells were subjected to PBM therapy. To evaluate the in vivo therapeutic effect of the liver spheroids treated with PBM, phosphate-buffered saline, liver spheroid, and PBM-treated liver spheroid were transplanted into a damaged host liver using conventional chimeric mouse models. To further characterize the maturation of transplanted PBM-liver spheroid compared with the newly generated non-PBM-liver spheroid or human liver tissues, the expression profiles of mature liver signature genes were analyzed. Liver spheroids expressed hepatocyte growth factors, including vascular endothelial growth factor and angiogenic factors. The cells in liver spheroid compensated for the low viability and improved the function of hepatocytes. Here, we demonstrate the formation of vascularized and functional human liver spheroid from human adipose-derived stem cells by transplantation of liver tissue created in vitro. Albumin secretion by PBM-treated liver spheroid was higher on Day 28 compared with liver spheroid-seeded transplant group. PBM-liver spheroids serve as individual vascularization units, promoting the simultaneous development of new microvascular networks at different locations inside the implanted tissue constructs. The vasculature in the liver spheroid transplants became functional by connecting to the host vessels within 48 h. These PBM-liver spheroids may be useful in designing artificial three-dimensional hepatic tissue constructs and in cell therapy with limited numbers of human hepatocytes.

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Photobiomodulation Therapy in the Proliferation and Differentiation of Human Umbilical Cord Mesenchymal Stem Cells: An In Vitro Study.

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Introduction: Since photobiomodulation therapy (PBMT) favors in vitro mesenchymal stem cell (MSC) preconditioning before MSC transplantation, increasing the proliferation of these cells without molecular injuries by conserving their characteristics, in the present in vitro study we analyzed the effect of PBMT on the proliferation and osteogenic differentiation of human umbilical cord mesenchymal stem cells (hUCMSCs).
Methods: Irradiation with an InGaAlP Laser (660 nm, 10 mW, 2.5 J/cm 2 , 0.08 cm 2 spot size, and 10 s) was carried out. The cells were divided into four groups: CONTROL [cells grown in Dulbecco's Modified Eagle Medium (DMEM)], OSTEO (cells grown in an osteogenic medium); PBMT (cells grown in DMEM+PBMT), and OSTEO+PBMT (cells grown in an osteogenic medium plus PBMT). The cell proliferation curve was obtained over periods of 24, 48 and 72 hours using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay. Osteogenic differentiation was analyzed by the formation of calcium nodules over periods of 7, 14 and 21 days. Morphometric analysis was performed to quantify the total area of nodular calcification.
Results: The highest cell proliferation and cell differentiation occurred in the OSTEO+PBMT group, followed by the PBMT, OSTEO and CONTROL groups respectively, at the observed times (P ;0.05). Conclusion: PBMT enhanced the osteogenic proliferation and the differentiation of hUCMSCs during the periods tested, without causing damage to the cells and preserving their specific characteristics, a fact that may represent an innovative pretreatment in the application of stem cells.

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Dental infection associated with exuberant gingival necrosis in a patient with paroxysmal nocturnal hemoglobinuria: A case report.

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Paroxysmal nocturnal hemoglobinuria (PNH) is a hematological disorder that affects hematopoietic stem cells. An association with other hematological diseases, such as hemolytic anemia and neutropenia, is observed with a high occurrence of aplastic anemia. The aim of the present study is to report a case of dental infection in a patient with PNH exhibiting exuberant gingival involvement. A 45-year-old male patient sought the Federal University of Ceara reporting severe toothache associated with tooth 24. Clinical examination revealed that the tooth was associated with an apparent fistula and a yellowish lesion with smooth surface located in the palate. The patient had interrupted the medication to control PNH. Blood transfusion was requested due to deficient hematological parameters. Tooth extraction and excisional biopsy were performed under antibiotic coverage. In the postoperative period, low-level laser therapy (LLLT) was performed. Histopathological examination revealed connective tissue showing extensive necrotic areas, accumulation of basophilic material, numerous cyst-like cavities, and degenerated cells. Histopathological findings were compatible with the initial clinical diagnosis of gingival necrosis. The patient evolved with febrile neutropenia, requiring hospitalization for 1 month. Improvement in the overall health was observed after the administration of antibiotics, eculizumab, and weekly LLLT at the biopsy site.

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The Effect of Laser Photobiomodulation on Periodontal Ligament Stem Cells.

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Photobiomodulation (PBM) is considered as a noninvasive procedure with the potential of inducing favorable changes in cellular behavior. In this study, we aimed to evaluate the effects of near-infrared low-intensity laser PBM on proliferation, viability and osteogenic differentiation of stem cells isolated from human periodontal ligament. A 940-nm diode laser with an energy density of 4 J cm -2 in a 100-mW continuous wave was used for irradiation in 3 sessions every 48h. Cell viability was measured 24, 48 and 72 h after irradiation. The effects of laser on mineralized tissue deposition were evaluated by using Alizarin red staining after dividing cells into three groups of nonosteogenic medium (C-), an osteogenic medium without laser (C+), and an osteogenic medium with laser irradiation (L+). Gene expression levels were also evaluated by real-time PCR. Our results showed no significant difference between MTT levels of the study and control groups. After 14 and 21 days, both L+ and C+ groups showed an increase in mineralized tissue formation compared to the C- group. There was an increase in VEGF and BMP expressions compared to C-. In conclusion, the irradiation setting used in this study may be able to improve mineralized tissue deposition.

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In Vitro Cytological Responses against Laser Photobiomodulation for Periodontal Regeneration.

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Periodontal disease is a chronic inflammatory disease caused by periodontal bacteria. Recently, periodontal phototherapy, treatment using various types of lasers, has attracted attention. Photobiomodulation, the biological effect of low-power laser irradiation, has been widely studied. Although many types of lasers are applied in periodontal phototherapy, molecular biological effects of laser irradiation on cells in periodontal tissues are unclear. Here, we have summarized the molecular biological effects of diode, Nd:YAG, Er:YAG, Er,Cr:YSGG, and CO 2 lasers irradiation on cells in periodontal tissues. Photobiomodulation by laser irradiation enhanced cell proliferation and calcification in osteoblasts with altering gene expression. Positive effects were observed in fibroblasts on the proliferation, migration, and secretion of chemokines/cytokines. Laser irradiation suppressed gene expression related to inflammation in osteoblasts, fibroblasts, human periodontal ligament cells (hPDLCs), and endothelial cells. Furthermore, recent studies have revealed that laser irradiation affects cell differentiation in hPDLCs and stem cells. Additionally, some studies have also investigated the effects of laser irradiation on endothelial cells, cementoblasts, epithelial cells, osteoclasts, and osteocytes. The appropriate irradiation power was different for each laser apparatus and targeted cells. Thus, through this review, we tried to shed light on basic research that would ultimately lead to clinical application of periodontal phototherapy in the future.

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Transplantation of photobiomodulation-preconditioned diabetic stem cells accelerates ischemic wound healing in diabetic rats.

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There were five groups of rats: (1) control, (2) control AD-MSCs [diabetic AD-MSCs were transplanted (grafted) into the wound bed], (3) AD-MSC + photobiomodulation in vivo (diabetic AD-MSCs were grafted into the wound, followed by in vivo PBM treatment), (4) AD-MSCs + photobiomodulation in vitro, and (5) AD-MSCs + photobiomodulation in vitro + in vivo.

Diabetic AD-MSCs preconditioned with photobiomodulation had significantly risen cell function compared to diabetic AD-MSC. Groups 3 and 5 had significantly decreased microbial flora correlated to groups 1 and 2 (all, p = 0.000). Groups 2, 3, 4, and 5 had significantly improved wound closure rate (0.4, 0.4, 0.4, and 0.8, respectively) compared to group 1 (0.2). Groups 2-5 had significantly increased wound strength compared to group 1 (all p = 0.000). In most cases, group 5 had significantly better results than groups 2, 3, and 4.

Preconditioning diabetic AD-MSCs with photobiomodulation in vitro plus photobiomodulation in vivo significantly hastened healing in the diabetic rat model of an ischemic infected delayed healing wound.

Stem Cell Res Ther, 2020 11 11(1) 494

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Recovering the osteoblastic differentiation potential of mesenchymal stem cells derived from diabetic rats by photobiomodulation therapy.

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Autologous cell-based therapy for bone regeneration might be impaired by diabetes mellitus (DM) due to the negative effects on mesenchymal stem cells (MSCs) differentiation. Strategies to recover their osteogenic potential could optimize the results. We aimed to evaluate the effect of photobiomodulation (PBM) therapy on osteoblast differentiation of rats with induced DM. Bone marrow MSCs of healthy and diabetic rats were isolated and differentiated into osteoblasts (OB and dOB, respectively). dOB were treated with PBM therapy every 72 hour (660 nm; 0.14 J; 20 mW; 0.714 W/cm 2 , and 5 J/cm 2). Cell morphology, viability, gene and protein expression of osteoblastic markers, alkaline phosphatase (ALP) activity, and the mineralized matrix production of dOB-PBM were compared to dOB. PBM therapy improved viability of dOB, increased the gene and protein expression of bone markers, the ALP activity and the mineralized matrix production. PBM therapy represents an innovative therapeutic approach to optimize the treatment of bone defects in diabetic patients.

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830 nm photobiomodulation therapy promotes engraftment of human umbilical cord blood-derived hematopoietic stem cells.

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Human umbilical cord blood (hUCB)-derived hematopoietic stem cells (HSCs) are an important source for HSCs in allogeneic HSC transplantation, but a limited number and a low efficacy of engraftment greatly restrict their clinical use. Here, we report the ability of photobiomodulation therapy (PBMT) to significantly enhance the engraftment efficacy of hUCB HSCs and progenitor cells (HSPCs). hUCB CD34 + cells were illuminated at a fluence of 2 J/cm 2 with a near-infrared light (830 nm) transmitted by an array of light-emitting diodes (LED) prior to infusion of NOD/SCID-IL2Rγ -/- mice. The pre-treatment resulted in a threefold higher of the mean percentage of human CD45 + cells in the periphery of the mice compared to sham-treated CD34 + cells. The enhanced engraftment may result from a PBMT-mediated increase of intracellular reactive oxygen species (ROS) levels and Src protein phosphorylation in CD34 + cells. The two events were causally related as suggested by the finding that elevation of ROS by hydrogen peroxide increased Src phosphorylation, while ROS reduction by N-acetyl cysteine partially reversed the phosphorylation. The investigation demonstrates that PBMT can promote engraftment of hUCB HPSCs, at least in part, via ROS-mediated Src signaling pathway. PBMT can be potentially a safe, convenient, and cost-effective modality to improve hematological reconstitution in patients.

Sci Rep, 2020 11 10(1) 19671

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The effects of 808-nm near-infrared laser light irradiation on actin cytoskeleton reorganization in bone marrow mesenchymal stem cells.

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Tailoring the cell organelles and thus changing cell homeostatic behavior has permitted the discovery of fascinating metabolic features enabling enhanced viability, differentiation, or quenching inflammation. Recently, photobiomodulation (PBM) has been accredited as an effective cell manipulation technique with promising therapeutic potential. In this prospective, in vitro results revealed that 808-nm laser light emitted by a hand-piece with a flat-top profile at an irradiation set up of 60 J/cm2 (1 W, 1 W/cm 2; 60 s, continuous wave) regulates bone marrow stromal cell (BMSC) differentiation toward osteogenesis. Considering the importance of actin cytoskeleton reorganization, which controls a range of cell metabolic activities, comprising shape change, proliferation and differentiation, the aim of the current work is to assess whether PBM therapy, using a flat-top hand-piece at higher-fluence irradiation on BMSCs, is able to switch photon signals into the stimulation of biochemical/differentiating pathways involving key activators that regulate de novo actin polymerization. Namely, for the first time, we unearthed the role of the flat-top hand-piece at higher-fluence irradiation on cytoskeletal characteristics of BMSCs. These novel findings meet the needs of novel therapeutically protocols provided by laser treatment and the manipulation of BMSCs as anti-inflammatory, osteo-inductive platforms.

Cell Tissue Res, 2020 Nov

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Cryptochrome 1 is modulated by blue light in human keratinocytes and exerts positive impact on human hair growth.

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Photoactivation of cryptochrome-family proteins by blue light is a well-established reaction regulating physiology of plants, fungi, bacteria, insects and birds, while impact of blue light on cryptochrome synthesis and/or activity in human non-visual cells remains unknown. Here, we show that 453 nm blue light induces cryptochrome 1 (CRY1) accumulation in human keratinocytes and the hair follicle. CRY1 is prominently expressed in the human anagen hair follicle, including epithelial stem cells. Specific silencing of CRY1 promotes catagen, while stimulation of CRY1 by KL001 prolongs anagen ex vivo by altering the expression of genes involved in apoptosis and proliferation. Together, our study identifies a role for CRY1 in sustaining human hair growth. Previously we demonstrated positive effects of 453 nm blue light on hair growth ex vivo. Taken all together, our study suggests that CRY1 might mediate blue light dependent positive effects on hair growth.

Exp Dermatol, 2020 Nov

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Laser-Induced Differentiation of Human Adipose-Derived Stem Cells to Temporomandibular Joint Disc Cells.

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After irradiation, the morphology, viability, and adenosine triphosphate (ATP) proliferation of the ADSCs were analyzed at different time intervals. The differentiation of ADSCs toward fibroblastic and chondrogenic phenotypes was supported using flow cytometry and immunofluorescence at 1- and 2-week post-irradiation.

More than 90% of viable cells were observed in all experimental groups, with an increase in ATP proliferation. Flow cytometry analyses and immunofluorescence demonstrated the presence of chondrogenic and fibroblastic cell surface markers at 1- and 2-week post-irradiation.

This study has demonstrated methods to induce the differentiation of ADSCs toward fibroblastic and chondrogenic phenotypes with a 660 nm diode laser. The study also proposes a future alternative method of treatment for patients with degenerative TMJ disc disorders and presents a positive prospect in the application of photobiomodulation and ADSCs in the treatment of degenerative TMJ disc. Lasers Surg. Med. © 2020 Wiley Periodicals LLC.

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Photobiomodulation therapy drives massive epigenetic histone modifications, stem cells mobilization and accelerated epithelial healing.

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Emerging evidence indicates the clinical benefits of photobiomodulation therapy (PBMT) in the management of skin and mucosal wounds. Here, we decided to explore the effects of different regiments of PBMT on epithelial cells and stem cells, and the potential implications over the epigenetic circuitry during healing. Scratch-wound migration, immunofluorescence (anti-acetyl-Histone H3, anti-acetyl-CBP/p300 and anti-BMI1), nuclear morphometry and western blotting (anti-Phospho-S6, anti-methyl-CpG binding domain protein 2 [MBD2]) were performed. Epithelial stem cells were identified by the aldehyde dehydrogenase enzymatic levels and sphere-forming assay. We observed that PBMT-induced accelerated epithelial migration and chromatin relaxation along with increased levels of histones acetylation, the transcription cofactors CBP/p300 and mammalian target of rapamycin. We further observed a reduction of the transcription repression-associated protein MBD2 and a reduced number of epithelial stem cells and spheres. In this study, we showed that PBMT could induce epigenetic modifications of epithelial cells and control stem cell fate, leading to an accelerated healing phenotype.

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Wound Healing and Cell Dynamics Including Mesenchymal and Dental Pulp Stem Cells Induced by Photobiomodulation Therapy: An Example of Socket-Preserving Effects after Tooth Extraction in Rats and a Literature Review.

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High-intensity laser therapy (HILT) and photobiomodulation therapy (PBMT) are two types of laser treatment. According to recent clinical reports, PBMT promotes wound healing after trauma or surgery. In addition, basic research has revealed that cell differentiation, proliferation, and activity and subsequent tissue activation and wound healing can be promoted. However, many points remain unclear regarding the mechanisms for wound healing induced by PBMT. Therefore, in this review, we present an example from our study of HILT and PBMT irradiation of tooth extraction wounds using two types of lasers with different characteristics (diode laser and carbon dioxide laser). Then, the effects of PBMT on the wound healing of bone tissues are reviewed from histological, biochemical, and cytological perspectives on the basis of our own study of the extraction socket as well as studies by other researchers. Furthermore, we consider the feasibility of treatment in which PBMT irradiation is applied to stem cells including dental pulp stem cells, the theme of this Special Issue, and we discuss research that has been reported on its effect.

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Potential of Photobiomodulation to Induce Differentiation of Adipose- Derived Mesenchymal Stem Cells into Neural Cells.

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Various strategies have been attempted to differentiate ADMSCs into neural cells for clinical use. Such methods have not been entirely successful in the development of functioning specialized cells for subsequent practical use. Therefore, the implementations of this differentiation technique in the clinical trial have not been effective. In this article, the potential of differentiating ADMSCs into neural cells and the various methods employed, including biological induction, chemical induction and photobiomodulation (PBM) will be discussed, where the combined use of transducers and PBM for neural differentiation of ADMSCs is also deliberated.

PBM shows promise as an avenue for effective ADMSCs differentiation into neural cells and their proliferation. Applying PBM with optimized biological factors and chemical inducers may prove to be an effective tool for clinical application.

Curr Stem Cell Res Ther, 2020 Sep

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Combined therapy of adipose-derived stem cells and photobiomodulation on accelerated bone healing of a critical size defect in an osteoporotic rat model.

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We investigated the impact of human demineralized bone matrix (hDBM) plus adipose-derived stem cells (hADS) plus photobiomodulation (PBM) on a critical-sized femoral defect (CSFD) in ovariectomy induced osteoporosis in rats. There were 6 groups as follows. In group 1 (control, C), only CSFDs were created. Groups 2-6 were implanted with DBM into the CSFD (DBM-CSFD). In group 2 (S), only DBM was transplanted into the CSFD. In group 3 (S + PBM), the DBM-CSFDs were treated with PBM. In group 4, the DBM-CSFDs were treated with alendronate (S + ALN). In group 5, ADSs were seeded into DBM-CSFD (S + ADS). In group 6, ADSs were seeded into DBM-CSFD and the CSFDs were treated with PBM (S + PBM + ADS). At week eight (catabolic phase of bone repair), the S + ALN, S + PBM + ADS, S + PBM, and S + ADS groups all had significantly increased bone strength than the S group (ANOVA, $p = 0.000$). The S + PBM, S + PBM + ADS, and S + ADS groups had significantly increased Hounsfield unit than the S group (ANOVA, $p = 0.000$). ALN, ADS, and PBM significantly increased healed bone strength in an experimental model of DBM-treated CSFD in the catabolic phase of bone healing in osteoporotic rats. However, ALN alone and PBM plus ADS were superior to the other protocols.

Effects of photobiomodulation on cellular viability and cancer stem cell phenotype in oral squamous cell carcinoma.

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Oral squamous cell carcinoma (OSCC) is the most common head and neck malignancy; it has been shown that cancer stem cells (CSC) are present in OSCC and associated with tumor growth, invasion, metastasis, and therapeutic resistance. Photobiomodulation (PBM) is an alternative tool for oncologic treatment adverse effects such as oral mucositis (OM); however, controversy exists regarding the undesirable effects of PBM on tumor or CSC. This study aimed to evaluate in vitro, the effects of PBM, with the same dosimetric parameters as those used in the clinic for OM prevention and treatment, on OSCC cellular viability, as well as PBM's effect on CSC properties and its phenotype. OSCC cell lines were submitted to single or daily PBM with 3 J/cm 2 and 6 J/cm 2 and then the cellular viability was evaluated by MTT, NRU (neutral red uptake), and CVS (crystal violet staining). The CSC populations were evaluated by clonogenic formation assay, flow cytometry, and RT-qPCR. The single PBM with the 3 J/cm 2 group was associated with increased cellular viability. Daily PBM with 3 J/cm 2 and 6 J/cm 2 was associated with a significant decrease in cellular viability. Additionally, daily PBM was not able to promote CSC self-renewal or the CD44 high/ESA low and CD44 high/ESA high cellular phenotypes. Moreover, a decrease in the number of spheres and in the expression of the CSC related gene BMI1 was observed after daily PBM with 6 J/cm 2. Daily PBM with 3 J/cm 2 and 6 J/cm 2 showed an inhibitory effect on cellular viability and was not able to promote the CSC self-renewal or phenotype.

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Preconditioning adipose-derived stem cells with photobiomodulation significantly increased bone healing in a critical size femoral defect in rats.

Khosravipour A, Amini A, Masteri Farahani R, Zare F, Mostafavinia A, Fallahnezhad S, Akbarzade S, Ava Parvandi M, Asgari A, Mohammadbeigi F, Rezaei SK, Ghoreishi S, Chien M, Bayat

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We assessed the combined impacts of human demineralized bone matrix (hDBM) scaffold, adipose-derived stem cells (hADS), and photobiomodulation (PBM) on bone repair of a critical size femoral defect (CSFD) in 72 rats. The rats were divided into six groups: control (group 1); ADS (group 2 - ADS transplanted into hDBM); PBM (group 3 - PBM-treated CSFDs); ADS + PBM in vivo (group 4 - ADS transplanted into hDBM and the CSFDs were treated with PBM in vivo); ADS + PBM in vitro (group 5 - ADS were treated with PBM in vitro, then seeded into hDBM); and ADS + PBM in vitro+in vivo (group 6 - PBM-treated ADS were seeded into hDBM, and the CSFDs were treated with PBM in vivo. At the anabolic phase (2 weeks after surgery), bone strength parameters of the groups 5, 6, and 4 were statistically greater than the control, ADS, and PBM in vivo groups (all, $p = 0.000$). Computed tomography (CT) scans during the catabolic phase (6 weeks after surgery) of bone healing revealed that the Hounsfield unit (HU) of CSFD in the groups 2 ($p = 0.000$) and 5 ($p = 0.019$) groups were statistically greater than the control group. The groups 5, 4, and 6 had significantly increased bone strength parameters compared with the PBM in vivo, control, and ADS groups (all, $p = 0.000$). The group 5 was statistically better than the groups 4, and 6 (both, $p = 0.000$). In vitro preconditioned of hADS with PBM significantly increased bone repair in a rat model of CSFD in vivo.

Effects of green light photobiomodulation on Dental Pulp Stem Cells: enhanced proliferation and improved wound healing by cytoskeleton reorganization and cell softening.

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Photobiomodulation (PBM) has been shown to improve cell proliferation and cell migration. Many cell types have been investigated, with most studies using deep penetrating red light irradiation. Considering the interest of surface biostimulation of oral mesenchymal cells after surgical wound, the present study aimed to assess green light irradiation effects on Dental Pulp Stem Cells' (DPSC) proliferation and migration. To understand the mechanisms underlying these effects, we investigated cytoskeleton organization and subsequent cell shape and stiffness. A 532-nm wavelength Nd:YAG laser (30 mW) was applied between 30 and 600 s on DPSC in vitro. Cell proliferation was analyzed at 24, 48, and 72 h after irradiation, by cell counting and enzymatic activity quantification (paranitrophenylphosphate phosphatase (pNPP) test). A wound healing assay was used to study cell migration after irradiation. Effects of PBM on cytoskeleton organization and cell shape were assessed by actin filaments staining. Elasticity changes after irradiation were quantified in terms of Young's modulus measured using Atomic Force Microscopy (AFM) force spectroscopy. Green light significantly improved DPSC proliferation with a maximal effect obtained after 300-s irradiation (energy fluence 5 J/cm 2). This irradiation had a significant impact on cell migration, improving wound healing after 24 h. These results were concomitant with a decrease of cells' Young's modulus after irradiation. This cell softening was explained by actin cytoskeleton reorganization, with diminution of cell circularity and more abundant pseudopodia. This study highlights the interest of green laser PMB for the proliferation and migration of mesenchymal stem cells, with encouraging results for clinical application, especially for surgical wound healing procedures.

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Comparative evaluation of low-level laser therapy on proliferation of long-term cryopreserved human dental pulp cells isolated from deciduous and permanent teeth.

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The aim of the current study was to evaluate the proliferative effect of low-level laser therapy on long-term cryopreserved dental pulp stem cells (DPSC S) and stem cells from human exfoliated deciduous teeth (SHED S). The DPSC S and SHED S were divided into 2 main groups according to gallium aluminum arsenide (GaAIAs) diode laser irradiation densities as 5 J/cm 2 and 7 J/cm 2. Each main group was further divided into 4 groups according to laser irradiation periods as 0, 24, 48, 72 h groups. During the incubation periods, cells received laser irradiation in every 24 h according to their groups and were put into incubator after irradiation. Cell groups that were not subjected to laser irradiation were served as control groups. Viabilities of cells were determined via MTT assay at the end of all incubation periods, and data were statistically analyzed. Laser irradiation demonstrated significant effects on proliferation rate of DPSCs and SHEDs in comparison with control. Intragroup comparison data of DPSC S revealed that repetitive laser irradiation for long term (72 h) increased the cellular viability significantly in comparison with all other treatment groups; however, no significant differences were found when energy densities were compared within each time interval, except for 48 h group at which irradiation with 7 J/cm 2 provided significantly higher cell viability rates of SHED S. DPSCs showed significantly higher cellular viability than SHEDs only for the 7 J/cm 2 energy density in 72 h. Longer term (72 h) repetitive laser irradiation with energy densities of 5 and 7 J/cm 2 (wavelength of 980 nm) may be recommended to induce the proliferative effect on long-term cryopreserved DPSC S and SHED S.

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Irradiation by high-intensity red light-emitting diode enhances human bone marrow mesenchymal stem cells osteogenic differentiation and mineralization through Wnt/β-catenin signaling pathway.

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Photobiomodulation therapy (PBMT) using a light-emitting diode (LED) has been employed for various photomedicine studies. The aim of this study was to determine the effects of a high-intensity red LED on the proliferation and osteogenic differentiation of human bone marrow mesenchymal stem cells (BMSCs) and the related mechanism. BMSCs were subjected to high-intensity red LED (LZ1-00R205 Deep Red LED) irradiations for 0 to 40 s with energy densities ranging from 0 to 8 J/cm 2. The distance from the LED to the cell layer was 40 mm. The spot size on the target was 4 cm 2. Cell proliferation was measured at 3, 24, 48, and 72 h. The effects of LED irradiation on osteogenic differentiation and mineralization were examined with a particular focus on the Wnt/β-catenin signaling pathway. The high-intensity red LED irradiations did not alter BMSC proliferation after 72 h. LED exposure of 6 J/cm 2 (30 s) led to significant enhancements of osteogenic differentiation and mineralization. Additionally, the high-intensity LED irradiation induced activation of Wnt/β-catenin. The effects of the high-intensity LED irradiation on BMSC osteogenic differentiation and mineralization were suppressed by treatment with the Wnt/β-catenin inhibitor XAV939. P ; 0.05 was considered significant. The results indicate that high-intensity red LED irradiation increases BMSC osteogenic differentiation and mineralization via Wnt/β-catenin activation. Therefore, short duration irradiation with a portable high-intensity LED may be used as a potential approach in hard tissue regeneration therapy.

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Effects of photobiomodulation combined with MSCs transplantation on the repair of spinal cord injury in rat.

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Stem cell transplantation has shown promising regenerative effects against neural injury, and photobiomodulation (PBM) can aid tissue recovery. This study aims to evaluate the therapeutic effect of human umbilical cord mesenchymal stem cells (hUCMSCs) and laser alone or combined on spinal cord injury (SCI). The animals were divided into SCI, hUCMSCs, laser treatment (LASER) and combination treatment (hUCMSCs + LASER) groups. Cell-enriched grafts of hUCMSCs (1 × 10 6 cells/ml) were injected at the site of antecedent trauma in SCI model rats. A 2 cm 2 damaged area was irradiated with 630 nm laser at 100 mW/cm 2 power for 20 min. Locomotion was evaluated using Basso-Beattie-Bresnahan (BBB) scores, and neurofilament repair were monitored by histological staining and diffusion tensor imaging (DTI). First, after SCI, the motor function of each group was restored with different degrees, the combination treatment significantly increased the BBB scores compared to either monotherapy. In addition, Nissl bodies were more numerous, and the nerve fibers were longer and thicker in the combination treatment group. Consistent with this, the in situ expression of NF-200 and glial fibrillary acidic protein in the damaged area was the highest in the combination treatment group. Finally, DTI showed that the combination therapy optimally improved neurofilament structure and arrangement. These results may show that the combination of PBM and hUCMSCs transplantation is a feasible strategy for reducing secondary damage and promoting functional recovery following SCI.

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The effect of photobiomodulation on human dental pulp-derived stem cells: systematic review.

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This systematic review assessed if photobiomodulation of human dental pulp tissue improved cell viability, proliferation, and/or differentiation compared with a placebo. This systematic review was conducted in line with PRISMA. PICO question was established; inclusion and exclusion criteria were established before a search had begun. A literature search was conducted through PubMed, Scopus, and Cochrane. Studies were included if published within the last 20 years in English language, or where translation was available; laser parameters were mentioned; human dental pulp tissue was studied in vitro. Studies were excluded if non-human dental pulp tissue was studied and where the study was an in vivo study. Out of the total 121 studies found, 109 were excluded. Of the twelve included studies, three full-text articles were not available despite attempts made to contact the respective authors, leaving nine studies. Four of the included studies reported the use of stem cells derived from human deciduous teeth (SHEDs), and five used those from human permanent teeth (DPSCs). Most included studies utilized InGaAlP laser with wavelengths 660 nm, and one study with 610 nm. Other types of lasers included LED InGaN, and GaAlAs. Out of all included studies, two had a moderate risk of bias, and the rest had a low risk of bias. All studies confirmed positive effects on proliferation. One study also found improved osteogenic differentiation of the stem cells derived from stem cells of deciduous teeth. After assessing SHEDs and DPSCs separately, it is found that photobiomodulation improved cell proliferation in both subgroups. Due to heterogeneity in design protocols and laser parameters, it was not possible to compare the studies together. However, this study indicated that cell viability and proliferation did improve with photobiomodulation.

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The impact of photobiomodulation therapy on the biology and behavior of head and neck squamous cell carcinomas cell lines.

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Photobiomodulation therapy (PBMT) is an emerging therapeutic modality designed to prevent and treat chemotherapy-driven oral mucositis (OM). However, the response of tumor cells to the effects of PBMT remains poorly understood. Our study explores the effects of PBMT in head and neck squamous cell carcinoma (HNSCC) based on cellular proliferation, migration, and survival of tumor cells and its population of cancer stem cells (CSC). We explored the behavior of two HNSCC cell lines (HN6 and HN13) under two distinct conditions, a physiological growing condition (10% FBS), and under stress growing condition (2% FBS) prior to irradiation using diode laser (InGaAlP; MM Optics, São Carlos, SP, Brazil). Diode laser (660 nm) was applied with a power of 100 mW delivering a total energy per point of 0.24 J. MTT and wound healing test (scratch assay) were performed to evaluate, respectively, proliferation and migration of tumor cells. Clonogenic and spheres formation assays were also performed to evaluate the survival and percentage of CSC upon irradiation. Overall, we observed that PBMT does not exacerbate the behavior of HNSCC. We could only observe a decrease in cellular proliferation of one cell line (HN6) when cultured under nutritional stress conditions (p ; .05). There were no significant differences between the control and the PBMT groups regarding cell migration, survival and the percentage of CSC. Collectively, our results suggest that in vitro administration of PBMT to HNSCC does not modify the behavior of tumor cells.

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Photobiomodulation-Induced Differentiation of Immortalized Adipose Stem Cells to Neuronal Cells.

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iASCs were differentiated to free-floating neural stem cell aggregates (neurospheres) using a combination of growth inducers. Cells in these spheres were induced to differentiate into neurons using low-intensity lasers by a process called photobiomodulation (PBM).

Laser at the near infrared (NIR) wavelength 825 nm and fluences 5, 10, and 15 J/cm 2 was capable of increasing the differentiation of neurospheres to neurons. Precisely, there was a statistically significant increase in the early neuronal marker at 5 J/cm 2 and a much appreciable increase at 15 J/cm 2 in correlation with the biphasic dose response of PBM. However, these differentiated cells failed to express late neuronal markers in vitro. Comparison of these differentiating iASCs with the primary ASCs revealed a sharp distinction between the metabolic processes of the primary ASCs, neurospheres, and newly differentiated neurons.

We found that PBM increased the yield of neurons and effected stem cell differentiation through modulation of cellular metabolism and redox status. Our study also identifies that iASCs are an excellent model for analysis of stem cell biology and for performing transdermal differentiation.

This study demonstrates that a combination of biological and physical inducers can advance the differentiation of adipose stem cells to neurons. We were able to establish the optimal energy for the neuronal differentiation of iASCs in vitro. Lasers Surg. Med. © 2020 Wiley Periodicals LLC.

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https://pubmed.ncbi.nlm.nih.gov/32525253

Photobiomodulation for spinal cord injury: A systematic review and meta-analysis.

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In recent years, photobiomodulation therapy (PBMT) has found many applications in various medical fields. Studies of PBMT on spinal cord injury (SCI) have mostly used laser sources in experimental animal models. The purpose of this study was to summarize studies that have employed PBMT for various kinds of SCI in animals. A thorough search in databases including MEDLINE, EMBASE, SCOPUS, and Web of Science, with the removal of unrelated articles, yielded 16 relevant articles. The meta-analysis showed that PBMT was effective in improving post-SCI movement in the first 14 days (MD = 1.593 (95% CI: 1.110 to 2.075; p ;0.001, I 2 = 51.9%) and this improvement became even greater thereafter (MD = 2.086 (95% CI: 1.570 to 2.603; p = ;0.001. I 2= 90.3%). Time of irradiation (;300 sec or >300 sec), gender (male or female), injury model (contusion or compression, radiation protocol (;14 days or ≥14days), laser wavelength (;800nm or >800nm) and injury severity (moderate or severe) were found to be factors that can affect PBM efficacy for SCI treatment. PBMT has an anti-inflammatory effect, is effective in reducing the size of spinal cord lesions and helps to absorb administrated proteins and stem cells to the lesion site.

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Photobiomodulation-Underlying Mechanism and Clinical Applications.

Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A, Bruska M, Dominiak M, Mozdziak P, Skiba THI, Shibli JA, Angelova Volponi A, Kempisty B, Dyszkiewicz-Konwińska M

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The purpose of this study is to explore the possibilities for the application of laser therapy in medicine and dentistry by analyzing lasers' underlying mechanism of action on different cells, with a special focus on stem cells and mechanisms of repair. The interest in the application of laser therapy in medicine and dentistry has remarkably increased in the last decade. There are different types of lasers available and their usage is well defined by different parameters, such as: wavelength, energy density, power output, and duration of radiation. Laser irradiation can induce a photobiomodulatory (PBM) effect on cells and tissues, contributing to a directed modulation of cell behaviors, enhancing the processes of tissue repair. Photobiomodulation (PBM), also known as low-level laser therapy (LLLT), can induce cell proliferation and enhance stem cell differentiation. Laser therapy is a non-invasive method that contributes to pain relief and reduces inflammation, parallel to the enhanced healing and tissue repair processes. The application of these properties was employed and observed in the treatment of various diseases and conditions, such as diabetes, brain injury, spinal cord damage, dermatological conditions, oral irritation, and in different areas of dentistry.

J Clin Med, 2020 Jun 9(6)

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Alterted Adipogenesis of Human Mesenchymal Stem Cells by Photobiomodulation Using 1064 nm Laser Light.

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To determine the effects of 1064 nm laser irradiation (fluence of 8.8-26.4 J/cm 2) on human mesenchymal stem cells (hMSCs) undergoing adipogenic differentiation, the ATP and ROS levels, and adipogenic markers were quantitatively measured.

At a low fluence (8.8 J/cm 2) the ATP increase was essentially negligible, whereas a higher fluence induced a significant increase. In the laser-stimulated cells, PBM over time decreased the ROS level compared with the non-treated control group and significantly reduced the extent of adipogenesis. A reduction in the ROS level was correlated with a diminished lipid accumulation, reduced production of adipose-specific genetic markers, and delayed the chemically intended adipogenesis.

We characterized the use of NIR light exposure to modulate adipogenesis. Both the ATP and ROS levels in hMSCs responded to different energy densities. The current study is expected to contribute significantly to the growing field of PBM as well as stem cell tissue engineering by demonstrating the wavelength-dependent responses of hMSC differentiation. Lasers Surg. Med. © 2020 Wiley Periodicals LLC.

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Photobiomodulation and Stem Cell Therapy for Temporomandibular Joint Disc Disorders.

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Background:
Temporomandibular disorder (TMD) refers to a group of disorders affecting the temporomandibular joint (TMJ) and its related muscles. The two commonly used treatment modalities for TMD are occlusal splint therapy and relaxation therapy. Neither comprises definitive treatment.

Objective:
The objective of this review was to report updated information on photobiomodulation and stem cells, as an alternative treatment for the degenerative TMJ disc as a part of TMJ disorders.
Materials and methods:
With only a few research studies reported till date, this review also proposes the mechanism of laser irradiation on inflammatory mediators to treat TMD.

Results:
Photobiomodulation of stem cells with and without scaffolds could be used indirectly or directly as modulation of degenerative changes of the TMJ disc.

Conclusions:
The need for a distinct shift of the research margin in this field of dentistry is evident, specifically regarding the application of photobiomodulation and stem cells for tissue engineering of the TMJ disc.

Photobiomodul Photomed Laser Surg, 2020 Jun

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Photobiomodulation with 808-nm diode laser enhances gingival wound healing by promoting migration of human gingival mesenchymal stem cells via ROS/JNK/NF-κB/MMP-1 pathway.

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Photobiomodulation (PBM) has been shown to improve wound healing by promoting mesenchymal stem cell migration and proliferation. However, it remains unknown whether an 808-nm diode laser can influence human gingival mesenchymal stem cells (HGMSCs), and which dose this works well. In the present study, it was found that PBM could promote the migration of HGMSCs but not the proliferation. Furthermore, PBM could activate mitochondrial ROS, which could elevate the phosphorylation levels of JNK and IKB in HGMSCs, and further activate NF-κB as the nuclear translocation of p65 is elevated. Taken together, these present results indicate that PBM might promote cell migration via the ROS/JNK/NF-κB pathway.

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The Effect of Low-Power Laser Therapy on the TGF/β Signaling Pathway in Chronic Kidney Disease: A Review.

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Objective: The purpose of this study is to investigate the effects of low-power lasers on kidney disease by investigating several studies.
Methods: A number of articles from 1998 to 2019 were chosen from the sources of PubMed, Scopus, and only the articles studying the effect of low-power lasers on kidney disease were investigated.
Results: After reviewing the literature, 21 articles examining only the effects of low-power lasers on kidney disease were found. The results of these studies showed that the parameter of the lowpower laser would result in different outcomes. So, a low-power laser with various parameters can be effective in the treatment of kidney diseases such as acute kidney disease, diabetes, glomerulonephritis, nephrectomy, metabolic syndrome, and kidney fibrosis. Most studies have shown that low-power lasers can affect TGFβ1 signaling which is the most important signaling in the treatment of renal fibrosis. Conclusion: Lasers can be effective in reducing or enhancing inflammatory responses, reducing fibrosis factors, and decreasing reactive oxygen species (ROS) levels in kidney disease and glomerular cell proliferation.

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Enhanced Inner-Ear Organoid Formation from Mouse Embryonic Stem Cells by Photobiomodulation.

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Photobiomodulation (PBM) stimulates different types of stem cells to migrate, proliferate, and differentiate in vitro and in vivo. However, little is known about the effects of PBM on the differentiation of embryonic stem cells (ESCs) toward the otic lineage. Only a few reports have documented the in vitro differentiation of ESCs into inner-ear hair cells (HCs) due to the complexity of HCs compared with other target cell types. In this study, we determined the optimal condition to differentiate the ESCs into the otic organoid using different culture techniques and PBM parameters. The efficiency of organoid formation within the embryoid body (EB) was dependent on the cell density of the hanging drop. PBM, using 630 nm wavelength light-emitting diodes (LEDs), further improved the differentiation of inner-ear hair cell-like cells coupled with reactive oxygen species (ROS) overexpression. Transcriptome analysis showed the factors that are responsible for the effect of PBM in the formation of otic organoids, notably, the downregulation of neural development-associated genes and the hairy and enhancer of split 5 (Hes5) gene, which inhibits the differentiation of prosensory cells to hair cells. These data enrich the current differentiation protocols for generating inner-ear hair cells.

Mol Ther Methods Clin Dev, 2020 Jun 17 556-567

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Nrf2 played an important role in radiation protection effect of low-level laser exposed on umbilical cord mesenchymal stem cell.

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To investigate the protective function of low-level laser irradiation (LLLI) against ionizing irradiation and explore the molecular mechanism of photomodulation of Nrf2 protein, the impact of LLLI (635 nm, 5.7 J/cm 2) before 2 Gy gamma ray radiation of radio-sensitive tissue hematopoietic stem cells was evaluated. As a result, reduced levels of reactive oxygen species and increased expression of antioxidant enzymes were detected. Moreover, increased expression of Nrf2 was observed after LLLI, whereas brusatol pretreatment before LLLI abolished this effect. In vivo, transplantation of human umbilical cord mesenchymal stem cells (hUC-MSCs) was employed for therapy of hematopoietic function in an acute radiation sickness (H-ARS) mouse model, which was induced by 6-Gy ionizing irradiation; different hUC-MSC pretreatments including LLLI and Nrf2 RNAi were accounted for during experimental grouping. LLLI treatment of cells significantly increased the erythrocyte count and number of myelopoiesis clones (P ; 0.05), but such improvements were reduced by Nrf2 RNAi pretreatment compared with cells transplanted without intervention. Therefore, LLLI may improve the radiation protection effect through molecular mechanisms related to the Nrf2 antioxidant pathway.

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Combined therapy of photobiomodulation and adipose-derived stem cells synergistically improve healing in an ischemic, infected and delayed healing wound model in rats with type 1 diabetes mellitus.

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We randomly assigned 24 rats with DM1 to four groups (n=6 per group). Group 1 was the control (placebo) group. In group 2, allograft human ADSs were transplanted. Group 3 was subjected to PBM (wavelength: 890 nm, peak power output: 80 W, pulse frequency: 80 Hz, pulsed duration: 180 ns, duration of exposure for each point: 200 s, power density: 0.001 W/cm 2, energy density: 0.2 J/cm 2) immediately after surgery, which continued for 6 days per week for 16 days. Group 4 received both the human ADS and PBM. In addition, we inflicted an ischemic, delayed healing, and infected wound simulation in all of the rats. The wounds were infected with methicillin-resistant Staphylococcus aureus (MRSA).

All three treatment regimens significantly decreased the amount of microbial flora, significantly increased wound strength and significantly modulated inflammatory response and significantly increased angiogenesis on day 16. Microbiological analysis showed that PBM+ADS was significantly better than PBM and ADS alone. In terms of wound closure rate and angiogenesis, PBM+ADS was significantly better than the PBM, ADS and control groups.

Combination therapy of PBM+ADS is more effective that either PBM or ADS in stimulating skin injury repair, and modulating inflammatory response in an MRSA-infected wound model of rats with DM1.

Photobiomodulation therapy improves human dental pulp stem cell viability and migration in vitro associated to upregulation of histone acetylation.

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This in vitro study evaluated the role of photobiomodulation therapy (PBMT) on viability and migration of human dental pulp stem cells (hDPSCs) and its association to epigenetic mechanisms such as histone acetylation. The hDPSCs were characterized and assigned into control and PBMT groups. For the PBMT, five laser irradiations at 6-h intervals were performed using a continuous-wave InGaAlP diode laser. Viability (MTT), migration (scratch), and histone acetylation H3 (H3K9ac immunofluorescence) were evaluated immediately after the last irradiation. PBMT significantly increased the viability ($P = 0.004$). Also, PBMT group showed significantly increased migration of cells in the wound compared to the control in 6 h ($P = 0.002$), 12 h ($P = 0.014$) and 18 h ($P = 0.083$) being faster than the control, which only finished the process at 24 h. PBMT induced epigenetic modifications in hDPSC due to increased histone acetylation ($P = 0.001$). PBMT increased viability and migration of hDPSCs, which are related with the upregulation of histone acetylation and could be considered a promising adjuvant therapy for regenerative endodontic treatment.

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The Effect of Photobiomodulation Therapy on the Differentiation, Proliferation, and Migration of the Mesenchymal Stem Cell: A Review.

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Introduction: The purpose of this study is to investigate the effect of a low-power laser on the proliferation, migration, differentiation of different types of mesenchymal stem cells (MSCs) in different studies.
Methods: The relevant articles that were published from 2004 to 2019 were collected from the sources of PubMed, Scopus, and only the articles specifically examining the effect of a lowpower laser on the proliferation, differentiation, and migration of the MSCs were investigated.
Results: After reviewing the literature, only 42 articles were found relevant. Generally, most of the studies demonstrated that different laser parameters increased the proliferation, migration, and differentiation of the MSCs, except the results of two studies which were contradictory. In fact, changing the parameters of a low-power laser would affect the results. On the other hand, the source of the stem cells was reported as a key factor. In addition, the combination of lasers with other therapeutic approaches was found to be more effective. Conclusion: The different parameters of lasers has been found to be effective in the proliferation, differentiation, and migration of the MSCs and in general, a low-power laser has a positive effect on the MSCs, helping to improve different disease models.

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Cerebrospinal Fluid and Photobiomodulation Effects on Neural Gene Expression in Dental Pulp Stem Cells.

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Introduction: Dental pulp cells, a unique source of ectomesenchymal pluripotent stem cells, are originated from the skull neural crest. They are considered as one ideal source of cells for the regenerative medicine applications. Cerebrospinal fluid (CSF), a transparent fluid found in the brain and spinal cord, is enriched with electrolytes, proteins, and growth factors such as EGF, bFGF, BDNF, GDNF, and neuropeptides and can be utilized as a trigger in order to induce the neural differentiation. On the other hand, photobiomodulation (PBM), with the ability to prevent cell apoptosis, can induce cell proliferation by means of increasing the ATP synthesis in mitochondria and facilitating the secretion of the growth factors. In this research, we first aimed to isolate and culture the dental pulp stem cells (DPSCs) and subsequently to investigate their potential for neural differentiation.
Methods: Human dental pulp stem cells (hDPSCs) were isolated from the pulp tissues using an outgrowth method and subsequently cultured. In order to access the cells' differentiation potential, cells were firstly classified into four groups which were treated with CSF, gallium aluminum arsenide diode laser irradiation (808 nm; 30 mW power output) and a combination of both, while the fourth group was considered as the control. MTT assay was then used to examine the viability of cells following the treatments. After 4, 7, and 14 days the cell morphology in the treated groups was evaluated while RT-PCR was used in order to evaluate the Nestin and β-tubulinIII neural gene marker expressions.
Results: It was shown that PBM has the ability to elevate the proliferation of DPSCs. Also, the differentiated morphology was obvious in the CSF treated group, especially on day 14 with the formation of three-dimensional (3D) structures. The results of gene expression analysis showed that on the fourth day of post-treatment, Nestin and β-tubulinIII gene expressions were reduced in all groups while a rising trend in their expression was observed subsequently on days 7 and 14. Conclusion: In accordance with previous studies, including functional and protein base researches, it has been demonstrated that CSF has a direct role in neural induction. Although past works have been significant, none of them shows a 3D structure. In this article, we investigated the dual effect of PBM and CSF. Initial results confirmed the upregulation of neural-related transcription factors. The 3D organization of the formed tissue could imply the initiation of organogenesis which has not been reported before. In sum, the dual effect of CSF and PBM has been shown to have the potential for contributing to the initiation of neurogenesis and organogenesis.

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Photobiomodulation effects on osteogenic differentiation of adipose-derived stem cells.

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Increasing interest has been observed in the use of photobiomodulation (PBM) to enhance the proliferation of stem cells and induce their differentiation. The effects of PBM at two different wavelengths (635 and 809 nm) with three different energy densities (0.5, 1 and 2 J/cm 2) on the osteogenic differentiation of adipose-derived stem cells (ADSC) were investigated. Cell viability and proliferation were evaluated by MTT and Alamar Blue assays. Osteoblast differentiation were assessed by alkaline phosphatase (ALP) activity, Alizarin red staining and reverse-transcription polymerase chain reaction (RT-PCR) for the expression of collagen type I (COL1A), ALP and osteocalcin. 635 nm and 809 nm laser irradiation had no effect on the cell viability on days 7 and 14, except for 0.5 J/cm 2 group at 14th day after 635 nm irradiation (p ; 0.05). Cell proliferation was not changed significantly. Mineralization was increased significantly in 809 nm laser groups but no enhancement was detected in the osteogenic differentiation by ALP activity and gene expression results. In 0.5 and 1 J/cm 2 groups, ALP and COL1A expressions were down regulated at day 7 after 809 nm laser exposure. These results suggest that PBM may alter osteogenic differentiation of ADSC and increase mineralization but further investigation is needed to define adequate parameters.

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Biological Responses of Stem Cells to Photobiomodulation Therapy.

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The literature investigated the articles written in English in four electronic databases of PubMed, Scopus, Google Scholar and Cochrane up to April 2019. Stem cell was searched by combining the search keyword of "low-level laser therapy" OR "low power laser therapy" OR "low-intensity laser therapy" OR "photobiomodulation therapy" OR "photo biostimulation therapy" OR " LED". In total, 46 articles were eligible for evaluation.

Studies demonstrated that red to near-infrared light is absorbed by the mitochondrial respiratory chain. Mitochondria are significant sources of reactive oxygen species (ROS). Mitochondria play an important role in metabolism, energy generation, and are also involved in mediating the effects induced by PBMT. PBMT may result in the increased production of (ROS), nitric oxide (NO), adenosine triphosphate (ATP), and cyclic adenosine monophosphate (cAMP). These changes, in turn, initiate cell proliferation and induce the signal cascade effect.

The findings of this review suggest that PBMT-based regenerative medicine could be a useful tool for future advances in tissue engineering and cell therapy.

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Photobiomodulation plus Adipose-derived Stem Cells Improve Healing of Ischemic Infected Wounds in Type 2 Diabetic Rats.

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In this study, we sought to investigate the impact of photobiomodulation and adipose-derived stem cells (ADS), alone and in combination, on the maturation step of wound healing in an ischemic infected delayed healing wound model in rats with type 2 diabetes mellitus (DM2). We randomly divided 24 adult male rats into 4 groups (n = 6 per group). DM2 plus an ischemic delayed healing wound were induced in all rats. The wounds were infected with methicillin-resistant Staphylococcus aureus. Group 1 was the control (placebo) group. Group 2 received only photobiomodulation (890 nm, 80 Hz, 0.324 J/cm 2, and 0.001 W/cm 2). Group 3 received only the allograft ADS. Group 4 received allograft ADS followed by photobiomodulation. On days 0, 4, 8, 12, and 16, we performed microbiological examination (colony forming units, [CFU]), wound area measurement, wound closure rate, wound strength, and histological and stereological examinations. The results indicated that at day 16, there was significantly decreased CFU (Analysis of variance, p = 0.001) in the photobiomodulation + ADS (0.0 ± 0.0), ADS (1350 ± 212), and photobiomodulation (0.0 ± 0.0) groups compared with the control group (27250 ± 1284). There was significantly decreased wound area (Analysis of variance, p = 0.000) in the photobiomodulation + ADS (7.4 ± 1.4 mm 2), ADS (11 ± 2.2 mm 2), and photobiomodulation (11.4 ± 1.4 mm 2) groups compared with the control group (25.2 ± 1.7). There was a significantly increased tensiometeric property (stress maximal load, Analysis of variance, p = 0.000) in the photobiomodulation + ADS (0.99 ± 0.06 N/cm 2), ADS (0.51 ± 0.12 N/cm 2), and photobiomodulation (0.35 ± 0.15 N/cm 2) groups compared with the control group (0.18 ± 0.04). There was a significantly modulated inflammatory response in (Analysis of variance, p = 0.049) in the photobiomodulation + ADS (337 ± 96), ADS (1175 ± 640), and photobiomodulation (69 ± 54) treatments compared to control group (7321 ± 4099). Photobiomodulation + ADS gave significantly better improvements in CFU, wound area, and wound strength compared to photobiomodulation or ADS alone. Photobiomodulation,

Dopaminergic induction of human dental pulp stem cells by photobiomodulation: comparison of 660nm laser light and polychromatic light in the nir.

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Human dental pulp stem cells (hDPSCs) are able to differentiate into dopaminergic neurons and help the maintenance of partially degenerated neurons, which makes them as an alternative cell source for treatment of Parkinsons' disease (PD) patients. Here, the effect of photobiomodulation with polychromatic light source in the near infrared (NIR) range (600-1200 nm) or low level 660 nm diode laser light on hDPSCs during dopaminergic induction was investigated. Real time RT-qPCR analysis indicated that expressions of brain derived neurotrophic factor (BDNF), glial cell line derived neurotropic factor (GNDF), matrix associated protein 2 (MAP2), nuclear receptor related 1 protein (NURR1) and dopamine transporter (DAT) were increased, especially in the first 7 days of dopaminergic induction when 660 nm laser light was applied with a total energy density of 1.6 J/cm 2. The activity of polychromatic light on hDPSCs depended on the differentiation media and protein type. BDNF, GDNF, NURR-1 and MAP2 expressions were increased in the presence of pre-induction factors, and decreased when the post-induction factors were added into the culture medium. In contrast with all these promising results, the dopaminergically induced hDPSCs did not show any functional characteristics of dopaminergic neurons and died after they were transferred to a new laminin coated culture plates. In conclusion, the expression of dopaminergic neuron protective protein mRNAs in hDPSCs was increased by photobiomodulation in defined conditions. However, the cells were not able to differentiate into functional dopaminergic neurons either in control or in photobiomodulated groups that are prone to cell death and exhibit immature dopaminergic neuron characteristics.

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Non-Invasive Transcranial Nano-Pulsed Laser Therapy Ameliorates Cognitive Function and Prevents Aberrant Migration of Neural Progenitor Cells in the Hippocampus of Rats Subjected to Traumatic Brain Injury.

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Traumatic brain injury (TBI) can lead to chronic diseases, including neurodegenerative disorders and epilepsy. The hippocampus, one of the most affected brain region after TBI, plays a critical role in learning and memory and is one of the only two regions in the brain in which new neurons are generated throughout life from neural stem cells (NSC) in the dentate gyrus (DG). These cells migrate into the granular layer where they integrate into the hippocampus circuitry. While increased proliferation of NSC in the hippocampus is known to occur shortly after injury, reduced neuronal maturation and aberrant migration of progenitor cells in the hilus contribute to cognitive and neurological dysfunctions, including epilepsy. Here, we tested the ability of a novel, proprietary non-invasive nano-pulsed laser therapy (NPLT), that combines near-infrared laser light (808 nm) and laser-generated, low-energy optoacoustic waves, to mitigate TBI-driven impairments in neurogenesis and cognitive function in the rat fluid percussion injury model. We show that injured rats treated with NPLT performed significantly better in a hippocampus-dependent cognitive test than did sham rats. In the DG, NPLT significantly decreased TBI-dependent impaired maturation and aberrant migration of neural progenitors, while preventing TBI-induced upregulation of specific microRNAs (miRNAs) in NSC. NPLT did not significantly reduce TBI-induced microglia activation in the hippocampus. Our data strongly suggest that NPLT has the potential to be an effective therapeutic tool for the treatment of TBI-induced cognitive dysfunction and dysregulation of neurogenesis, and point to modulation of miRNAs as a possible mechanism mediating its neuroprotective effects.

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Opposite effects of low intensity light of different wavelengths on the planarian regeneration rate.

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Planarian freshwater flatworms have the unique ability to regenerate due to stem cell activity. The process of regeneration is extremely sensitive to various factors, including light radiation. Here, the effect of low-intensity LED light of different wavelengths on regeneration, stem cell proliferation and gene expression associated with these processes was studied. LED matrices with different wavelengths (red (λ max = 635 nm), green (λ max = 520 nm) and blue (λ max = 463 nm), as well as LED laser diodes (red (λ max = 638.5 nm), green (λ max = 533 nm) and blue (λ max = 420 nm), were used in the experiments. Computer-assisted morphometry, whole-mount immunocytochemical study and RT-PCR were used to analyze the biological effects of LED light exposure on the planarian regeneration in vivo. It was found that a one-time exposure of regenerating planarians with low-intensity red light diodes stimulated head blastema growth in a dose-dependent manner (up to 40%). The green light exposure of planarians resulted in the opposite effect, showing a reduced head blastema growth rate by up to 21%. The blue light exposure did not lead to any changes in the rate of head blastema growth. The maximum effects of light exposure were observed at a dose of 175.2 mJ/cm 2. No significant differences were revealed in the dynamics of neoblasts' (planarian stem cells) proliferation under red and green light exposure. However, the RT-PCR gene expression analysis of 46 wound-induced genes revealed their up-regulation upon red LED light exposure, and down-regulation upon green light exposure. Thus, we have demonstrated that the planarian regeneration process is rather sensitive to the effects of low-intensity light radiation of certain wavelengths, the biological activity of red and green light being dictated by the different expression of the genes regulating transcriptional activity.

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Exposure to blue light stimulates the proangiogenic capability of exosomes derived from human umbilical cord mesenchymal stem cells.

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We used blue (455 nm) and red (638 nm) monochromatic light exposure to investigate the processing of stimuli. Exosomes were prepared by QIAGEN exoEasy Maxi kit and confirmed to be present by transmission electron microscopy and immunoblotting analyses. The proangiogenic activity of blue light-treated human umbilical vein endothelial cells (HUVECs), when co-cultured with hUC-MSCs, was assessed by EdU (5-ethynyl-2'-deoxyuridine) incorporation, wound closure, and endothelial tube formation assays. The in vivo angiogenic activity of blue light-treated MSC-derived exosomes (MSC-Exs) was evaluated using both murine matrigel plug and skin wound models. We found that 455-nm blue light is effective for promoting proliferation, migration, and tube formation of HUVECs co-cultured with MSCs. Furthermore, MSC-Exs stimulated in vivo angiogenesis and their proangiogenic potential were enhanced significantly upon blue light illumination. Finally, activation of the endothelial cells in response to stimulation by blue light-treated exosomes was demonstrated by upregulation of two miRNAs, miR-135b-5p, and miR-499a-3p.

Protective effect of Photobiomodulation Therapy and Bone Marrow Stromal Stem Cells Conditioned Media on Pheochromocytoma Cell Line 12 Against Oxidative Stress Induced by Hydrogen Peroxide.

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Introduction: Bone marrow stromal stem cells (BMSCs), a type of adult stem cells, secrete bioactive molecules such as trophic factors, growth factors, chemokine and cytokines that may be effective against oxidative stress in neurodegenerative diseases. In this study, we examined the protective effect of BMSCs conditioned media (CM) and photobiomodulation therapy (PBMT) on PC12 cells exposed to H2O2 as an oxidative injury model.
Methods: BMSCs were cultured and confirmed by flow cytometry analysis and underwent osteogenic and adipogenic differentiation. Then, PC12-H2O2 cells were co-treated with BMSCs-CM and PBMT. The effect of BMSCs-CM and PBMT (He-Ne laser, 632.8nm, 3mW, 1.2J/ cm 2 , 378s) on Bax/Bcl2 expression, cell viability, was assessed by real-time PCR and MTT assay. The length of the Neurite and cell body areas were assessed by Cell A software.
Results: Flowcytometry analysis, as well as osteogenic and adipogenic staining, confirmed the BMSCs. The length of the Neurite was the highest in the group which received CM+PBMT and cell body areas were significant in CM +PBMT compared to other groups. Based on our results, elevating H2O2 concentration increased cell death significantly and using concentrations of 250 µM resulted in a dramatic increase in the mortality compared to the other groups. Conclusion: Our result demonstrated that the combination of CM +PBMT has a protective effect on PC12 cells against oxidative stress.

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Photobiomodulation with 630 plus 810 nm wavelengths induce more in vitro cell viability of human adipose stem cells than human bone marrow-derived stem cells.

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The goal of the current experiment is to explore the influence of combined and/or single applications of red and near infrared (NIR) photobiomodulation (PBM) at different wavelengths, energy densities and times on cell viability, population doubling time (PDT), and apoptosis of in vitro cultures of human bone marrow-derived mesenchymal stem cells (hBM-MSCs) and h adipose-derived stem cells (hASCs). Both in vitro hBM-MSCs and hASCs were irradiated with 36 protocols using two different laser types (helium□neon [He-Ne] and diodes), four different laser wavelengths (HeNe laser, 630 nm, 810 nm, 630 + 810 nm); three different energy densities (0.6 J/cm 2, 1.2 J/cm 2, 2.4 J/cm 2); and three different PBM times (1, 2, and 3). One-way ANOVA analysis showed that PBM with the 630 nm red laser significantly stimulated cellular viability of both hBM-MSCs and hASCs. The 630 nm red laser significantly decreased PDT of hBM-MSCs. One-way ANOVA demonstrated that the 630 + 810 laser significantly stimulated cellular viability, and significantly decreased PDT and apoptosis of hBM-MSCs and hASCs. Two-way ANOVA analysis showed that PBM with the 630 nm red laser and 630 + 810 nm laser significantly stimulated cellular viability of hASCs compared to the control hASCs, and experimental and control hBM-MSCs. Our study demonstrated that PBM with the combined 630 + 810 nm lasers significantly stimulated cell viability, and significantly decreased PDT and apoptosis of hBM-MSCs and hASCs in vitro. We reported new in vitro evidence where PBM administered at 630 nm (one and two times, 0.6 and 1.2 J/cm 2) and 630 + 810 nm (three times, 2.4 J/cm 2) significantly increased hASC cell viability compared to its control and the PBM-treated hBM-MSC groups.

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Laser Photobiomodulation Over Teeth Subjected to Orthodontic Movement.

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Background:
Orthodontics of the 21st century requires aesthetic, painless, predictable, and quick treatments. This demand for faster results generated orthodontic movement acceleration protocols (OMAPs); among other OMAPs we present low-level laser (LLL) as a candidate.

Objective:
To evaluate levels of interleukin (IL)-1, IL-10, and type 1 collagen in the periodontal ligament of first molars of rats subjected to orthodontic traction with and without LLL irradiation, compared with untreated controls (CO), and to evaluate whether the dose of LLL used in this work is eligible as an OMAP.
Materials and methods:
A total of 35 male Wistar rats were distributed into three groups: group 1 NI (nonirradiated) n = 15, group 2 IR (laser irradiated using 5 J, 177 J/cm 2, and 100 mW applied in contact to the vestibular mesial, vestibular distal, and palatal faces of gum tissue around molar region for 50 sec each point, for 3 consecutive days, immediately 24 and 48 h after orthodontic device placement.) n = 15, and group 3 CO n = 5; groups 1 and 2 were subjected to orthodontic force and each group was divided into three subgroups that were sacrificed after 3, 5, and 7 days, IL -1/10 and COL-1 levels were analyzed.

Results:
In the IR group, levels of IL-1/10 and COL-1 showed peak anticipation after LLL irradiation compared with those in the NI and CO groups.

Conclusions:
These results can also infer that this dose of LLL can be used as an OMAP.

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Combined Adipose-Derived Mesenchymal Stem Cells and Photobiomodulation Could Modulate the Inflammatory Response and Treat Infected Diabetic Foot Ulcers.

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Impact of Photobiomodulation and Condition Medium on Mast Cell Counts, Degranulation, and Wound Strength in Infected Skin Wound Healing of Diabetic Rats.

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Background:
Numerous people suffer from diabetes mellitus (DM) and resultant diabetic foot ulcers (DFU), which lack effective treatment. Photobiomodulation (PBM) has accelerated wound healing in diabetic animals and patients in some studies. However, there is scant information on the number and activation state of skin mast cells (MCs) in PBM-treated diabetic wounds.

Objective:
We intend to assess the influence of the number of MCs and degranulation in the remodeling step of an infected wound model on wound strength and its microbial flora in a type 1 DM (T1DM) rat model by administration of PBM, condition medium (CM) derived from human bone marrow mesenchymal stem cells (hBMMSCs), and the combination of PBM+CM.

Methods:
We prepared CM by culturing hBMMSCs. T1DM was induced in 72 rats and, after 1 month, we created one excisional wound in each rat. All wounds were infected with methicillin-resistant Staphylococcus aureus (MRSA). We divided the rats into four groups: (n = 18): (i) control; (ii) PBM; (iii) CM, and (iv) PBM+CM. On days 4, 7, and 15, we conducted microbiological, tensiometrical, and stereological analyses. The type of MCs (T1MCs, T2MCs, or T3MCs) and total number of MCs (TOMCs) were counted by light microscopy.

Results:
On day 15, the PBM+CM, PBM, and CM groups had significantly increased wound strength compared with the control group. There was a significant decrease in colony-forming units (CFU) at all time points in the PBM+CM and PBM groups. The PBM+CM and PBM groups had more stable MCs (T1MCs), less significant degranulated MCs (T2MCs), less significant disintegrated MCs (T3MCs), and less significant TOMCs compared with the control group at all time points.

Conclusions:
PBM+CM and PBM treatments significantly increased the healing process in an ischemic and MRSA-infected wound model of T1DM rats. PBM+CM and PBM significantly decreased both TOMCs and their degranulation, and

Is There a Role for Photobiomodulation in Treating Damaged Articular Cartilage Due to Injury or Degeneration?

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Articular cartilage lesions are either focal (traumatic) or generalized (degenerative). Spontaneous healing is not possible for these lesions. They are mainly healed by fibrocartilage tissue, which is less durable compared with hyaline cartilage. Novel techniques have been proposed to regenerate hyaline cartilage such as developments in orthobiologics, tissue engineering, and scaffolding structures employed as carriers for mesenchymal stem cells.1 However, most of these methods have complications or side effects, and better treatment methods that are not harmful are necessary.2

We searched histological and magnetic resonance imaging alterations after irradiation of cartilage and meniscus using holmium:YAG laser in vitro and in vivo.3–5 We concluded that when the holmium:YAG laser is used at an optimal dosage (optimal joule and hertz) with an optimal technique (keeping the handpiece at an appropriate angle and distance) and for an optimal time (avoiding overtreatment), it does not cause neither cartilage damage nor osteonecrosis.

Recently, photobiomodulation (PBM) has emerged as a promising option for the management of cartilage damage. PBM uses either low-level laser therapy (LLLT) or light-emitting diodes to increase stem cell multiplication and differentiation, and finally modulation of functions in the cells.6

Bayat et al. investigated the effect of low-power (632.8 nm, helium–neon, 13 J/cm2) laser on immobilized articular cartilage in knee joints of rabbits.7 They concluded that low-power helium–neon laser irradiation neutralized adverse effects of immobilization on articular cartilage.

Using LLLT, Cho et al. studied healing of damaged articular cartilage in knee joints of rabbits with osteoarthropathy.8 The effect was evaluated by biochemical, radiological, and histopathological analysis. There was healing of articular cartilage in treatment group.

Alves et al. searched the effect of LLLT on joint damage in rats by histopathology and analysis of metalloproteinase 2 and 9 production.9 Both laser groups (50 and 100 mW) provided healing, decreasing collagen type III, and increasing type I.

Recently, Felizatti et al. investigated the effects of LLLT using the gallium arsenide laser ($\lambda = 830$ nm) on the articular cartilage in knee joint with arthritis in rats. They concluded that AsGa-830 nm preserved glycosaminoglycans, reduced the cellular changes and inflammation.10

Fekrazad et al. studied to evaluate the effectiveness of cultured autologous bone marrow mesenchymal stem cells (BMSCs) with scaffold and LLLT on healing of articular cartilage defects in rabbits.11 They concluded that better healing was seen when combining BMSCs with scaffold and LLLT. However, this was predominantly caused by new bone formation.

In a recent review article, Fekrazad et al. reported that PBM provides multiplication of MSCs.12 Energy density, power output, frequency of radiation, type of light source, and type of cell or medium culture were crucial, and doses of 0.7–4 J/cm2, wavelengths from 600 to 700 nm were the most suitable for this procedure.

In conclusion, PBM has probably positive effects of biostimulation on cartilage tissue. There might be a role for PBM in treating damaged articular cartilage due to injury or degeneration without eventual side effects or complications. Although there are also studies showing opposite results, standardization of parameters in PBM and long-term follow-up with more patients will lead to better results. Eventually, PBM may be an effective and safe treatment option for traumatic or degenerative cartilage lesions.

Photobiomodul Photomed Laser Surg 2019 Oct 04

Modulatory effect of photobiomodulation on stem cell epigenetic memory: a highlight on differentiation capacity.

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Differentiation potential of stem cells into various lineages makes these cells as promising sources to treat multiple diseases. In this regard, the use of different strategies and protocols to increase differentiation capacity is highly demanded. Low-level laser therapy, a relatively noninvasive technique, has the capacity to accelerate the healing of numerous injuries and a portion of restorative capacity could be correlated with the stem cell activation and differentiation. Several mechanisms have been diagnosed to participate in orientation of stem cells to functional mature cells. Among them, the status of DNA methylation orchestrates the maintenance of tissue-specific gene expression during the differentiation procedure. DNA methylation is a momentous event in embryogenesis and functional maturation. This review article highlighted the potency of laser irradiation (low-level intensities) in the differentiation of stem cells by modulation of methylation. The analysis of these modalities could help us to understand the underlying mechanisms participating in the therapeutic effects of photobiomodulation.

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Influence of photobiomodulation therapy on root development of rat molars with open apex and pulp necrosis.

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This study aimed to evaluate the role of photobiomodulation (PBM) in apexification and apexogenesis of necrotic rat molars with an open apex. Rat molars were exposed to the oral environment for 3 weeks. Canals were rinsed with 2.5% NaOCl and 17% EDTA, filled with antibiotic paste and sealed. After 7 days, canals were rinsed and divided into six groups (n=6): mineral trioxide aggregate (MTA); blood clot (BC); human dental pulp stem cells (hDPSC); MTA+PBM; BC+PBM; and hDPSC+PBM. In hDPSC groups, a 1% agarose gel scaffold was used. Two groups were not exposed: healthy tooth+PBM (n = 6), healthy tooth (n = 3); and one was exposed throughout the experiment: necrotic tooth (n = 3). In PBM groups, irradiation was performed with aluminum gallium indium phosphide (InGaAlP) diode laser for 30 days within 24-h intervals. After that, the specimens were processed for histological and immunohistochemical analyses. Necrotic tooth showed greater neutrophil infiltrate (p ; 0.05). Necrotic tooth, healthy tooth, and healthy tooth+PBM groups showed absence of a thin layer of fibrous condensation in the periapical area. All the other groups stimulated the formation of a thicker layer of fibers (p ; 0.05). All groups formed more mineralized tissue than necrotic tooth (p ; 0.05). PBM associated with MTA, BC, or hDPSC formed more mineralized tissue (p ; 0.05). MTA+PBM induced apexification (p ; 0.05). Rabbit polyclonal anti-bone sialoprotein (BSP) antibody confirmed the histological findings of mineralized tissue formation, and hDPSC groups exhibited higher percentage of BSP-positive cells. It can be concluded that PBM improved apexification and favored apexogenesis in necrotic rat molars with an open apex.

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Photobiomodulation therapy compensate the impairments of diabetic bone marrow mesenchymal stem cells.

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Pathophysiologic conditions associated with diabetes mellitus affect mesenchymal stem cells (MSCs), and this phenomenon may lead to some diabetic secondary complications. The present study was conducted to evaluate the impact of photobiomodulation (PBM) on rat diabetic MSC (DMSC) behavior in vitro. For the purpose of PBM, we used helium-neon laser with a wavelength of 632.8 nm at three different energy densities (0.5, 1, 2 J/cm 2) and radiation periodicity of once, twice, and thrice. The survival, proliferation, and apoptosis in the normal MSCs (NMSCs), DMSCs, and diabetic MSCs, which were laser irradiated (DMSCs+L), were assessed using MTT assay, Ki67 immunofluorescence staining, and TUNEL assay, respectively. Our results demonstrated that DMSCs have significantly lower survival (P ; 0.05) and proliferation rates (P ; 0.001), and dramatically higher population doubling time (PDT, P ; 0.001) and apoptosis rates (P ; 0.001) as compared to NMSCs. Moreover, PBM with energy density of 1 J/cm 2 and the periodicity of 1 or 2 times could improve diabetic MSC capabilities in the term of survival, proliferation, and apoptosis. Considering these findings, it is suggested that PBM could improve the ability of diabetic MSCs in vitro prior to transplantation or may rise their capabilities in their native niche in vivo.

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Physical energies to the rescue of damaged tissues.

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Rhythmic oscillatory patterns sustain cellular dynamics, driving the concerted action of regulatory molecules, microtubules, and molecular motors. We describe cellular microtubules as oscillators capable of synchronization and swarming, generating mechanical and electric patterns that impact biomolecular recognition. We consider the biological relevance of seeing the inside of cells populated by a network of molecules that behave as bioelectronic circuits and chromophores. We discuss the novel perspectives disclosed by mechanobiology, bioelectromagnetism, and photobiomodulation, both in term of fundamental basic science and in light of the biomedical implication of using physical energies to govern (stem) cell fate. We focus on the feasibility of exploiting atomic force microscopy and hyperspectral imaging to detect signatures of nanomotions and electromagnetic radiation (light), respectively, generated by the stem cells across the specification of their multilineage repertoire. The chance is reported of using these signatures and the diffusive features of physical waves to direct specifically the differentiation program of stem cells in situ, where they already are resident in all the tissues of the human body. We discuss how this strategy may pave the way to a regenerative and precision medicine without the needs for (stem) cell or tissue transplantation. We describe a novel paradigm based upon boosting our inherent ability for self-healing.

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Effect of single and multiple doses of low-level laser therapy on viability and proliferation of stem cells from human exfoliated deciduous teeth (SHED).

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The present study aimed to evaluate in vitro whether the low-level laser (LLL) delivering fractionated total energy (multiple irradiation) or single irradiation stimulates regeneration-associated events (viability and proliferation) in stem cells from human exfoliated deciduous teeth (SHED). Cells received LLL irradiation (InGaAlP-660 nm), according to the following experimental groups: G1 (single irradiation 2.5 J/cm 2 , 10 mW, 10 s, 0.10 J), G2 (single irradiation 5.0 J/cm 2 , 10 mW, 20 s, 0.20 J), G3 (single irradiation 7.5 J/cm 2 , 10 mW, 30 s, 0.30 J), G4 (two irradiations 2.5 J/cm 2 , 10 mW, 10 s; total energy 0.20 J), G5 (three irradiations 2.5 J/cm 2 , 10 mW, 10 s; total energy 0.30 J), and G6 (non-irradiated). Cell viability was assessed by MTT and trypan blue exclusion (TBE) methods, while cell proliferation was evaluated by crystal violet (CV) and sulforhodamine B (SRB) assays after 24, 48, and 72 h after the first irradiation. By MTT, there was no difference between groups at 24 and 72 h. At 48 h, the groups subjected to multiple irradiation (G4 and G5) presented higher cell viability rates. The average percentages of viable cells for all groups by TBE method were 91.04%, 96.63%, and 97.48% at 24, 48, and 72 h, respectively. By CV, there was no significant difference between groups at 24 and 48 h; at 72 h, G2, G3, and G4 presented higher cell proliferation. By SRB, G1 and G4 presented lower proliferation rates in all the periods. When the groups presenting the same total energy were compared, G2 (0.20 J) presented lower cell viability rates and higher cell proliferation rates in comparison with G4; G3 (0.30 J) presented similar results to those of G5, with higher cell viability and proliferation. The application of laser delivering fractionated total energy (two or three applications of 2.5 J/cm 2) induced higher cell viability at 48 h, while the single irradiation with 2.5 J/cm 2 did not stimulate metabolic activity in such period and the proliferation over time. The 5.0 and 7.5 J/cm 2 single doses and the three applications of 2.5 J/cm 2 maintained cell viability and stimulated proliferation of SHED at 72 h.

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Co-administration of human adipose-derived stem cells and low-level laser to alleviate neuropathic pain after experimental spinal cord injury.

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BACKGROUND: Evidence has suggested that human adipose-derived stem cells (hADSCs) and low-level laser has neuroprotective effects on spinal cord injury (SCI). Therefore, the combined effect of the hADSCs and laser on neuregeneration and neuropathic pain after SCI was investigated. METHODS: Forty-eight adult male Wistar rats with 200-250 g weight were used. Thirty minutes after compression, injury with laser was irritated, and 1 week following SCI, about 1×10^6 cells were transplanted into the spinal cord. Motor function and neuropathic pain were assessed weekly. Molecular and histological studies were done at the end of the fourth week. RESULTS: The combined application of hADSCs and laser has significantly improved motor function recovery ($p = 0.0001$), hyperalgesia ($p < 0.05$), and allodynia ($p < 0.05$). GDNF mRNA expression was significantly increased in hADSCs and laser+hADSC-treated animals ($p < 0.001$). Finally, co-administration of hADSCs and laser has enhanced the number of axons around cavity more than other treatments ($p < 0.001$). CONCLUSIONS: The results showed that the combination of laser and ADSCs could significantly improve the motor function and alleviate SCI-induced allodynia and hyperalgesia. Therefore, using a combination of laser and hADSCs in future experimental and translational clinical studies is suggested.

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Effect of Photobiomodulation Therapy on the Increase of Viability and Proliferation of Human Mesenchymal Stem Cells.

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Cells isolated surgically from the femoral bone during surgery were identified by flow cytometry and cell differentiation assays. For irradiation, two wavelengths (808 and 905 nm) with the following parameters were used: power density 195, 230, and 318 mW/cm 2 , doses of energy 3, 10, and 20 J (energy density 0.93-6.27 J/cm 2), and in continuous (CW) or pulsed emission (PE) (frequencies 1,000 and 2,000 Hz).

There were statistically significant increases of cell viability and proliferation after irradiation at 3 J (CW; 1,000 Hz), 10 J (1,000 Hz), and 20 J (2,000 Hz).

Irradiation with the MLS M1 system can be used in vitro to modulate MSCs in preparation for therapeutic applications. This will assist in designing further studies to optimize the radiation parameters and elucidate the molecular mechanisms of action of the radiation. Lasers Surg. Med. © 2019 Wiley Periodicals, Inc.

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Evaluation of treatment of experimentally induced canine model of multiple sclerosis using laser activated non-expanded adipose derived stem cells.

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Multiple sclerosis (MS) is a progressive demyelinating disease of the central nervous system that destroys oligodendrocytes. This work aims to evaluate the treatment of experimentally induced MS in dogs using laser activated non-expanded adipose derived stem cells. The results showed amelioration of the clinical signs over time confirmed by the resolution of the previous lesions on MRI. Positive migration of the injected cells to the site of lesion, increased remyelination detected by Myelin Basic Proteins, positive differentiation into Olig2 positive oligodendrocytes, prevented the glial scar formation and restored axonal architecture. The study concluded that treatment using laser activated stem cells holds a promising therapeutic option for treatment of MS in a canine model.

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The Combined Effects of Mesenchymal Stem Cell Conditioned Media and Low-Level Laser on Stereological and Biomechanical Parameter in Hypothyroidism Rat Model.

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Introduction: Many studies have shown the positive effect of laser radiation and application of the mesenchymal stem cells (MSCs) and their secretion in stimulating bone regeneration. The aim of this study was determining effects of MSC conditioned media (CM) and low-level laser (LLL) on healing bone defects in the hypothyroid male rat. Methods: We assigned 30 male Wistar rats randomly to 3 groups: control, hypothyroidism, CM+LLL. Four weeks after surgery, the right tibia was removed. Biomechanical examination and histological examinations were performed immediately. Results: Our results showed significant increase in bending stiffness (116.09±18.49), maximum force (65.41±8.16), stress high load (23.30±7.14), energy absorption (34.57±4.10), trabecular bone volume (1.34±0.38) and the number of osteocyte, osteoblast, and osteoclast (12.77±0.54, 6.19±0.80, 1.12±0.16 respectively) in osteotomy site in the LLL+CM group compared to the hypothyroidism group ($P<0.05$). Conclusion: The results indicated that using the LLL + CM may improve fracture regeneration and it may hasten bone healing in the hypothyroid rat.

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Biological effects of low-level laser irradiation (LLLI) on stem cells from human exfoliated deciduous teeth (SHED).

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OBJECTIVES: To investigate the effects of low-level laser irradiation (LLLI) on viability/proliferation, migration, osteo/odontogenic differentiation, and in vitro biomineralization of stem cells from human exfoliated deciduous teeth (SHED). MATERIALS AND METHODS: SHED cultures were established by enzymatic dissociation from pulps of deciduous teeth. SHED were irradiated with a diode laser (InGaAsP; 940 nm; 0.2 W, continuous mode) at energy fluences 4, 8, and 16 J/cm2 in the dark, while non-irradiated SHED served as control. Cell viability/proliferation was evaluated by MTT assay and cell mobilization by Transwell™ migration assay. Expression of osteo/odontogenesis-related genes (ALP, BMP-2, BGLAP, DSPP, MSX2, RUNX2) was assessed by real-time PCR, while in vitro biomineralization by Alizarin Red staining. Statistical analysis was performed by two-way ANOVA and Tukey's post hoc tests (*$p < 0.05$, **$p < 0.01$). RESULTS: Statistically significant stimulation of cell viability/proliferation was observed at all energy fluences, reaching the highest effect for the 4 and 16 J/cm2. Although the 8 J/cm2 fluence showed the lowest stimulatory effect on cell viability/proliferation, it was the most effective in inducing SHED migration, upregulation of odontogenesis-related genes (DSPP, ALP, BMP-2) at specific time-points, and the in vitro biomineralization potential of SHED compared to the other two energy fluences. CONCLUSIONS: LLLI proved beneficial in promoting SHED biological processes critical for pulp repair in deciduous teeth. Overall, the 8 J/cm2 energy fluence showed the most beneficiary effects.CLINICAL RELEVANCE: These results provide insights on a narrow "therapeutic window" of LLLI application in vital pulp therapies of deciduous teeth, paving the way for the establishment of effective clinical protocols.

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Photobiomodulation Therapy of Cells in the Bone Marrow: A Novel Therapeutic Approach in Cell Therapy and Regenerative Medicine.

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Regenerative medicine is currently a very active field of research and clinical trials. There are many new approaches, and extensive research focuses on cell-based therapies for impaired organs that allow for reconstruction.....
Photobiomodulation (PBM) can increase mitochondrial respiration adenosine triphosphate (ATP) synthesis and can modulate various biological processes. This facilitates healing of wounds and promotes skeletal muscle regeneration and angiogenesis.1,2
PBM therapy (PBMT) has been shown to be able to enhance skeletal muscle regeneration. It should be noted that muscle-derived scaffold was used as an acellular biomaterial for enhancement of muscle regeneration and bone repair.3
It has been demonstrated with the use of an infarcted heart experimental model of dogs and rats that PBM showed significant reduction in the formation of scar tissue following myocardial infarction (MI).
An elevation in ATP content and healing of shock proteins, together with .....
.....This study showed that when in the BM, the MSCs that follow remote photobiomodulation therapy (rPBMT) in vivo can be induced to proliferate at a higher rate than nontreated MSCs.
In addition, laser application at ~20-min post-MI to the BM caused a significant and marked 79% reduction in infarct size at 3 weeks post-MI.
The reduction in scarring of infarct size was more effective than the application of laser directly to an infarcted heart.4,5.....
.....A follow-up clinical study was designed to determine the long-term safety and possible feasibility of PBM application to the BM in patients with acute myocardial infarction (AMI).20 The study comprised patients suffering from acute ST segment elevation myocardial infarction (STEMI) and candidates for primary percutaneous coronary intervention (PPCI). In the active group (rPBMT, LT group), PBMT was applied to the tibia bone noninvasively before PPCI, 24 and 72 h post-PPCI. In the placebo group (NLT group) laser source was powered-off. Blood samples were taken on admission and during the first week post-STEMI as well as echocardiography flow up. Twenty-four patients in total (12 in treated and 12 in placebo group) were enrolled. No adverse effects of the treatment were detected, as indicated by blood markers and kinetics of echocardiography. Levels of creatinine phosphokinase accumulation in the blood (indicator of cardiac muscle leakage) in the NLT patients group was 49 ± 12, whereas in the LT patients group a lower ($p = 0.08$) level of 22 ± 10 was detected. Peak troponin-I was 5.2 ± 1.8 ng/mL in the NLT group, which was significantly higher ($p < 0.05$) than the value in the LT group (2.7 ± 1.4 ng/mL), indicating possible cardioprotection of the ischemic heart by rPBMT to the BM. Application of rPBMT to the BM to photobiostimulate stem cells for the benefit of the infarcted heart seems to be a safe procedure for application in humans, and offers a novel approach in cell therapy adjunctive to the PPCI in patients post-AMI.

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Photobiomodulation and gametogenic potential of human Wharton's jelly-derived mesenchymal cells.

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Recently, light emitting diode (LED) irradiation has been introduced as a new strategy to enhance proliferation and affect differentiation of stem cells. Human Wharton's jelly-derived mesenchymal (hWJM) cells have unique characteristics that make them an appropriate source of stem cells for use in basic and clinical applications. In this study, we aimed to evaluate the effect of polarized (PL) and non-polarized (NPL) red light irradiation on gametogenic differentiation of hWJM cells in the presence or absence of bone morphogenetic protein 4 (BMP4) and retinoic acid (RA). Exposure of hWJM cells to PL and NPL red LED (625 nm, 1.9 J/cm 2) with or without BMP4 +RA pre-treatment effectively differentiated them into germ lineage when the gene expression pattern (Fragilis, DAZL, VASA, SCP3 and Acrosin) and protein synthesis (anti-DAZL, anti-VASA, anti-SCP3 and anti-Acrosin antibodies) of the induced cells was evaluated. These data demonstrated that photobiomodulation may be applied for gametogenic differentiation in-vitro.

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Effects of photobiomodulation therapy on the extracellular matrix of human dental pulp cell sheets.

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Thawed cells were recharacterized by the expression profile of the surface molecules of mesenchymal stem cells (MSCs) using flow cytometry. Clonogenic medium supplemented with vitamin C (20 μg/ml) was used for obtaining the CSs. PBMT was performed with continuous-wave diode laser (660 nm, 20 mW, 0.028cm 2, 0.71 W/cm 2) in punctual and contact mode. The CSs were allocated in 3 experimental groups: Control: no further treatment; PBMT1 [4 s, 3 J/cm 2 (lower energy density), 0.08 J/point] and PBMT2 [7 s, 5 J/cm 2 (higher energy density), 0.14 J/point]. Statistical comparisons were performed ($p \leq .05$).

The cells presented the classical immunoprofile of MSCs. Type I and type III collagens and fibronectin were present in the ECM of the CSs. PBMT1 induced higher amount of fibronectin. The overall ultrastructure of the CSs in the PBMT1 was epithelial-like, whereas the PBMT2 leads to CSs with fusiform cells arranged in bundles. TEM identified a more mature ECM and signs of apoptosis and necrosis in the PBMT2 group.

PBMT influence the composition and ultrastructure of the ECM of CSs of hDPSCs. Thus, PBMT, specifically when applied in the lower energy density, could be of importance in the determination of the mechanical quality of CSs, which may favor cell therapy by improving the CS transplantation approach.

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A transient protective effect of low-level laser irradiation against disuse-induced atrophy of rats.

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Satellite cells, a population of skeletal muscular stem cells, are generally recognized as the main and, possibly, the sole source of postnatal muscle regeneration. Previous studies have revealed the potential of low-level laser (LLL) irradiation in promoting satellite cell proliferation, which, thereby, boosts the recovery of skeletal muscle from atrophy. The purpose of this study is to investigate the beneficial effect of LLL on disuse-induced atrophy. The optimal irradiation condition of LLL (808 nm) enhancing the proliferation of Pax7+ve cells, isolated from tibialis anterior (TA) muscle, was examined and applied on TA muscle of disuse-induced atrophy model of the rats accordingly. Healthy rats were used as the control. On one hand, transiently, LLL was able to postpone the progression of atrophy for 1 week through a reduction of apoptosis in Pax7-veMyoD+ve (myocyte) population. Simultaneously, a significant enhancement was observed in Pax7+veMyoD+ve population; however, most of the increased cells underwent apoptosis since the second week, which suggested an impaired maturation of the population. On the other hand, in normal control rats with LLL irradiation, a significant increase in Pax7+veMyoD +ve cells and a significant decrease of apoptosis were observed. As a result, a strengthened muscle contraction was observed. Our data showed the capability of LLL in postponing the progression of disuse-induced atrophy for the first time. Furthermore, the result of normal rats with LLL irradiation showed the effectiveness of LLL to strengthen muscle contraction in healthy control.

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Photobiomodulation Enhances the Angiogenic Effect of Mesenchymal Stem Cells to Mitigate Radiation-Induced Enteropathy.

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Radiation-induced enteropathy remains a major complication after accidental or therapeutic exposure to ionizing radiation. Recent evidence suggests that intestinal microvascular damage significantly affects the development of radiation enteropathy. Mesenchymal stem cell (MSC) therapy is a promising tool to regenerate various tissues, including skin and intestine. Further, photobiomodulation (PBM), or low-level light therapy, can accelerate wound healing, especially by stimulating angiogenesis, and stem cells are particularly susceptible to PBM. Here, we explored the effect of PBM on the therapeutic potential of MSCs for the management of radiation enteropathy. In vitro, using human umbilical cord blood-derived MSCs, PBM increased proliferation and self-renewal. Intriguingly, the conditioned medium from MSCs treated with PBM attenuated irradiation-induced apoptosis and impaired tube formation in vascular endothelial cells, and these protective effects were associated with the upregulation of several angiogenic factors. In a mouse model of radiation-induced enteropathy, treatment with PBM-preconditioned MSCs alleviated mucosal destruction, improved crypt cell proliferation and epithelial barrier functions, and significantly attenuated the loss of microvascular endothelial cells in the irradiated intestinal

Low-level laser and adipose-derived stem cells altered remodelling genes expression and improved collagen reorganization during tendon repair.

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OBJECTIVES: The cellular therapy using adipose-derived mesenchymal stem cells (ASCs) aims to improve tendon healing, considering that repaired tendons often result in a less resistant tissue. Our objective was to evaluate the effects of the ASCs combination with a low-level laser (LLL), an effective photobiostimulation for the healing processes. MATERIALS AND METHODS: Rats calcaneal tendons were divided into five groups: normal (NT), transected (T), transected and ASCs (SC) or LLL (L), or with ASCs and LLL (SCL). RESULTS: All treated groups presented higher expression of Dcn and greater organization of collagen fibres. In comparison with T, LLL also up-regulated Gdf5 gene expression, ASCs up-regulated the expression of Tnmd, and the association of LLL and ASCs down-regulated the expression of Scx. No differences were observed for the expression of Il1b, Timp2, Tgfb1, Lox, Mmp2, Mmp8 and Mmp9, neither in the quantification of hydroxyproline, TNF-α, PCNA and in the protein level of Tnmd. A higher amount of IL-10 was detected in SC, L and SCL compared to T, and higher amount of collagen I and III was observed in SC compared to SCL. CONCLUSIONS: Transplanted ASCs migrated to the transected region, and all treatments altered the remodelling genes expression. The LLL was the most effective in the collagen reorganization, followed by its combination with ASCs. Further investigations are needed to elucidate the molecular mechanisms involved in the LLL and ASCs combination during initial phases of tendon repair.

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Mechanisms of repigmentation induced by photobiomodulation therapy in vitiligo.

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Photobiomodulation (PBM) therapy is based on the exposure of biological tissues to low-level laser light (coherent light) or light-emitting diodes (LEDs; noncoherent light), leading to the modulation of cellular functions, such as proliferation and migration, which result in tissue regeneration. PBM therapy has important clinical applications in regenerative medicine. Vitiligo is an acquired depigmentary disorder resulting from disappearance of functional melanocytes in the involved skin. Vitiligo repigmentation depends on available melanocytes derived from (a) melanocyte stem cells located in the bulge area of hair follicles and (b) the epidermis at the lesional borders, which contains a pool of functional melanocytes. Since follicular melanoblasts (MBs) are derived from the melanocyte stem cells residing at the bulge area of hair follicle, the process of vitiligo repigmentation presents a research model for studying the regenerative effect of PBM therapy. Previous reports have shown favourable response for treatment of vitiligo with a low-energy helium-neon (He-Ne) laser. This review focuses on the molecular events that took place during the repigmentation process of vitiligo triggered by He-Ne laser (632.8 nm, red light). Monochromatic radiation in the visible and infrared A (IRA) range sustains matrix metalloproteinase (MMP), improves mitochondrial function, and increases adenosine triphosphate (ATP) synthesis and O 2 consumption, which lead to cellular regenerative pathways. Cytochrome c oxidase in the mitochondria was reported to be the photoacceptor upon which He-Ne laser exerts its effects. Mitochondrial retrograde signalling is responsible for the cellular events by red light. This review shows that He-Ne laser initiated mitochondrial retrograde signalling via a Ca 2+ -dependent cascade. The impact on cytochrome c oxidase within the mitochondria, an event that results in activation of CREB (cyclic-AMP response element binding protein)-related cascade, is responsible for the He-Ne laser promoting functional development at different stages of MBs and boosting functional melanocytes. He-Ne laser irradiation induced (a) melanocyte stem cell differentiation; (b) immature outer root sheath MB migration; (c) differentiated outer root sheath MB melanogenesis and migration; and (d) perilesional melanocyte migration and proliferation. These photobiomodulation effects result in perifollocular and marginal repigmentation in vitiligo.

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New insights into the treatment of non-healing diabetic foot ulcers.

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Diabetic foot ulcers (DFUs) are one of the most serious and devastating complication of diabetes mellitus, affecting about 15% of diabetic patients. This review describes the innovative treatment options currently available in the treatment of non-healing DFUs. The use of Platelet-Rich-Plasma (PRP) is a safe and valid approach in the treatment of DFUs. However, the methods used to obtain and prepare autologous PRP vary between the studies, thus further evidences are eagerly awaited. Adipose tissue-derived mesenchymal stem cells (ADSCs) are a promising tool in the treatment of DFUs, but additional largescale and long-term follow-up clinical trials are needed. Bone marrow mesenchymal stem cells (BM-MSCs) transplantation, on the other hand, revealed effective in reducing incidents and improving the quality of life of patients with amputations. Autologous Peripheral Blood Mononuclear Cells (A-PBMNCs) showed a good efficacy in the treatment of diabetic patients with CLI, but further RCTs are awaited to best investigate this new therapeutic approach. Photobiomodulation (PBM) therapy revealed effective in the treatment of DFUs in two RCTs, but a standardization of therapeutic protocols as well as level-I studies are needed.

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Evaluation of low-level diode laser irradiation and various irrigant solutions on the biological response of stem cells from exfoliated deciduous teeth.

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This study aimed to evaluate cytotoxic effects and the apoptosis of Gallium-Aluminum-Arsenide (GaAlAs) diode laser irradiation, sodium hypochlorite (NaOCl), ozonated water and ethylene diamine tetraacetic acid (EDTA) on stem cells from human exfoliated deciduous teeth (SHEDs). Cells were exposed to EDTA (5%, 8.5%, 17%), NaOCl (1%, 2.5%, 5%) ozonated water (5, 10, 20 µg/ml) and GaAlAs diode laser irradiation (energy densities of 0.5, 1, 1.5 j/cm2). Culture medium included D-MEM, supplemented with 15% foetal bovine serum, 1% l-glutamine, 1% penicillin-streptomycin, 1% gentamycin, amphotericin-B and served as control group. The prepared irrigants were added to the relevant wells and incubated with the cells at 37 °C for 5, 10 and 15 min. The cells in the laser group were also incubated at 37 °C for 5, 10 and 15 min after the laser application. Cell viability and proliferation were analysed with the 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay. The percentage of cell viability showed a significant reduction in all concentrations of the EDTA and NaOCl groups when compared to the control group, diode laser irradiation and ozonated water groups at 5th, 10th and 15th minutes respectively but high cytotoxic effects of all EDTA and NaOCl groups with decreased over 50% of cell viability were observed at the 15th minute. Also EDTA group with 17% concentration (17%E) presented the lowest survival rate on SHEDs with mean of 21.67% ± 6.101 at this time interval. The lowest toxic effects were observed at the 5th minutes compared to other time periods at experimental groups. For detection of apoptotic cells, the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labelling (TUNEL) method was performed. According to the MTT results, doses showed the highest toxicity (cell survival decreased over 50%) in each group were selected for TUNEL assay (17% EDTA; 1% NaOCl; 10 µg/ml Ozonated water; 1.5 j/cm2 diode laser irradiation). The significantly lowest percentages of TUNEL-positive cells were detected in ozonated water (10.67% ± 2.93) and diode laser irradiation (13.24% ± 7.61) compared to EDTA (39.89% ± 11.54) and NaOCl (31.15% ± 10.64) respectively. Also the difference between percentage of TUNEL-positive cells in EDTA and NaOCl groups was not significant. Synergistic combination of ozonated water and diode laser irradiation may be used in the disinfection step of necrotic root canals.

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[Cytotoxic Effect of Low-Intensity Infrared Laser Irradiation on Human Melanoma Cells].

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Continuous low-intensity laser irradiation (LILI) affects the state of cells in culture, including their proliferation rate. Data collected with various cell models vary significantly, but most studies have reported positive effects of LILI on cell proliferation. The effects of continuous infrared LILI (835 nm) was studied using three independent different melanoma cell lines. The LILI effect was shown to strongly depend on the irradiation dose. Higher doses (230 kJ/m2) significantly suppressed the cell growth. A further increase in LILI dose led to a significant cytotoxic effect, which increased disproportionately quickly with the increasing light intensity. Human mesenchymal stem cells (MSCs) were found to be significantly more resistant to the cytotoxic effect of higher-dose LILI. Importantly, the effects were not due to the difference in culture conditions. Control experiments showed that 15 non-melanoma tumor cell lines were more resistant to LILI than melanoma cells. Selective sensitivity of melanoma cells to LILI in vitro was assumed to provide a basis for LILI-based approaches to melanoma treatment.

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Radiation-induced skin reactions: mechanism and treatment.

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Radiotherapy (RT) is a major treatment for malignant tumors. The latest data show that >70% of patients with malignant tumors need RT at different periods. Skin changes can be experienced by up to 95% of patients who underwent RT. Inflammation and oxidative stress (OS) have been shown to be generally associated with radiation-induced skin reactions (RISRs). Inflammatory response and OS interact and promote each other during RISRs. Severe skin reactions often have a great impact on the progress of RT. The treatment of RISRs is particularly critical because advanced RT technology can also lead to skin reactions. RISRs are classified into acute and chronic reactions. The treatment methods for acute RISRs include steroid treatment, creams, ointments, and hydrocolloid dressings, depending on the reaction grading. Chronic RISRs includes chronic ulcerations, telangiectasias, and fibrosis of the skin, and advanced treatments such as mesenchymal stem cells, hyperbaric oxygen therapy, superoxide dismutase, and low-intensity laser therapy can be considered. Here, we review and summarize the important mechanisms that cause RISRs as well as the standard and advanced treatments for RISRs.

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Improvement in infected wound healing in type 1 diabetic rat by the synergistic effect of photobiomodulation therapy and conditioned medium.

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We investigated the effects of photobiomodulation therapy (PBMT) and conditioned medium (CM) of human bone marrow mesenchymal stem cells (hBM-MSC) individually and/or in combination on the stereological parameters and the expression of basic fibroblast growth factor (bFGF), hypoxia-inducible factor (HIF-1α), and stromal cell-derived factor-1α (SDF-1α) in a wound model infected with methicillin-resistant Staphylococcus aureus (MRSA) in diabetic rats. CM was provided by culturing hBM-MSCs. Type 1 diabetes mellitus (T1DM) was induced in 72 rats, divided into four groups, harboring 18 rats each: group 1 served as a control group, group 2 received PBMT, group 3 received CM, and group 4 received CM + PBMT. On days 4, 7, and 15, six animals from each group were euthanized and the skin samples were separated for stereology examination and gene expression analysis by real-time polymerase chain reaction. In the CM + PBMT, CM, and PBMT groups, significant decreases were induced in the number of neutrophils (1460 ± 93, 1854 ± 138, 1719 ± 248) and macrophages (539 ± 69, 804 ± 63, 912 ± 41), and significant increases in the number of fibroblasts (1073 ± 116, 836 ± 75, 912 ± 41) and angiogenesis (15 230 ± 516, 13 318 ± 1116, 14 041 ± 867), compared with those of the control group (2690 ± 371, 1139 ± 145, 566 ± 90, 12 585 ± 1219). Interestingly, the findings of the stereological examination in the CM + PBMT group were statistically more significant than those in the other groups. In the PBMT group, in most cases, the expression of bFGF, HIF-1α, and SDF-1α, on day 4 (27.7 ± 0.14, 28.8 ± 0.52, 27.5 ± 0.54) and day 7 (26.8 ± 1.4, 29.6 ± 1.4, 28.3 ± 1.2) were more significant than those in the control (day 4, 19.3 ± 0.42, 25.5 ± 0.08, 22.6 ± 0.04; day 7, 22.3 ± 0.22, 28.3 ± 0.59, 24.3 ± 0.19) and other treatment groups. The application of PBMT + CM induced anti-inflammatory and angiogenic activities, and hastened wound healing process in a T1 DM model of MRSA infected wound.

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Photobiomodulation (PBM) promotes angiogenesis in-vitro and in chick embryo chorioallantoic membrane model.

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The application of light in various therapeutic settings known as Photobiomodulation (PBM) is well established. Indications are the improvement of wound healing and tissue regeneration, scarring, and perfusion as well as pain therapy. Tissue perfusion is mandatory for successful wound healing. Nevertheless, there is a lack of mechanistic studies. We investigate the potential effect of PBM from light emitting diodes (LED) at 635 nm, 80 mW/cm 2, 24 J/cm 2 on angiogenesis in a two-part study: 1.) Investigation of the effect of PBM on the proliferation of endothelial cells and on vasculogenesis in a co-culture model of endothelial cells and stem cells. 2.) Investigation of the influence of PBM at chick egg chorioallantoic membrane (CAM) assays with fresh human skin xenografts. In both study phases, we observed a stimulating effect of PBM at 635 nm; in part 1: for proliferation of HUVEC (human umbilical vein endothelial cells) (25833 ± 12859 versus 63002 ± 35760 cells/well, p ; 0.05, for cellular network formation (2.1 ± 2.1 versus 4.6 ± 3.5, p ; 0.05) and for less cell compactness p = 0.01; in part 2: for the increase of number of vessel junctions per ROI (region of interest) (15.9 ± 2.6 versus 20.8 ± 5.4, p ; 0.05). Our results suggest significant promotion of angiogenesis by PBM at 635 nm in vitro and in vivo.

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Adipogenic differentiation of murine bone marrow mesenchymal stem cells induced by visible light via photo- induced biomodulation.

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BACKGROUND: Bone marrow mesenchymal stem cells (BM-MSCs) are undifferentiated cells that can proliferate and differentiate into specialized cells for tissue self-repair. Low-level laser (LLL) can induce biomodulatory effects such as cellular proliferation, differentiation, and migration. We investigated the biomodulatory effects of the photoactive compound chloroaluminum phthalocyanine nanoemulsion (AlClPc/NE) on the adipogenic differentiation of BM-MSCs, when combined with LLL (AlClPc/NE-LLL). METHODS: The BM-MSCs used in this work were isolated from green fluorescent protein-positive (GFP RESULTS: Our results showed that the isolated cell population was consistent with murine BM-MSCs. The cellular cytotoxicity analysis revealed that the optimal nanoemulsion dose to induce BM-MSC biomodulation was 5.0 µmol/L. Twenty-four hours following treatment with AlClPc/NE, BM-MSC were subjected to visible light irradiation of 20 mJ/cm CONCLUSIONS: Our results indicated that photo-induced biomodulation via visible light using AlClPc/NE and LLL can induce adipogenic differentiation of murine BM-MSCs. Therefore, cell therapy with BM-MSCs and photo-induced biomodulation may contribute to the development of new therapeutic strategies that are faster and more effective than traditional methods to trigger MSC differentiation.

Photodiagnosis Photodyn Ther 2018 Nov 17

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Low-level laser irradiation modulates the proliferation and the osteogenic differentiation of bone marrow mesenchymal stem cells under healthy and inflammatory condition.

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The aim of this in vitro study was to evaluate the effects of low-level laser therapy (LLLT) at different energy intensities on proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) under healthy and inflammatory microenvironments. Human BMSCs and BMSCs from inflammatory conditions (i-BMSCs, BMSCs treated with tumor necrosis factor α; TNF-α) were subject to LLLT (Nd:YAG;1064 nm) at different intensities. We designed one control group (without irradiation) and four testing groups (irradiation at 2, 4, 8, and 16 J/cm2) for both BMSCs and i-BMSCs. Cell proliferation was measured using colony-forming unit fibroblast assay and 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyltetrazolium bromide assay. Osteogenic capacity of cells was determined by alkaline phosphatase (ALP) staining, ALP activity assay, Alizarin Red S staining and the mRNA transcript levels of genes runt-related transcription factor 2 (Runx2), ALP, and osteocalcin. Moreover, the effects of LLLT on secretion of TNF-α in BMSCs and i-BMSCs were measured by enzyme-linked immunosorbent assay. Our results demonstrated LLLT could significantly promote BMSC proliferation and osteogenesis at densities of 2 and 4 J/cm2. LLLT at density of 8 J/cm2 could promote the proliferation and osteogenesis of i-BMSCs. However, LLLT at 16 J/cm2 significantly suppressed the proliferation and osteogenesis of BMSCs both in healthy and in inflammatory microenvironment. Moreover, we also found that the expression of TNF-α was obviously inhibited by LLLT at 4, 8, and 16 J/cm2, in an inflammatory microenvironment. Considering these findings, LLLT could improve current in vitro methods of differentiating BMSCs under healthy and inflammatory microenvironments prior to transplantation.

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Adipose-derived mesenchymal stem cells treatments for fibroblasts of fibrotic scar via downregulating TGF-β1 and Notch-1 expression enhanced by photobiomodulation therapy.

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<AbstractText/>

Lasers Med Sci, 2019 Feb 34(1) 1-10

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[Effects of low level laser irradiation on the osteogenic capacity of sodium alginate/gelatin/human adipose-derived stem cells 3D bio-printing construct].

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OBJECTIVE: To explore the effects of low level laser irradiation (LLLI) on the osteogenic capacity of three-dimensional (3D) structure by 3D bio-printing construct used human adipose-derived stem cells (hASCs) as seed cells. METHODS: Using hASCs as seed cells, we prepared sodium alginate/gelatin/hASCs 3D bio-printing construct, and divided them into four groups: PM (proliferative medium), PM+LLLI, OM (osteogenic medium) and OM+LLLI, and the total doses of LLLI was 4 J/cm^2. Immunofluorescence microscopy was used to observe the viability of the cells, and analyze the expression of the osteogenesis-related protein Runt-related transcription factor 2 (Runx2) and osteocalcin (OCN). RESULTS: The 3D constructs obtained by printing were examined by microscope. The sizes of these 3D constructs were 10 mm×10 mm×1.5 mm. The wall thickness of the printed gelatin mold was approximately 1 mm, and the pores were round and had a diameter of about 700 μm. The cell viability of sodium alginate/gelatin/hASCs 3D bio-printing construct was high, and the difference among the four groups was not significant. On day 7, the expression of OCN from high to low was group OM+LLLI, PM+LLLI, OM and PM. There were significant differences among these groups ($P<0.01$), but there was no significant difference between group PM+LLLI and OM. On day 14, the expression of OCN in each group was higher than that on day 7, and there was no significant difference between group OM+LLLI and OM. The expression of Runx2 in group OM+LLLI was more than 90%, significantly higher than that in group OM ($P<0.01$). But the expression of Runx2 in group PM+LLLI and OM+LLLI were significantly lower than that in the non-irradiated groups. The expression of osteogenesis-related protein Runx2 and OCN were higher in OM groups than in PM groups. Furthermore, the irradiated groups were significantly higher than the non-irradiated groups. CONCLUSION: LLLI does not affect the cell viability of sodium alginate/gelatin/hASCs 3D bio-printing construct, and may promote the osteogenic differentiation of hASCs.

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Photobiomodulation effect on the proliferation of adipose tissue mesenchymal stem cells.

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The use of mesenchymal stem cells (MSCs) in tissue engineering has been extensively investigated. The greater the proliferation of this cellular group, the greater the regenerative and healing capacity of the tissue to which they belong. In this context, photobiomodulation (PBM) is an efficient technique in proliferation of distinct cell types. However, its parameters and mode of action are still unclear and require further investigation. This study aimed to evaluate the PBM action with different energies in MSCs of adipose tissue (hASCs). We used hASCs, seeded in 24-well plates, with 3 × 10 4 cells per well, in culture media. We used a total of four experimental groups, one with hASCs and simulated PBM and three other groups, which received PBM irradiation at 24, 48, and 72 h, with a 660-nm laser and power of 40 mW and energy of 0.56, 1.96, and 5.04 J. We performed analyses of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromidefor) and trypan blue to evaluate cell proliferation and viability, 1 h after PBM irradiation. Software Graph PadPrism 7.0 was used. Intergroup comparisons were performed with ANOVA two-way and we used the Tukey post hoc test. Mitochondrial activity evaluated by MTT revealed the statistical difference in the first 24 h for group with more high energy when compared to control group; and in the 72 h for two irradiated groups when compared to the control group. The trypan blue test showed significant differences at the end of the experiment for two irradiated groups LG1 (4.52 × 10 4 ± 0.2) and LG2 (4.85 × 104 ± 0.8), when compared to the control group (1.87 × 10 4 ± 0.7). Both tests failed to be statistically different at the end of the experiment for groups LG1 and LG2 and observed a reduction in cellular mitochondrial growth and activity for group LG3. We conclude that PBM with energy close to 0.56 and 1.96 J promote proliferation of hASCs, and higher energy, such as 5.04 J, can be harmful.

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Photobiomodulation with single and combination laser wavelengths on bone marrow mesenchymal stem cells: proliferation and differentiation to bone or cartilage.

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Tissue engineering aims to take advantage of the ability of undifferentiated stem cells to differentiate into multiple cell types to repair damaged tissue. Photobiomodulation uses either lasers or light-emitting diodes to promote stem cell proliferation and differentiation. The present study aimed to investigate single and dual combinations of laser wavelengths on mesenchymal stem cells (MSCs). MSCs were derived from rabbit iliac bone marrow. One control and eight laser irradiated groups were designated as Infrared (IR, 810 nm), Red (R, 660 nm), Green (G, 532 nm), Blue (B, 485 nm), IR-R, IR-B, R-G, and B-G. Irradiation was repeated daily for 21 days and cell proliferation, osseous, or cartilaginous differentiation was then measured. RT-PCR biomarkers were SOX9, aggrecan, COL 2, and COL 10 expression for cartilage and ALP, COL 1, and osteocalcin expression for bone. Cellular proliferation was increased in all irradiated groups except G. All cartilage markers were significantly increased by IR and IR-B except COL 10 which was suppressed by IR-B combination. ALP expression was highest in R and IR groups during osseous differentiation. ALP was decreased by combinations of IR with B and with R, and also by G alone. R and B-G groups showed stimulated COL 1 expression; however, COL 1 was suppressed in IR-B, IR-R, and G groups. IR significantly increased osteocalcin expression, but in B, B-G, and G groups it was reduced. Cartilage differentiation was stimulated by IR and IR-B laser irradiation. The effects of single or combined laser irradiation were not clear-cut on osseous differentiation. Stimulatory effects on osteogenesis were seen for R and IR lasers, while G laser had inhibitory effects.

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Short-term evaluation of photobiomodulation therapy on the proliferation and undifferentiated status of dental pulp stem cells.

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The aim of this in vitro study was to analyze the effect of photobiomodulation therapy (PBMT) on the proliferation and undifferentiating status of stem cell from human exfoliated deciduous teeth (SHEDs). PBMT was carried out with an aluminum gallium indium phosphide (InGaAlP) diode laser in contact and punctual mode (continuous wave, 660 nm, 20 mW, 0.028 cm 2, and average energy densities of 1 (1 s), 3 (4 s), 5 (7 s), 10 (14 s), 15 (21 s), or 20 (28 s) J/cm 2 per point). The immunoprofile of the SHEDs was analyzed using flow cytometry. Cell proliferation was assessed by the MTT reduction assay. Gene expressions of mesenchymal stem cell markers (OCT4, Nestin, CD90, and CD105) were assessed by RT-qPCR 48 h after PBMT. Data were compared by analysis of variance (ANOVA) and Tukey's test ($p \leq 0.05$). Cells cultured under nutritional deficit and treated with PBMT at 5 J/cm 2 presented similar cell growth than those of positive control group. Cell growth was significantly higher than those of other groups. Mesenchymal stem cell gene markers were still expressed after PBMT at 5 J/cm 2. In a short-term analysis, PBMT increases the number of stem cells with no interference in the undifferentiated state of the irradiated cells, which opens wide possibilities for application in tissue regeneration.

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Effect of photobiomodulation on neural differentiation of human umbilical cord mesenchymal stem cells.

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Photobiomodulation therapy (PBMT) can enhance the mesenchymal stem cell (MSC) proliferation, differentiation, and tissue repair and can therefore be used in regenerative medicine. The objective of this study is to investigate the effects of photobiomodulation on the directional neural differentiation of human umbilical cord mesenchymal stem cells (hUC-MSCs) and provide a theoretical basis for neurogenesis. hUC-MSCs were divided into control, inducer, laser, and lasers combined with inducer groups. A 635-nm laser and an 808-nm laser delivering energy densities from 0 to 10 J/cm 2 were used in the study. Normal cerebrospinal fluid (CSF) and injured cerebrospinal fluid (iCSF) were used as inducers. The groups were continuously induced for 3 days. Cellular proliferation was evaluated using MTT. The marker proteins nestin (marker protein of the neural precursor cells), NeuN (marker protein of neuron), and GFAP (glial fibrillary acidic protein, marker proteins of glial cells) were detected by immunofluorescence and western blot. We found that irradiation with 635-nm laser increased cell proliferation, and that with 808 nm laser by itself and combined with cerebrospinal fluid treatment generated significant neuron-like morphological changes in the cells at 72 h. Nestin showed high positive expression at 24 h in the 808 nm group. The expression of GFAP increased in the 808-nm combined inducer group at 24 h but decreased at 72 h. The expression of neuN protein increased only at 72 h in both the 808-nm combined inducer group and inducer group. We concluded that 808 nm laser irradiation could help CSF to induce neuronal differentiation of hUC-MSCs in early stage and tend to change to neuron rather than glial cells.

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Photobiomodulation therapy improves multilineage differentiation of dental pulp stem cells in three-dimensional culture model.

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Photobiomodulation therapy (PBM) has shown positive effects on stem cell differentiation in monolayer cell culture model, but little is known about its effect on three-dimensional (3-D) agarose gel culture. This study evaluated the PBM effect of human dental pulp stem cells (hDPSCs) differentiation and phosphatase alkaline activity (ALP) using an agarose 3-D model under different nutritional conditions. hDPSCs were characterized and seeded on a 0.3% agarose gel layer with different media (osteogenic, adipogenic, chondrogenic) and were assigned into four groups: control 10% fetal bovine serum (FBS), control 5% FBS, PBM 10% FBS, and PBM 5% FBS. Irradiation was performed with continuous-wave InGaAlP laser, 660 nm, 100 mW, 3,3 J / cm2, spot size 0.3 cm2, 10 s of exposure time, and 1 J of energy per point with 6-h interval between sessions. All groups were evaluated at 7 and 14 days. ALP assay was performed to analyze the deposition of mineralized tissue. At 7 days, PBM 5% FBS group presented better stimulation in osteogenic and adipogenic differentiation compared with control. After 14 days, hDPSCs cultured in 3-D exhibited osteogenic, adipogenic, and chondrogenic differentiation; furthermore, compared to control, PBM significantly stimulated all differentiation processes (p ; 0.05). It can be concluded that hDPSCs cultured in 3-D agarose associated to PBM could be a promising tool for tissue engineering applications.

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A preliminary comparison between the effects of red and infrared laser irradiation on viability and proliferation of SHED.

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The aim of this preliminary study was to compare the effects of different energy densities from red and infrared low-level laser (LLL) on viability and proliferation of stem cells from human exfoliated deciduous teeth (SHED). SHED were irradiated with red laser (R) or infrared laser (IR) set with the following dosimetry: 1.2 J/cm 2 (0.05 J), 2.5 J/cm 2 (0.1 J), 5.0 J/cm 2 (0.2 J), and 7.5 J/cm 2 (0.3 J). Positive (C+) and negative (C-) control groups comprised non-irradiated cells. Data were analyzed by two-way ANOVA followed by Tukey's test ($P < 0.05$). At 24- and 48-h period, group R5.0 showed significantly higher cell viability rates than R1.2 and R2.5. At 48 h, R2.5 also revealed lower proliferation than R5.0. Comparing to the C+ group, R2.5 exhibited lower viability at 72 h, and proliferation at 24 and 48 h. Groups R1.2, IR1.2, and IR5.0 were less viable at 24 h, while R1.2, IR2.5, and IR5.0 revealed lower proliferative capacity at 48 h. Overall, our results showed that LLL can favor viability and proliferation of SHED, especially when cells receive red laser irradiation at 5.0 J/cm 2 . Therefore, according to this preliminary investigation, 5 J/cm 2 applied by red LLL induced high rates of cell viability and proliferation, while the same irradiation dose using infrared laser led to negative effects. LLL irradiation with 1.2 and 2.5 J/cm 2 was deleterious to metabolic activity and proliferation of SHED regardless of the type of laser. Further studies are necessary to gain in-depth knowledge about the effects of different wavelengths of LLL on SHED viability and proliferation.

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High-fluence low-power laser irradiation promotes odontogenesis and inflammation resolution in periodontitis by enhancing stem cell proliferation and differentiation.

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Periodontitis can exert a severe impact on the life of patients, and the use of stem cell therapy for this disease is promising. The inflammatory response consequent to periodontitis can promote stem cell proliferation. Activated inflammation triggers inhibitory cytokine secretion, thus reducing inflammation subsequent to stem cell activation. High□fluence low□power laser irradiation (HF□LPLI) has the ability to regulate stem cell function through its effect on inflammation. Thus, the aim of the present study was to examine whether HF□LPLI is able to activate stem cells to promote regeneration in periodontitis by promoting inflammation resolution, as well as to evaluate the underlying mechanism of action if an effect is observed. Stem cells were treated with HF□LPLI following inflammation activation. Reverse transcription□quantitative polymerase chain reaction and EdU assay were used to evaluate cell proliferation and differentiation. Flow cytometry and immunofluorescence were also used to detect the ability of HF□LPLI to regulate the surrounding inflammatory environment. Animal models of periodontal disease were treated with stem cells and HF□LPLI, and regeneration was detected by hematoxylin and eosin staining and in vivo imaging. It was observed that HF□LPLI promoted inflammation resolution by reducing the excessive inflammatory response, and finally stimulated stem cell proliferation and differentiation. Furthermore, in vivo results revealed that stem cells treated with HF□LPLI induced bone regeneration. HF□LPLI stimulated stem cell proliferation and differentiation by promoting inflammation resolution subsequent to stem cell activation, providing a new strategy for the clinical treatment of periodontitis.

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Effects of Photobiomodulation on Degranulation and Number of Mast Cells and Wound Strength in Skin Wound Healing of Streptozotocin-Induced Diabetic Rats.

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The aim of this study is to examine the effect of degranulation of mast cells and total number of mast cells in the remodeling step of an ischemic model of wound healing under the influence of photobiomodulation and conditioned medium (CM) from human bone marrow-derived mesenchymal stem cells (hBM-MSCs-CM), or CM, administered alone and or in combination.

Initially, type 1 diabetes mellitus was induced in 72 male adult rats. Then, after a month, one incision was made on the back of each rat. Subsequently, the rats were divided into four groups. The first group was considered as the control (placebo) group, the second group received CM, the third group received photobiomodulation, and the fourth group received photobiomodulation+CM. On days 4, 7, and 15, samples were extracted from the wound for histological and tensiometric examinations. The total number of mast cells, including the three types of mast cells, was counted by the stereological methods. The tensiometric properties of the repairing tissue were examined.

The administration of photobiomodulation and CM, alone or in combination, significantly increased the tensiometric properties within the healing wounds. Histologically, photobiomodulation+CM, CM, and photobiomodulation groups showed a significant decrease in the three types of mast cells and in the total number of mast cells compared with the control group on day 15.

We conclude that photobiomodulation and CM alone and or in combination significantly accelerated the healing process in a rat with a diabetic and ischemic wound, and significantly decreased the total number of mast cells and degranulation of mast cells. We suggest that the increased number of type 2 mast cells in the control group adversely affected the tensiometric properties of wounds in this group.

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Adjunctive laser-stimulated stem-cells therapy to primary reperfusion in acute myocardial infarction in humans: Safety and feasibility study.

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BACKGROUND: Low-level laser therapy (LLLT) has photobiostimulatory effects on stem cells and may offer cardioprotection. This cell-based therapy may compliment primary percutaneous coronary intervention (PPCI) in patients with ST-segment elevation myocardial infarction (STEMI). OBJECTIVE: In this randomized control trial, our primary objective was to determine the safety and feasibility of LLLT application to the bone marrow in patients with STEMI undergoing PPCI. METHODS: We randomly assigned patients undergoing PPCI to LLLT or non-laser therapy (NLT). In the LLLT group, 100 s of laser therapy was applied to the tibia bone prior to PPCI, as well as 24 and 72 h post-PPCI. In the control group, the power source was turned off. The primary outcome was the difference in door-to-balloon (D2B) time, and additional outcomes included differences in circulating cell counts, cardiac enzymes, and left-ventricular ejection fraction (LVEF) at pre-specified intervals post-PPCI. RESULTS: Twenty-four patients were randomized to LLLT (N = 12) or NLT (N = 12). No adverse effects of the treatment were detected. The D2B time was not significantly different between the groups (41 ± 8 vs 48 ± 1 min; P = 0.73). Creatinine Phosphokinase area under the curve, was lower after LLLT (22 ± 10) compared to NLT (49 ± 12), but this was not statistically significant (P = 0.08). Troponin-T was significantly lower after LLLT (2.7 ± 1.4 ng/mL) in comparison to NLT (5.2 ± 1.8 ng/mL. P < 0.05). At 9 months, LVEF improved in both groups without a significant difference between LLLT (55 ± 9%) and NLT (52 ± 9%; P = 0.90). CONCLUSION: LLLT is a safe and feasible adjunctive cell-based therapy to PPCI that may benefit ischemic myocardium.

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Laser treatment contributes to maintain membrane integrity in stem cells from human exfoliated deciduous teeth (shed) under nutritional deficit.

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This study aimed to analyze the effects of laser irradiation on the membrane integrity and viability of stem cells from human exfoliated deciduous teeth (SHED) that were kept in serum starvation. Nutritional deficit was used to mimic the cellular stress conditions of SHED isolation for regenerative dental approaches, where laser therapy could be beneficial. SHED were cultured under serum starvation (MEMα + 1%FBS) for 1 or 24 h pre-irradiation (protocols A and B, respectively). Then, cells received low-level laser therapy (LLLT; 660 nm) at 2.5 J/cm 2 (0.10 W; groups I and V), 5.0 J/cm 2 (0.20 W; groups II and VI), 7.5 J/cm 2 (0.30 W; groups III and VII), or remained non-irradiated (groups IV and VIII). During irradiation, cells were maintained in 1% FBS (groups I-IV) or 10% FBS (normal culture conditions; groups V-VIII). Membrane integrity was evaluated by quantifying lactate dehydrogenase (LDH) release (immediately after irradiation), and cell viability was assessed by the MTT assay (24, 48, and 72 h post-irradiation). Serum starvation did not alter LDH release by non-irradiated SHED, while LDH release decreased significantly in groups irradiated in 1% FBS (I and III), but not in groups irradiated in 10% FBS (V-VII), regardless the pre-irradiation conditions (protocols A/B). Cell viability was significantly higher 24 h after irradiation, in most protocol A groups. In contrast, cell viability remained mostly unaltered in protocol B groups. LLLT contributed to maintain membrane integrity in SHED subjected to nutritional deficit before and during irradiation with 0.10 or 0.30 W. Short serum starvation before irradiation improved SHED viability at 24 h post-irradiation.

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Low-level laser irradiation promotes the differentiation of bone marrow stromal cells into osteoblasts through the APN/Wnt/β-catenin pathway.

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OBJECTIVE: The relationship between adiponectin (APN) pathway and Wnt pathway was explored through BMSCs, and the effect of low-level laser irradiation (LLLI) on bone marrow stromal cells (BMSCs) and its mechanism were further studied. MATERIALS AND METHODS: 3-week-old Sprague-Dawley (SD) rats were selected, and mesenchymal stem cells were separately cultured and purified. 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to analyze cell proliferation. After osteogenic and adipogenic induction, cultures were conducted, respectively, cells were stained with alizarin red and oil red O. Reverse transcription-polymerase chain reaction (RT-PCR) was used to detect the expressions of osteogenesis-related genes, runt-related transcription factor 2 (RUNX2), and osteocalcin (OC) and those of adipogenesis-related genes, peroxisome proliferator-activated receptor-gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (c/EBPα). Western blotting was used to detect the expressions of β-catenin in the cytoplasm and nucleus. The lentiviral expression vector of adiponectin receptors (APN-R) was constructed, and the expression of APN receptor genes was silenced. The expressions of β-catenin in APN receptors and the nucleus within cells were detected. RESULTS: LLLI promoted the bone formation by inducing the differentiation direction of mesenchymal stem cells, increasing the number of osteoblasts in the bone marrow and inhibiting the reduction of the number of adipocytes. LLLI regulates the Wnt pathway, promotes the entry of β-catenin into the nucleus, activates the osteogenic effect of the Wnt pathway so as to promote the bone formation of osteoblasts and inhibit bone resorption of osteoclasts. LLLI promotes the entry of β-catenin into the nucleus and the osteogenic differentiation of BMSCs through the APN pathway. CONCLUSIONS: In summary, LLLI can promote osteogenesis and inhibit adipocytes formation, thus attenuating bone resorption of osteoclasts. The mechanism of LLLI is that it promotes the entry of β-catenin into the nucleus and regulates the Wnt pathway and the differentiation direction of mesenchymal stem cells through the APN signal pathway, thus promoting bone formation.

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Photobiomodulation therapy and vitamin C on longevity of cell sheets of human dental pulp stem cells.

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Photobiomodulation therapy (PBMT) can improve processes relevant to tissue regeneration, such as survival, proliferation, migration, and differentiation of cells, including stem cells. Thus, PBMT could be applied as auxiliary therapy for tissue regeneration. Cell sheets (CSs) induced by vitamin C (VC) can generate large amount of cells, which would also be useful for tissue regeneration. VC and PBMT cause opposite effects on cell metabolism (e.g., VC is antioxidative, and PBMT generates reactive oxygen species); however, hDPSC CSs were formed when VC and PBMT+VC were applied. Thus, this study showed that PBMT does not interfere with the formation of cell sheets induced by VC. Additionally, PBMT improved the functional differentiation of the cells isolated from the CSs. Thus, due to the clinical benefits of PBMT, the association of this therapy with cell sheets seems promising for future applications in tissue regeneration.

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Hemolasertherapy: A Novel Procedure for Gingival Papilla Regeneration-Case Report.

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BACKGROUND: Interdental papilla is of major importance to patients' orofacial aesthetics, especially regarding anterior teeth as part of the smile's harmony. Loss of gingival tissue, which constitutes interdental papilla, forms what in odontology is called black spaces. This loss, besides affecting the smile's aesthetics, also provokes phonetic and functional damage. OBJECTIVE: The objective of the authors is to present the result of three clinical cases treated with an innovative technique called hemolasertherapy, which stimulates growth of gingival papilla and thus permanently fills in the black spaces. METHODS: The photobiomodulation therapy (PBMT) used a 660 nm diode laser (Laser Duo, MMO-São Carlos, SP, Brazil), punctual, contact mode in two steps: before the bleeding (first PBMT) and immediately after bleeding (second PBMT). Parameters used were power output: 100 mW, CW; diameter tip: 5 mm; spot area: 0.19 cm 2 ; irradiation exposure time per point: 20 sec; 14 points per daily session; total of 2 sessions, with a 1-week interval; E: 2 J per point; E: per daily session, 28 J; irradiance per point: 0.52 W/cm 2 ; fluence per point: 10.4 J/cm 2 . Total in two daily sessions: total energy: 56 J; total fluence: 294.75 J/cm, 560 sec total time. An in vitro preliminary study was simultaneously carried out to demonstrate what could happen at cellular level in hemotherapy clinical cases associated with PBMT laser application. RESULTS: This initial study demonstrated that the blood clot originated from the bleeding provoked in the gingival area is rich in mesenchymal stem cells. PBMT enables preservation, viability, and further differentiation, stimulating the return of gingival stem cells, which would support their survival and differentiation in the blood clot, thus favoring interdental papilla regeneration. CONCLUSIONS: Follow-up was done for a time span of 4-5 years and considered excellent with regard to papilla preservation.

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Combined effects of photobiomodulation and alendronate on viability of osteoporotic bone marrow-derived mesenchymal stem cells.

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Osteoporotic bone marrow mesenchymal stem cells (BMMSCs) are involved in the pathogenesis of osteoporosis (OP). Photobiomodulation (PBM) has positive effects on healthy BMMSCs. The goal of current experiment was to evaluate the combined influence of photobiomodulation PBM and alendronate (ALN) incubation on ovariectomized induced osteoporosis(OVX)- BMMSC viability in vitro. 15 female adult Wistar rats were distributed into the 2 groups: (1) 3 healthy (sham)control rats, (2) 12 OVX- rats. All OVX rats underwent ovariectomy. After 3.5 months sham and OVX rats were euthanized and their MSC harvested and cultured in a complete osteogenic incubation medium (OM). As the next step, in sham and OVX groups flowcytometry and osteogenic differentiation assays were performed. OVX- rats were divided into (2) OVX-control, (3) OVX- PBM (HeNe laser, 623.8 nm, 1.2 J/cm 2, one time), (4) OVX-ALN (10 -8 M, three times incubations), and (5) OVX-PBM + ALN, Finally BMMSC viability of all five groups were evaluated using MTT (3-(4, 5-dimethylthiazol-2-yl)-2,5diphenyltetrazolium bromide) assay. Based on our observations, PBM significantly increased optical density of OVX-BMMSCs (2.15 ± 0.11) compared to control -OVX-BMMSCs (1.55 ± 0.10) and healthy -BMMSCs (1.65 ± 0.10)(LSD test, both p ; 0.05). Further, we found that both ALN, and ALN + PBM significantly increased optical densities of OVX-BMMSCs (24 h:2.40 ± 0.03;48 h:2.06 ± 0.00[ALN],both p ; 0.01) and 1.88 ± 0.05[ALN + PBM], p ; 0.05 compared to control -OVX-BMMSCs (24 h: 1.46 ± 0.01; 48 h: 1.83 ± 0.00 and 1.57 ± 0.08). It was concluded that PBM significantly increased cell viability of OVX-BMMSCs compared to control -OVX-BMMSCs and healthy -BMMSCs.

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Low power laser irradiation and human adipose-derived stem cell treatments promote bone regeneration in critical-sized calvarial defects in rats.

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Both stem cell therapy and physical treatments have been shown to be beneficial in accelerating bone healing. However, the efficacy of combined treatment with stem cells and physical stimuli for large bone defects remains uncertain. The aim of this study was to evaluate the bone regeneration effects of low-power laser irradiation (LPLI) and human adipose-derived stem cell (ADSC) treatments during fracture repair using a comparative rat calvarial defect model. We evaluated the viability of human ADSCs, which were cultured on a porous PLGA scaffold using an MTS assay. The critical-sized calvarial bone defect rats were divided into 4 groups: control group, LPLI group, ADSC group, and ADSC+LPLI group. Bone formation was evaluated using micro-CT. New bone formation areas and osteogenic factor expression levels were then examined by histomorphological analysis and immunohistochemical staining. Our data showed that PLGA had no cytotoxic effect on human ADSCs. Micro-CT analyses revealed that both the LPLI and ADSC groups showed improved calvarial bone defect healing compared to the control group. In addition, the ADSC+LPLI group showed significantly increased bone volume at 16 weeks after surgery. The area of new bone formation ranked as follows: control group < LPLI group < ADSC group < ADSC+LPLI group. There were significant differences between the groups. In addition, both ADSC and ADSC+LPLI groups showed strong signals of vWF expression. ADSC and LPLI treatments improved fracture repair in critical-sized calvarial defects in rats. Importantly, the combined treatment of ADSCs and LPLI further enhances the bone healing process.

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Stereological and molecular studies on the combined effects of photobiomodulation and human bone marrow mesenchymal stem cell conditioned medium on wound healing in diabetic rats.

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We investigated the effects of conditioned medium (CM) from human bone marrow mesenchymal stem cells (h BMMSC)s and pulse wave photobiomodulation (PW PBM), applied alone or in combination, on the stereological parameters and gene expression of some growth factors, during wound healing in a streptozotocin (STZ)-induced rat model of type one diabetes mellitus (T1DM). T1DM was induced in 72 rats and two incisions were made in each animal. The rats were assigned to one of four groups: a control (placebo) group, a Laser group (890 nm, 80 Hz, 0.2 J/cm 2); a CM group, and a combined CM + Laser group. On post-surgical days 4, 7, and 15, skin samples were extracted for stereology and reverse transcription PCR (RT-PCR) analyses of gene expression of basic fibroblast growth factor (bFGF), hypoxia-inducible factor (HIF-1α), and stromal cell-derived factor-1α (SDF-1α). The stereological examinations of the proximal and distal wounds revealed significantly enhanced healing in all the treated groups, compared to the control group. The extent of healing was significantly greater in the CM + Laser group than in the other treatment groups. The RT-PCR results also indicated greater gene expression in the CM + Laser and Laser groups than in the CM and control groups. Application of CM and PW PBM, alone or in combination accelerated the process of wound healing in T1DM rats. The results of combined application of CM and PW PBM, indicated a synergistic effect, and the combination treatment was statistically more effective than single applications of CM or PW PBM.

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Photobiomodulation of freshly isolated human adipose tissue-derived stromal vascular fraction cells by pulsed light-emitting diodes for direct clinical application.

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A highly interesting source for adult stem cells is adipose tissue, from which the stromal vascular fraction (SVF)-a heterogeneous cell population including the adipose-derived stromal/stem cells-can be obtained. To enhance the regenerative potential of freshly isolated SVF cells, low-level light therapy (LLLT) was used. The effects of pulsed blue (475 nm), green (516 nm), and red (635 nm) light from light-emitting diodes applied on freshly isolated SVF were analysed regarding cell phenotype, cell number, viability, adenosine triphosphate content, cytotoxicity, and proliferation but also osteogenic, adipogenic, and proangiogenic differentiation potential. The colony-forming unit fibroblast assay revealed a significantly increased colony size after LLLT with red light compared with untreated cells, whereas the frequency of colony-forming cells was not affected. LLLT with green and red light resulted in a stronger capacity to form vascular tubes by SVF when cultured within 3D fibrin matrices compared with untreated cells, which was corroborated by increased number and length of the single tubes and a significantly higher concentration of vascular endothelial growth factor. Our study showed beneficial effects after LLLT on the vascularization potential and proliferation capacity of SVF cells. Therefore, LLLT using pulsed light-emitting diode light might represent a new approach for activation of freshly isolated SVF cells for direct clinical application.

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Can photobiomodulation associated with implantation of mesenchymal adipose-derived stem cells attenuate the expression of MMPs and decrease degradation of type II collagen in an experimental model of osteoarthritis?

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This study aimed to determine whether photobiomodulation therapy (PBMT) could improve the bioavailability and chondroprotective benefits of mesenchymal stem cells injected into the knees of rats used as an experimental model of osteoarthritis (OA) as well as reduce the expression of matrix metalloproteinases (MMPs) and degradation of type II collagen (COL2-1) in the cartilage. Adipose-derived stem/stromal cells (ADSCs) were collected from three male Fischer 344 rats and characterized by flow cytometry. Fifty female Fischer 344 rats were distributed into five groups of 10 animals each. These groups were as follows: control, OA, OA PBMT, OA ADSC, and OA ADSC PBMT. OA was induced in the animals using a 4% papain solution. Animals from the OA ADSC and OA ADSC PBMT groups received an intra-articular injection of 10 × 10 6 ADSCs and were treated with PBMT by irradiation (wavelength: 808 nm, power: 50 mW, energy: 42 J, energy density: 71.2 J/cm 2, spot size: 0.028). Euthanasia was performed 7 days after the first treatment. The use of PBMT alone and the injection of ADSCs resulted in downregulation of pro-inflammatory cytokines and MPs in cartilage compared to the OA group. PBMT and ADSCs caused upregulation of tissue inhibitors of MPs 1 and 2 and mRNA and protein expression of COL2-1 in cartilage compared to the OA group. The intra-articular injection of ADSCs and PBMT prevented joint degeneration resulting from COL2-1 degradation and modulated inflammation by downregulating cytokines and MMPs in the OA group.

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Preconditioning With Low Level Laser Irradiation Enhances the Therapeutic Potential of Human Adipose-derived Stem Cells in a Mouse Model of Photoaged Skin.

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The present study was conducted to explore the therapeutic potential of human adipose-derived stem cells (ADSCs) irradiated with a low level laser (LLL). Cultured ADSCs were treated with 650-nm GaAlAs laser irradiation at 2, 4, and 8 J/cm

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Effects of pulsing of light on the dentinogenesis of dental pulp stem cells in vitro.

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Low power light (LPL) treatment has been widely used in various clinical trials, which has been known to reduce pain and inflammation and to promote wound healing. LPL was also shown to enhance differentiation of stem cells into specific lineages. However, most studies have used high power light in mW order, and there was lack of studies about the effects of very low power light in μW. In this study, we applied 810 nm LPL of 128 μW/cm 2 energy density in vitro. Upon this value, continuous wave (CW) irradiation did not induce any significant changes for differentiation of human dental pulp stem cells (hDPSCs). However, the membrane hyperpolarization, alkaline phosphatase activity, and intracellular oxidative stress were largely enhanced in the pulsed wave (PW) with 30% of duty cycle and 300-3000 Hz frequencies-LPL in which LED driver work in the form of square wave. After 21 days of daily LPL treatment, Western blot revealed the dentinogenesis in this condition in vitro. This study demonstrates that the very low power light at 810 nm enhanced significant differentiation of hDPSCs in the PW mode and there were duty cycle dependency as well as pulsing frequency dependency in the efficiency.

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Exosomes secreted by mice adipose-derived stem cells after low-level laser irradiation treatment reduce apoptosis of osteocyte induced by hypoxia.

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OBJECTIVE: Kienböck's disease is a commonly seen posttraumatic avascular necrosis characterized by avascular necrosis of the lunate bone of the wrist which involves the dominant hand. In our study, we aimed to present midterm outcomes of 12 cases treated with radial metaphyseal core decompression. PATIENTS AND METHODS: In our clinic, 12 patients who applied to our outpatient clinic with intractable pain despite at least six weeks of conservative treatment were previously diagnosed and evaluated as Kienböck's disease between the years 2006 and 2014. Patients at early stage received radial metaphyseal core decompression. RESULTS: The patients were evaluated as postoperative grip strength, flexion-extension gap, ulnar-radial deviation gap, VAS, Quick DASH and MAYO wrist scoring and patient satisfaction. CONCLUSIONS: We determined that interventions performed for Kienböck's disease cannot halt radiological progression. We are of the opinion that radial metaphyseal core decompression, aiming at increasing blood perfusion, improve early diagnosis and treatment of Kienböck's disease, increasing the patient satisfaction.

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Photostimulation of osteogenic differentiation on silk scaffolds by plasma arc light source.

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Low-level laser therapy (LLLT) has been used for more than 30 years to heal wounds. In recent years, LLLT or photostimulation has been indicated as an effective tool for regenerative and dental medicine by using monochromatic light. The aim of this study is to indicate the usability of plasma arc light source for bone regeneration. This is why we used polychromatic light source providing effective wavelengths in the range of 590 -1500 nm for cellular response and investigated photostimulation effects on osteogenic differentiation of human mesenchymal stem cells (hMSCs) seeded on 3D silk scaffolds. Cellular responses were examined by using cell culture methods in terms of proliferation, differentiation, and morphological analyses. The results showed that photostimulation with a polychromatic light source (applied for 5 min from the 3rd day after seeding up to the 28th day in 2-day intervals with 92-mW/cm2 power from 10-cm distance to the cells) enhanced osteogenic differentiation of hMSCs according to higher alkaline phosphatase (ALP) activity, collagen and calcium content, osteogenic gene expressions, and matrix mineralization. In conclusion, we suggest that the plasma arc light source that was used here has a great potential for bone regeneration.

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Use of low-level laser therapy in treatment of the androgenic alopecia, the first systematic review.

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Alopecia is a common disease affecting more than half of the world total number of people. Alopecia exists in different types, but one of the most common of these types is the Androgenic Alopecia which has affected approximately 51% of the total number of males ranging between the age bracket of 40 years and 75 years. This type of alopecia is more common in females who are above the age of 65 years and above. Despite this widespread effect, much has not been done regarding identifying the possible drugs for treating this disease. At present, there exist only two possible medications that have been scientifically approved to cure this disease, include finasteride and minoxidil. Also, another possible form of treatment has been the case of hair transplantation. Despite the new possible treatment options available for treatment of different types of hair loss, there is a need for the invention for more efficient management and treatment options that are less costly, environmentally friendly, and most importantly human consumption friendly. Due to the recent evaluation that low-level laser therapy stimulated hair growth. This systematic review and meta-analysis was to determine whether the use of low-level laser therapy is an effective therapy for treatment of the Androgenic alopecia and also to some degree we reviewed the level of the patient's satisfaction. Some earlier studies had shown that the use of low-level laser therapy stimulated the hair growth when mice were treated with chemotherapy which was induced by the alopecia and also the other type of alopecia called alopecia areata. The researchers hypothesized that the primary mechanism of treating Androgenic alopecia to be the stimulation of the epidermal stem cells which are in the hair follicle making them bulge and shift the follicles into the anagen phase.

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Aging of lymphoid organs: Can photobiomodulation reverse age-associated thymic involution via stimulation of extrapineal melatonin synthesis and bone marrow stem cells?

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Thymic atrophy and the subsequent reduction in T-cell production are the most noticeable age-related changes affecting lymphoid organs in the immune system. In fact, thymic involution has been described as "programmed aging." New therapeutic approaches, such as photobiomodulation (PBM), may reduce or reverse these changes. PBM (also known as low-level laser therapy) involves the delivery of non-thermal levels of red or near-infrared light that are absorbed by mitochondrial chromophores, in order to prevent tissue death and stimulate healing and regeneration. PBM may reverse or prevent thymic involution due to its ability to induce extrapineal melatonin biosynthesis via cyclic adenosine monophosphate (AMP) or NF-kB activation, or alternatively by stimulating bone marrow stem cells that can regenerate the thymus. This perspective puts forward a hypothesis that PBM can alter thymic involution, improve immune functioning in aged people and even extend lifespan.

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Photobiomodulation of mesenchymal stem cells encapsulated in an injectable rhBMP4-loaded hydrogel directs hard tissue bioengineering.

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Photobiomodulation (PBM) therapy displays relevant properties for tissue healing and regeneration, which may be of interest for the tissue engineering field. Here, we show that PBM is able to improve cell survival and to interact with recombinant human Bone Morphogenetic Protein 4 (rhBMP4) to direct and accelerate odonto/osteogenic differentiation of dental derived mesenchymal stem cells (MSCs). MSCs were encapsulated in an injectable and thermo-responsive cell carrier (Pluronic ® F-127) loaded with rhBMP4 and then photoactivated. PBM improved MSCs self-renewal and survival upon encapsulation in the Pluronic ® F-127. In the presence of rhBMP4, cell odonto/osteogenic differentiation was premature and markedly improved in the photoactivated MSCs. An in vivo calvarial critical sized defect model demonstrated significant increase in bone formation after PBM treatment. Finally, a balance in the reactive oxygen species levels may be related to the favorable results of PBM and rhBMP4 association. PBM may act in synergism with rhBMP4 and is a promise candidate to direct and accelerate hard tissue bioengineering.

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Photobiomodulation Inhibits Long-term Structural and Functional Lesions of Diabetic Retinopathy.

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Previous studies demonstrated that brief (3 to 4 min) daily application of light at 670 nm to diabetic rodents inhibited molecular and pathophysiologic processes implicated in the pathogenesis of diabetic retinopathy (DR) and reversed diabetic macular edema in small numbers of patients studied. Whether or not this therapy would inhibit the neural and vascular lesions that characterize the early stages of the retinopathy was unknown. We administered photobiomodulation (PBM) therapy daily for 8 months to streptozotocin-diabetic mice and assessed effects of PBM on visual function, retinal capillary permeability, and capillary degeneration using published methods. Vitamin D receptor and Cyp24a1 transcripts were quantified by quantitative real-time PCR, and the abundance of c-Kit + stem cells in blood and retina were assessed. Long-term daily administration of PBM significantly inhibited the diabetes-induced leakage and degeneration of retinal capillaries and also significantly inhibited the diabetes-induced reduction in visual function. PBM also inhibited diabetes-induced reductions in retinal Cyp24a1 mRNA levels and numbers of circulating stem cells (CD45 -/c-Kit +), but these effects may not account for the beneficial effects of PBM on the retinopathy. PBM significantly inhibits the functional and histopathologic features of early DR, and these effects likely are mediated via multiple mechanisms.

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Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation.

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Photobiomodulation (PBM) involves the use of red or near-infrared light at low power densities to produce a beneficial effect on cells or tissues. PBM therapy is used to reduce pain, inflammation, edema, and to regenerate damaged tissues such as wounds, bones, and tendons. The primary site of light absorption in mammalian cells has been identified as the mitochondria and, more specifically, cytochrome c oxidase (CCO). It is hypothesized that inhibitory nitric oxide can be dissociated from CCO, thus restoring electron transport and increasing mitochondrial membrane potential. Another mechanism involves activation of light or heat-gated ion channels. This review will cover the redox signaling that occurs in PBM and examine the difference between healthy and stressed cells, where PBM can have apparently opposite effects. PBM has a marked effect on stem cells, and this is proposed to operate via mitochondrial redox signaling. PBM can act as a preconditioning regimen and can interact with exercise on muscles.

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Pulse frequency dependency of photobiomodulation on the bioenergetic functions of human dental pulp stem cells.

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Photobiomodulation (PBM) therapy contributes to pain relief, wound healing, and tissue regeneration. The pulsed wave (PW) mode has been reported to be more effective than the continuous wave (CW) mode when applying PBM to many biological systems. However, the reason for the higher effectiveness of PW-PBM is poorly understood. Herein, we suggest using delayed luminescence (DL) as a reporter of mitochondrial activity after PBM treatment. DL originates mainly from mitochondrial electron transport chain systems, which produce reactive oxygen species (ROS) and adenosine triphosphate (ATP). The decay time of DL depends on the pulse frequencies of applied light, which correlate with the biological responses of human dental pulp stem cells (hDPSCs). Using a low-power light whose wavelength is 810 nm and energy density is 38 mJ/cm 2, we find that a 300-Hz pulse frequency prolonged the DL pattern and enhanced alkaline phosphatase activity. In addition, we analyze mitochondrial morphological changes and their volume density and find evidence supporting mitochondrial physiological changes from PBM treatment. Our data suggest a new methodology for determining the effectiveness of PBM and the specific pulse frequency dependency of PBM in the differentiation of hDPSCs.

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Comparison of the in vitro effects of low-level laser therapy and low-intensity pulsed ultrasound therapy on bony cells and stem cells.

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To compare the in vitro effectiveness of Low-Level Laser Therapy (LLLT) and Low Intensity Pulsed Ultrasound (LIPUS) on bony cells and related stem cells. In this study, we aim to systematically review the published scientific literature which explores the use of LLLT and LIPUS to biostimulate the activity or the proliferation of bony cells or stem cells in vitro. We searched the database PubMed for LLLT or LIPUS, with/without bone, osteoblast, osteocyte, stem cells, the human osteosarcoma cell line (MG63), bone-forming cells, and cell culture (or in vitro). These studies were subdivided into categories exploring the effect of LLLT or LIPUS on bony cells, stem cells, and other related cells. 75 articles were found between 1987 and 2016; these included: 50 full paper articles on LLLT and 25 full papers on LIPUS. These articles met the eligibility criteria and were included in our review. A detailed and concise description of the LLLT and the LIPUS protocols and their individual effects on bony cells or stem cells and their results are presented in five tables. Based on the main results and the conclusions of the reviewed articles in the current work, both, LLLT and LIPUS, apply a biostimulatory effect on osteoblasts, osteocytes, and enhance osteoblast proliferation and differentiation on different bony cell lines used in in vitro studies, and therefore, these may be useful tools for bone regeneration therapy. Moreover, in consideration of future cell therapy protocols, both, LLLT and LIPUS (especially LLLT), enhnce a significant increase in the initial number of SCs before differentiation, thus increasing the number of differentiated cells for tissue engineering, regenerative medicine, and healing. Further studies are necessary to determine the LLLT or the LIPUS parameters, which are optimal for biostimsulating bony cells and SCs for bone healing and regenerative medicine.

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Low-level laser irradiation promotes proliferation of cryopreserved adipose-derived stem cells.

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OBJECTIVE: To evaluate the effect of low-level laser irradiation on proliferation and viability of murine adipose-derived stem cells previously submitted to cryopreservation. METHODS: Adipose-derived stem cells were isolated from inguinal fat pads of three mice, submitted to cryopreservation in fetal bovine serum with 10% dimethylsulfoxide for 30 days and then thawed and maintained in normal culture conditions. Culture cells were either irradiated or not (control) with an InGaAIP diode laser at zero and 48 hours, using two different energy densities (0.5 and 1.0J/cm2). Cell proliferation was evaluated by trypan blue exclusion method and MTT assay at intervals of zero, 24, 48, and 72 hours after the first laser application. Cell viability and apoptosis of previously cryopreserved cells submitted to laser therapy were evaluated by flow cytometry. RESULTS: The Irradiated Groups (0.5 and 1.0J/cm2) showed an increased cell proliferation ($p<0.05$) when compared to the Control Group, however no significant difference between the two energy densities was observed. Flow cytometry revealed a percentage of viable cells higher than 99% in all groups. CONCLUSION: Low-level laser irradiation has stimulatory effects on the proliferation of adipose-derived stem cells previously submitted to cryopreservation.

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The effects of low level laser irradiation on proliferation of human dental pulp: a narrative review.

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Mesenchymal stem cells (MSCs) have the capability for self-renewal, proliferation, and differentiation in various types of specialized cells, so they are very important in cellular therapies. MSC from dental pulp are simply obtainable and have high proliferative capability. Among the therapies that can stimulate the proliferation of certain cell types, low-level laser therapy (LLLT) stands out. The target of this study is to perform a literature review to investigate these effects of low-level laser irradiation on proliferation of human dental pulp.The electronic search of scientific papers was conducted in the Lilacs, Scielo, Medline and PubMed databases through scientific articles published in national and international journals in the past 20 years.The results of this review suggest that LLLT may be a useful and important tool for future advances in cell therapy and tissue engineering associated to stem cells. Studies on cell therapy for regenerating dental tissues has already been done, and shows promising results.

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Low-level laser irradiation induces in vitro proliferation of stem cells from human exfoliated deciduous teeth.

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The aim of this study was to evaluate the effect of low-level laser irradiation (LLLI) on the proliferation and viability of stem cells from human exfoliated deciduous teeth (SHED). Cells were irradiated or not (control) with an InGaAlP laser diode (660 nm, 30 mW, continuous action mode) using two different energy densities (0.5 J/cm(2)-16 s; 1.0 J/cm(2)-33 s). Irradiation was performed at 0 and 48 h, with the laser probe fixed at a distance of 0.5 cm from the cells. Cell proliferation was analyzed at 0, 24, 48, and 72 h by the Trypan blue exclusion method and MTT assay. Cell cycle and Ki67 expression were analyzed by flow cytometry. Apoptosis-related events were evaluated by expression of annexin V/PI and nuclear morphological changes by staining with DAPI. Differences between groups at each time were analyzed by the Kruskal-Wallis and Mann-Whitney tests, adopting a level of significance of 5% ($p < 0.05$). The results showed that an energy density of 1.0 J/cm(2) promoted an increase in cell proliferation at 48 and 72 h compared to the control and 0.5 J/cm(2) groups. Cell cycle analysis revealed a predominance of cells in the S and G2/M phases in the irradiated groups. This finding was confirmed by the increased expression of Ki67. Low positive staining for annexin V and PI was observed in all groups, and no nuclear changes were detected, indicating that cell viability was not affected by the energy densities tested. It can be concluded that the LLLI parameters used (660 nm, 30 mW, 1.0 J/cm(2)) promote the proliferation of SHEDs and the maintenance of cell viability.

Lasers Med Sci 2017 Oct 12

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The Effects of Photobiomodulation Delivered by Light-Emitting Diode on Stem Cells from Human Exfoliated Deciduous Teeth: A Study on the Relevance to Pluripotent Stem Cell Viability and Proliferation.

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Cultures were irradiated with LED (2, 4, 8, 16, and 32 J/cm 2). After 24 h, the cell cycle and mitochondrial membrane potential of the cultures were evaluated using flow cytometry. Nonirradiated cultures served as control.

Cultures irradiated with 16 J/cm 2 had higher percentages of cells in the synthesis phase than control cultures (p < 0.05), and no significant differences were found regarding the percentage of cells with viable mitochondria between irradiated and control cultures. No significant difference in cell senescence was found between control cultures and cultures irradiated with 2 or 16 J/cm 2.

LED irradiation at 630 nm (37 mW/cm 2, 75 mW) with radiant exposure of 16 J/cm 2 was capable of inducing a proliferative response in stem cells from the pulp tissue of deciduous teeth without affecting mitochondrial function or inducing senescence.

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The impact of wavelengths of LED light-therapy on endothelial cells.

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Low level light therapy receives increasing interest in the fields of tissue regeneration and wound healing. Several in vivo studies demonstrated the positive effects of LLLT on angiogenesis. This study aimed to investigate the underlying properties in vitro by comparing the effects of light therapy by light emitting diodes of different wavelengths on endothelial cells in vitro. Human umbilical vein endothelial cells were treated with either 475 nm, 516 nm or 635 nm light. Control cells were not illuminated. 2D proliferation was quantified by manual counting. HUVEC migration was analyzed by performing a 2D wound scratch assay and a 3D bead assay. The influence of LLLT on early vasculogenic events was determined in a 3D fibrin co-culture model with adipose-derived stem cells. Stimulation with both red and green pulsed LED light significantly increased HUVEC proliferation and 3D migration. Moreover, HUVEC showed increased 2D migration potential with green light stimulation. The treatment with blue light was ineffective. Several parameters showed that green light was even more potent to stimulate proliferation and migration of endothelial cells than clinically well-established red light therapy. Further studies have to focus on intracellular mechanisms induced by different wavelengths in order to optimize this promising therapy in tissue regeneration.

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Effect of in vivo low-level laser therapy on bone marrow-derived mesenchymal stem cells in ovariectomy-induced osteoporosis of rats.

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18 female rats were distributed into the following groups: 1) control healthy, 2) LASER-healthy (890nm, 80Hz, 1.5J/cm 2, three days weekly, 60days), 3) control OVX, 4) LASER-OVX, 5) Alendronate (Alen.)-OVX [0.5mg/kg, 5days per week, 60days], and 6) Alen.+LASER-OVX. Ovariectomy was done on rats of groups 3, 4, 5 and 6. After that all rats were euthanized and their MSC harvested and cultured in complete osteogenic medium. In all groups, BMMSC viability, and calcium colorimetric assay were performed.

We observed a significant increase in optical density (OD) of BMMSCs viability in LASER healthy group compared to control-OVX, Alen.-OVX, LASER-OVX, LASER+Alen.-OVX, groups. LASER+Alen.-OVX group displayed a significant escalation in OD of BMMSCs viability compared to LASER-OVX, Alen.-OVX, and control-OVX groups. There were a significant increase in calcium ion release of LASER-healthy group compared to control healthy, control-OVX, Alen.-OVX, LASER-OVX, and LASER+Alen.-OVX groups. LASER+Alen.-OVX group displayed a significant escalation in calcium ion release compared to LASER-OVX, Alen.-OVX, and control-OVX groups.

Pulse wave (PW) PBM significantly stimulated viability and cell proliferation of healthy BMMSCs compared to those of control-OVX, OVX-alendronate, OVX-LASER, and LASER+alendronate-OVX. In addition stimulatory effect of LASER+alendronate on viability and cell proliferation of OVX-BMMSCs compared to those of control-OVX, alendronate-OVX, and LASER-OVX groups were found.

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Enhanced survival of ischemic skin flap by combined treatment with bone marrow-derived stem cells and low-level light irradiation.

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The aim of this study is to examine the enhanced survival effect of ischemic skin flap by combined treatment with bone marrow-derived stem cells (BMSCs) and low-level light irradiation (LLLI). The neovasculogenic effect of BMSCs induced by LLLI was detected using a wound healing and tube formation assay. ICR mice were divided into four groups: control group, LLLI group, BMSCs group, and combine-treated group. The percentage of skin flap necrosis area was calculated on the seventh post-operative day. Specimens were harvested for histologic analyses. LLLI promoted BMSC migration and tube formation. The flap survival rate of combined treated group was significantly higher than that of the control group. Histologic results demonstrated a significant increase in neovascularization in the combined treatment group. This study demonstrates that combination treatment of BMSCs and LLLI could enhance the survival of ischemic skin flap in a mouse model.

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Red (660 nm) or near-infrared (810 nm) photobiomodulation stimulates, while blue (415 nm), green (540 nm) light inhibits proliferation in human adipose-derived stem cells.

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We previously showed that blue (415 nm) and green (540 nm) wavelengths were more effective in stimulating osteoblast differentiation of human adipose-derived stem cells (hASC), compared to red (660 nm) and near-infrared (NIR, 810 nm). Intracellular calcium was higher after blue/green, and could be inhibited by the ion channel blocker, capsazepine. In the present study we asked what was the effect of these four wavelengths on proliferation of the hASC? When cultured in proliferation medium there was a clear difference between blue/green which inhibited proliferation and red/NIR which stimulated proliferation, all at 3 J/cm 2. Blue/green reduced cellular ATP, while red/NIR increased ATP in a biphasic manner. Blue/green produced a bigger increase in intracellular calcium and reactive oxygen species (ROS). Blue/green reduced mitochondrial membrane potential (MMP) and lowered intracellular pH, while red/NIR had the opposite effect. Transient receptor potential vanilloid 1 (TRPV1) ion channel was expressed in hADSC, and the TRPV1 ligand capsaicin (5uM) stimulated proliferation, which could be abrogated by capsazepine. The inhibition of proliferation caused by blue/green could also be abrogated by capsazepine, and by the antioxidant, N-acetylcysteine. The data suggest that blue/green light inhibits proliferation by activating TRPV1, and increasing calcium and ROS.

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Combine effect of Chondroitinase ABC and low level laser (660nm) on spinal cord injury model in adult male rats.

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After spinal cord injury (SCI) there are many recoveries inhibiting factors such as chondroitin sulfate proteoglycan (CSPG) and inflammation. The present study investigated the combinational effect of low level laser therapy (LLLT) as anti-inflammatory agent and Chondroitinase ABC (ChABC) enzyme as CSPG digesting factor on spinal cord after injury. This study performed on 44 male Wistar rats, spinal cord injury induced by a clip compression injury. Animals received two-weeks treatment of 660nm low level laser (LLL) and intraspinal injection of 1μg ChABC. Functional recovery, cavity size, myelination, axonal projections around the cavity, fibroblast invasion and expression of glycogen synthase kinase-3β (GSk 3β), CSPG and aquaporin 4 (AQP4) expression were evaluated. In statistical evaluation $p<0.05$ considered significant. Result showed the combination of LLLT and ChABC have more effect on reduction of cavity size, improvement of myelination and number of axons around the cavity and decreasing the expression of GSK3β, CSPG and AQP4 expression compared to LLLT and ChABC alone. In the laser and laser+enzyme groups AQP4 expression decreased significantly after SCI. Functional recovery, improved in LLLT and ChABC treated animals, but higher recovery belonged to the combination therapy group. The current study showed combination therapy by LLLT and ChABC is more efficient than a single therapy with each of them.

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Low laser Therapy: a strategy to promote the osteogenic differentiation of deciduous dental pulp stem cells from Cleft Lip and Palate patients.

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Dental pulp stem cells (DPSC) can undergo several types of differentiation, including osteogenic differentiation. One osteogenesis-inducing factor that has been previously described is "in vitro" low-level laser irradiation of cells. Laser irradiation promotes the acceleration of bone matrix mineralization of the cell strain. However, no consensus exists regarding the dose and treatment time. We used DPSC strains from cleft lip and palate patients because new bone tissue engineering strategies have used DPSC in preclinical and clinical trials for the rehabilitation of alveolar bone clefts. Optimizing bone tissue engineering techniques for cleft and lip palate patients by applying low-level laser therapy to DPSC obtained from these patients can help improve current strategies to quickly close large alveolar clefts. The aim of this study was to investigate the effects of low-level laser therapy at different energy densities in DPSC strains obtained from cleft lip and palate patients during "in vitro" osteogenic differentiation. Ten DPSC strains were obtained from cleft lip and palate patients and then used in the following study groups: group 1: control, the strains underwent osteogenic differentiation for 21 days; and groups 2, 3 and 4: the strains were irradiated each day with a low-level red laser (5 J,10 J, and 20 J) during 21 days of osteogenic differentiation. Using Bonferroni's test, a statistically significant difference in the mean values was found between the irradiated groups (2, 3 and 4) and the control group ($p<0.001$). However, no significant difference in osteogenic potential was found among the irradiated groups. Our findings showed the osteogenic potential of DPSC increases with red laser irradiation at 5 J, 10 J and 20 J, and this treatment could be considered a new approach for preconditioning these cells to be used in bone tissue engineering.

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EFFECT OF LOW-LEVEL LASER THERAPY AND OXYTOCIN ON OSTEOPOROTIC BONE MARROW-DERIVED MESENCHYMAL STEM CELLS.

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Postmenopausal osteoporosis (OP) is a major concern for public health. Low-level laser therapy (LLLT) has a positive effect on the health of bone marrow mesenchymal stem cells (BMMSCs). The purpose of this study is to evaluate the influence of LLLT and oxytocin (OT) incubation-individually and in combination-on osteoporotic BMMSCs in ovariectomized rats. Twelve female rats were randomized into two groups to undergo either a sham surgery (sham group) or ovariectomy-induced osteoporosis OP (OVX group). MSCs harvested from the BM of healthy and OVX rats underwent culture expansion. There were five groups. In Groups one (sham-BMMSC) and two (OVX-BMMSC) the cells were held in osteogenic condition medium without any intervention. In the group three (OT), OT incubation with optimum dose was performed for 48 hours (two times, 10(-12) molar). In Group four, laser-treated-OVX-BMMSCs were treated with optimum protocol of LLLT (one time, 1.2 J/cm(2)). In Group five (laser + OT group), the OT incubation plus the laser irradiation was performed. The biostimulatory effect of LLLT is demonstrated by a significant increase in the viability of OVX-BMMSCs, cell cycle, and extracellular levels of Transforming growth factor beta (TGF-β), insulin-like growth factor-I (IGF-I), and Alkaline phosphatase (ALP) compared to control OVX-BMMSCs and/or the sham group. OT incubation and laser + OT incubation have a positive effect on OVX-BMMSCs. However, LLLT is more effective statistically. We conclude that LLLT significantly improved cell viability, enhanced the osteogenic potential of the OVX-BMMSCs, and increased the extracellular levels of the TGF-β, IGF-I, and ALP.

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Effect of low-level laser-treated mesenchymal stem cells on myocardial infarction.

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Cardiovascular disease is the leading cause of death worldwide. Although cardiac transplantation is considered the most effective therapy for end-stage cardiac diseases, it is limited by the availability of matching donors and the complications of the immune suppressive regimen used to prevent graft rejection. Application of stem cell therapy in experimental animal models was shown to reverse cardiac remodeling, attenuate cardiac fibrosis, improve heart functions, and stimulate angiogenesis. The efficacy of stem cell therapy can be amplified by low-level laser radiation. It is well established that the bio-stimulatory effect of low-level laser is influenced by the following parameters: wavelength, power density, duration, energy density, delivery time, and the type of irradiated target. In this review, we evaluate the available experimental data on treatment of myocardial infarction using low-level laser. Eligible papers were characterized as in vivo experimental studies that evaluated the use of low-level laser therapy on stem cells in order to attenuate myocardial infarction. The following descriptors were used separately and in combination: laser therapy, low-level laser, low-power laser, stem cell, and myocardial infarction. The assessed low-level laser parameters were wavelength (635-804 nm), power density (6-50 mW/cm(2)), duration (20 -150 s), energy density (0.96-1 J/cm(2)), delivery time (20 min-3 weeks after myocardial infarction), and the type of irradiated target (bone marrow or in vitro-cultured bone marrow mesenchymal stem cells). The analysis focused on the cardioprotective effect of this form of therapy, the attenuation of scar tissue, and the enhancement of angiogenesis as primary targets. Other effects such as cell survival, cell differentiation, and homing are also included. Among the evaluated protocols using different parameters, the best outcome for treating myocardial infarction was achieved by treating the bone marrow by one dose of low-level laser with 804 nm wavelength and 1 J/cm(2) energy density within 4 h of the infarction. This approach increased stem cell survival, proliferation, and homing. It has also decreased the infarct size and cell apoptosis, leading to enhanced heart functions. These effects were stable for 6 weeks. However, more studies are still required to assess the effects of low-level laser on the genetic makeup of the cell, the nuclei, and the mitochondria of mesenchymal stromal cells (MSCs).

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Photobiomodulation of breast and cervical cancer stem cells using low-intensity laser irradiation.

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Breast and cervical cancers are dangerous threats with regard to the health of women. The two malignancies have reached the highest record in terms of cancer-related deaths among women worldwide. Despite the use of novel strategies with the aim to treat and cure advanced stages of cancer, post-therapeutic relapse believed to be caused by cancer stem cells is one of the challenges encountered during tumor therapy. Therefore, further attention should be paid to cancer stem cells when developing novel anti-tumor therapeutic approaches. Low-intensity laser irradiation is a form of phototherapy making use of visible light in the wavelength range of 630-905 nm. Low-intensity laser irradiation has shown remarkable results in a wide range of medical applications due to its biphasic dose and wavelength effect at a cellular level. Overall, this article focuses on the cellular responses of healthy and cancer cells after treatment with low-intensity laser irradiation alone or in combination with a photosensitizer as photodynamic therapy and the influence that various wavelengths and fluencies could have on the therapeutic outcome. Attention will be paid to the biomodulative effect of low-intensity laser irradiation on cancer stem cells.

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Comparative study on the effect of low intensity laser and growth factors on stem cells used in experimentally-induced liver fibrosis in mice.

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BACKGROUND AND STUDY AIMS: The therapeutic effects of human umbilical cord-derived mesenchymal stem cells (UC-MSCs) exposed to diode laser and/or hepatocyte growth factor (HGF) were compared in mice with experimental liver fibrosis induced by carbon tetra chloride (CCl_4). MATERIAL AND METHODS: Animal model of liver cirrhosis was induced by intraperitoneal injection of CCl_4 in a dose of 0.4ml/kg, twice a week for 6weeks. UC-MSCs were obtained from normal full term placentas and were exposed to diode laser and/or HGF. Before treatment, UC-MSCs were labelled with red fluorescent PKH26. Fifty four male mice weighing 25-35g were randomly divided into four groups control, stem cells, CCl_4, and treated groups. After the experimental period, body and liver weights were recorded, and the liver specimens were processed for histological examination using haematoxylin and eosin, Periodic Acid-Schiff (PAS), and Masson's Trichrome staining (MT). RESULTS: Results showed that administration of UC-MSCs stimulated by diode laser and/or HGF improved body and liver weights, reduced vascular dilatation and congestion, reduced mononuclear cellular infiltration, reduced hepatocyte vacuolation, eosinophilia, and pyknosis. Furthermore, periportal fibrosis was minimized and PAS reaction was increased. These effects were maximum when UC-MSCs were exposed to both diode laser and HGF. CONCLUSION: UC-MSCs stimulated by both diode laser and HGF proved to be an effective therapeutic option in experimental liver fibrosis induced by CCl_4 in mice.

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Presenting a Method to Improve Bone Quality Through Stimulation of Osteoporotic Mesenchymal Stem Cells by Low-Level Laser Therapy.

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OBJECTIVE: This review aims to present a method to improve bone quality through stimulation of osteoporotic mesenchymal stem cells (MSCs) by low-level laser therapy (LLLT). BACKGROUND: Osteoporosis (OP) is characterized by decreased bone mass and bone strength, which results in an increased incidence of bone fractures. These fractures often lead to additional disability and mortality. Osteoporotic MSCs have reduced osteogenic differentiation when cultured in their standard differentiation media. LLLT has a biostimulatory effect on fibroblasts and osteoblasts. MSCs have the ability to generate cells of connective tissue lineages, which includes the bones. Recently, transplantation of in vitro cultured bone marrow (BM) MSCs into sites at risk for development of osteoporotic bone has resulted in improved bone structure. METHODS: Comprehensive research was performed using PubMed, and biostimulatory effect of LLLT on bony cells and MSCs were studied. RESULTS: LLLT can stimulate growth, proliferation, and differentiation of SCs in vitro and in vivo. This ability of LLLT is an essential prerequisite for performing experiments related to disease control in humans. Thus, laser-treated osteoporotic autologous BMMSCs may represent a promising therapeutic method to protect the bones in patients with OP and prevent fractures in these patients. Therefore, researchers hypothesize that transplantation of in vitro laser-treated autologous cultured osteoporotic BMMSCs that have the appropriate osteogenic phenotype into sites at risk for development of osteoporotic bone may result in improved bone structure. In this respect, investigators have successfully used LLLT to restore autologous osteoporotic MSCs in vitro. Subsequently, these cells have been differentiated into osteoblast cell lines with the use of laser treatment after which they were transplanted into osteoporotic animal models. CONCLUSIONS: This technique might improve bone quality and structure. However, additional research must be undertaken to understand the underlying mechanisms of this treatment, validate its effectiveness, and assess the feasibility for clinical application of LLLT to treat MSCs in regeneration of osteoporotic bone.

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Low level laser (LLL) attenuate LPS-induced inflammatory responses in mesenchymal stem cells via the suppression of NF-κB signaling pathway in vitro.

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BACKGROUND: Considering promising results in animal models and patients, therapeutic use of MSCs for immune disease is likely to undergo continued evaluation. Low-lever laser (LLL) has been widely applied to retard the inflammatory reaction. LLL treatment can potentially be applied in anti-inflammatory therapy followed by stem cell therapy. AIM OF THE STUDY: The purpose of this study was to investigate the effect of LLL (660 nm) on the inflammatory reaction induced by LPS in human adipose derived mesenchymal stem cells (hADSCs) and pertinent mechanism. MATERIALS AND METHODS: Anti-inflammatory activity of LLL was investigated by LPS-induced mesenchymal stem cells. The production and expression of pro-inflammatory cytokines were evaluated by ELISA kits and RT-qPCR. Nuclear translocation of NF-κB was indicated by immunofluorescent staining. Phosphorylation status of NF-κB p65 and IκBα were illustrated by western blot assay. ROS generation was measured with CM-H2DCFDA, and NO secretion was determined by DAF-FM. We studied surface expression of lymphocyte activation markers when Purified peripheral blood mononuclear cell (PBMC) were activated by phytohaemagglutinin (PHA) in the presence of 3 types of treated MSCs. RESULTS: LLL reduced the secretion of IL-1β, IL-6, IL8, ROS and NO in LPS treated MSCs. Immunofluorescent assay demonstrated the nuclear translocation decrease of NF-κB in LLL treated LPS induced MSCs. Western blot analysis also suggested that LLL suppressed NF-κB activation via regulating the phosphorylation of p65 and IκBα. MSC significantly reduced the expression of activation markers CD25 and CD69 on PHA-stimulated lymphocytes. CONCLUSION: The results indicate that LLL suppressed the activation of NF-κB signaling pathway in LPS treated MSCs through inhibiting phosphorylation of p65 and IκBα, which results in good anti-inflammatory effect. In addition, LLL attenuated activation-associated markers CD25 and CD69 in co-cultures of PBMC and 3 types of treated MSCs.

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3D printing scaffold coupled with low level light therapy for neural tissue regeneration.

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3D printing has shown promise for neural regeneration by providing customized nerve scaffolds to structurally support and bridge the defect gap as well as deliver cells or various bioactive substances. Low-level light therapy (LLLT) exhibits positive effects on rehabiliation of degenerative nerves and neural disorders. With this in mind, we postulate that 3D printed neural scaffold coupling with LLLT will generate a new strategy to repair neural degeneration. To achieve this goal, we applied red laser light to stimualte neural stem cells on 3D printed scaffolds and investigated the subsequent cell response with respect to cell proliferation and differentiation. Here we show that cell prolifeartion rate and intracellular reactive oxgen species synthesis were significantly increased after 15 s laser stimulation follwed by 1 d culture. Over culturing time of 14 d in vitro, the laser stimulation promoted neuronal differentiation of neural stem cells, while the glial differentiation was suppressed based on results of both immunocytochemistry studies and real-time quantitative reverse transcription polymerase chain reaction testing. These findings suggest that integration of 3D printing and LLLT might provide a powerful methodology for neural tissue engineering.

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Light-Emitting Diode (LED) therapy improves occipital cortex damage by decreasing apoptosis and increasing BDNF-expressing cells in methanol-induced toxicity in rats.

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Methanol-induced retinal toxicity, frequently associated with elevated free radicals and cell edema, is characterized by progressive retinal ganglion cell (RGC) death and vision loss. Previous studies investigated the effect of photomodulation on RGCs, but not the visual cortex. In this study, the effect of 670nm Light-Emitting Diode (LED) therapy on RGCs and visual cortex recovery was investigated in a seven-day methanol-induced retinal toxicity protocol in rats. Methanol administration showed a reduction in the number of RGCs, loss of neurons (neuronal nuclear antigen, NeuN+), activation of glial fibrillary acidic protein (GFAP+) expressing cells, suppression of brain-derived neurotrophic factor (BDNF+) positive cells, increase in apoptosis (caspase 3+) and enhancement of nitric oxide (NO) release in serum and brain. On the other hand, LED therapy significantly reduced RGC death, in comparison to the methanol group. In addition, the number of BDNF positive cells was significantly higher in the visual cortex of LED-treated group, in comparison to methanol-intoxicated and control groups. Moreover, LED therapy caused a significant decrease in cell death (caspase 3+ cells) and a significant reduction in the NO levels, both in serum and brain tissue, in comparison to methanol-intoxicated rats. Overall, LED therapy demonstrated a number of beneficial effects in decreasing oxidative stress and in functional recovery of RGCs and visual cortex. Our data suggest that LED therapy could be a potential condidate as a non-invasive approach for treatment of retinal damage, which needs further clinicl studies.

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Low level lasers effect on proliferation, migration and anti-apoptosis of mesenchymal stem cells.

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Mesenchymal stem cells (MSCs) have been found to be helpful elements in tissue regeneration. Photobiomodulation (PBM) used extremely low level lasers (LLL) to affect the behaviour of cells. The effect mechanism of LLL on MSCs remained to be discovered. Here cell viability was assessed using MTS assays and cell cycle was evaluated by FACS. The influence of LLL on mitochondrial biogenesis (fission or fusion) and function (ATP, ROS, NO) were evaluated by TEM, FACS, RT-PCR, immunocytochemistry. Cell migration and cytoskeleton alteration (actin and tubulin) were evaluated using transwell assay, immunocytochemistry, ELISA and Western blotting. Cell apoptosis was evaluated using FACS, immunocytochemistry, and Western blotting. We investigated that certain influence of low level lasers (LLL) on MSCs from human (hMSCs) in vitro 6 hours or 24 hours after 1 hour of low level lasers (LLL) irradiation. The mechanism of the effects included proliferation rate increasing mediated by increased S phase proportion; mitochondria biogenesis and function altering mediated by fission (Fis1 and 2, Drp-1), fusion (Mfn1 and 2, Opa-1) regulators , NRF1, TFAM , PGC-1a and upregulated intracellular ROS and NO concentration; migration acceleration via ERK1/2 and FAK pass way and upregulation of grow factors such as HGF and PDGF; resistant to apoptosis with increased Bcl-2 and decreased Bax, or through Tunneling nanotubes (TNTs) formation between LLL treated MSCs and 5-fluorouracil induced apoptotic MSCs . These observations suggested LLL enhanced stem cell survival and therapeutic function, which could appear to an innovative pre-treatment in the application of MSCs.

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Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy.

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Photobiomodulation (PBM) also known as low-level laser (or light) therapy (LLLT), has been known for almost 50 years but still has not gained widespread acceptance, largely due to uncertainty about the molecular, cellular, and tissular mechanisms of action. However, in recent years, much knowledge has been gained in this area, which will be summarized in this review. One of the most important chromophores is cytochrome c oxidase (unit IV in the mitochondrial respiratory chain), which contains both heme and copper centers and absorbs light into the near-infra-red region. The leading hypothesis is that the photons dissociate inhibitory nitric oxide from the enzyme, leading to an increase in electron transport, mitochondrial membrane potential and ATP production. Another hypothesis concerns light-sensitive ion channels that can be activated allowing calcium to enter the cell. After the initial photon absorption events, numerous signaling pathways are activated via reactive oxygen species, cyclic AMP, NO and Ca2+, leading to activation of transcription factors. These transcription factors can lead to increased expression of genes related to protein synthesis, cell migration and proliferation, anti-inflammatory signaling, anti-apoptotic proteins, antioxidant enzymes. Stem cells and progenitor cells appear to be particularly susceptible to LLLT.

Ieee J Sel Top Quantum Electron, 22(3)

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Effects of light-emitting diode irradiation on the osteogenesis of human umbilical cord mesenchymal stem cells in vitro.

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The aim of this study was to examine the effects of light-emitting diode (LED) photobiomodulation therapy on the proliferation and differentiation of human umbilical cord mesenchymal stem cells (hUMSCs) cultured in osteogenic differentiation medium. HUMSCs were irradiated with an LED light at 620nm and 2J/cm(2) and monitored for cell proliferation and osteogenic differentiation activity. The experiment involved four groups of cells: the control group; the osteogenic group (osteo group); the LED group; the osteogenic+LED group (LED+osteo group). HUMSC proliferation was detected by performing a3-(4,5-dimethylthiazol-2yl)-2,5 diphenyltetrazolium bromide(MTT) assay. Osteogenic activity was evaluated by performing alkaline phosphatase (ALP) and Von Kossa staining, and osteopontin (OPN) gene mRNA expression was evaluated byreverse transcription polymerase chain reaction (RT-PCR). The hUMSCs in the LED+osteo group exhibited a significantly higher proliferation rate than the other subgroups. Additionally, there were greater numbers of ALP-positive cells and Von Kossa nodules in the LED +osteo group. OPN mRNA expression in the LED+osteo group was higher than other subgroups. In conclusion, low levels of LED light at a wavelength of 620nm enhance the proliferation and osteogenic differentiation of hUMSCs during a long culture period.

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Special Issue on Stem Cells and Photobiomodulation Therapy.

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Photobiomodulation Therapy: Communicating with Stem Cells for Regeneration?

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Photobiomodulation Therapy Promotes Expansion of Epithelial Colony Forming Units.

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Regenerative medicine is at the brink of exploiting the tremendous potential offered by advances in stem cell biology. The two distinct aspects for utilization of stem cells, either resident (endogenous) or transplanted (exogenous), rely on cells amenable to expansion and being directed toward mature, functional tissues. Despite major progress in fundamental understanding of stem cell pluripotency, there remain fundamental challenges in applying these insights into clinical practice.

PBM treatments with various devices, wavelengths, and doses were used on two epithelial cell lines and colony forming assays were performed.

This study noted a dose-dependent effect of 810 nm laser on increasing eCFUs, either in terms of size or numbers. Comparisons of different wavelengths and light sources noted better efficacy of collimated and coherent lasers compared to LEDs and broad-band light.

PBM therapy promotes expansion of eCFUs that represent progenitors and stem cell populations capable of contributing to tissue repair and regeneration. Further exploration of the precise mechanisms would allow optimization of PBM clinical protocols to harness the regenerative potential of stem cells for wound healing and other clinical regenerative applications.

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Odontogenic differentiation and biomineralization potential of dental pulp stem cells inside Mg-based bioceramic scaffolds under low-level laser treatment.

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This study aimed to investigate the potential of low-level laser irradiation (LLLI) to promote odontogenic differentiation and biomineralization by dental pulp stem cells (DPSCs) seeded inside bioceramic scaffolds. Mg-based, Zn-doped bioceramic scaffolds, synthesized by the sol-gel technique, were spotted with DPSCs and exposed to LLLI at 660nm with maximum output power of 140mw at fluencies (a) 2 and 4J/cm(2) to evaluate cell viability/proliferation by the MTT assay and (b) 4J/cm(2) to evaluate cell differentiation, using real-time PCR (expression of odontogenic markers) and a p-nitrophenylphosphate (pNPP)-based assay for alkaline phosphatase (ALP) activity measurement. Scanning electron microscopy (SEM) and X-ray diffraction (XRD) analysis were used for structural/chemical characterization of the regenerated tissues. Exposure of the DPSCs/scaffold complexes to the proposed LLLI scheme was associated with statistically significant increase of odontogenesis-related markers (bone morphogenetic protein 2 (BMP-2): 22.4-fold, dentin sialophosphoprotein (DSPP): 28.4-fold, Osterix: 18.5-fold, and Runt-related transcription factor 2 (Runx2): 3.4-fold). ALP activity was significantly increased at 3 and 7days inside the irradiated compared to that in the non-irradiated SC/DPSC complexes, but gradually decreased until 14days. Newly formed Ca-P tissue was formed on the SC/DPSC complexes after 28days of culture that attained the characteristics of bioapatite. Overall, LLLI treatment proved to be beneficial for odontogenic differentiation and biomineralization of DPSCs inside the bioceramic scaffolds, making this therapeutic modality promising for targeted dentin engineering.

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Combined effects of electromagnetic field and low-level laser increase proliferation and alter the morphology of human adipose tissue-derived mesenchymal stem cells.

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In recent years, electromagnetic field (EMF) and low-level laser (LLL) have been found to affect various biological processes, the growth and proliferation of cells, and especially that of stem cells. The aim of this study was to investigate the effects of EMF and LLL on proliferation of human adipose tissue-derived mesenchymal stem cells (hAT-MSCs) and thus to examine the impact of these therapeutic physical modalities on stem cell engraftment. hAT-MSCs were isolated from subcutaneous adipose tissue of six persons ranging in age from 21 to 56years. EMF was applied for a period of 7days, once a day for 30min, via a magnetic cushion surface at a frequency of 50Hz and an intensity of 3mT. LLL was applied also for 7days, once a day for 5min, at radiation energies of 3J/cm(2), with a wavelength of 808nm, power output of 200mW, and power density of 0.2W/cm(2). Nonexposed cells (control) were cultivated under the same culture conditions. Seven days after treatment, the cells were examined for cell viability, proliferation, and morphology. We found that after 7days, the number of EMF-treated hAT-MSCs was significantly higher than the number of the untreated cells, LLL-treated hAT-MSCs were more numerous than EMF-treated cells, and hAT-MSCs that were treated with the combination of EMF and LLL were the most numerous. EMF and/or LLL treatment did not significantly affect hAT-MSC viability by itself. Changes in cell morphology were also observed, in terms of an increase in cell surface area and fractal dimension in hAT-MSCs treated with EMF and the combination of EMF and LLL. In conclusion, EMF and/or LLL treatment accelerated the proliferation of hAT-MSCs without compromising their viability, and therefore, they may be used in stem cell tissue engineering.

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Photobiomodulation of human adipose-derived stem cells using 810nm and 980nm lasers operates via different mechanisms of action.

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Photobiomodulation (PBM) using red or near-infrared (NIR) light has been used to stimulate the proliferation and differentiation of adipose-derived stem cells. The use of NIR wavelengths such as 810nm is reasonably well accepted to stimulate mitochondrial activity and ATP production via absorption of photons by cytochrome c oxidase. However, the mechanism of action of 980nm is less well understood. Here we study the effects of both wavelengths (810nm and 980nm) on adipose-derived stem cells in vitro. Both wavelengths showed a biphasic dose response, but 810nm had a peak dose response at 3J/cm 2 for stimulation of proliferation at 24h, while the peak dose for 980nm was 10-100 times lower at 0.03 or 0.3J/cm 2. Moreover, 980nm (but not 810nm) increased cytosolic calcium while decreasing mitochondrial calcium. The effects of 980nm could be blocked by calcium channel blockers (capsazepine for TRPV1 and SKF96365 for TRPC channels), which had no effect on 810nm. To test the hypothesis that the chromophore for 980nm was intracellular water, which could possibly form a microscopic temperature gradient upon laser irradiation, we added cold medium (4°C) during the light exposure, or pre-incubated the cells at 42°C, both of which abrogated the effect of 980nm but not 810nm. We conclude that 980nm affects temperature-gated calcium ion channels, while 810nm largely affects mitochondrial cytochrome c oxidase.

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Low-level laser therapy with helium-neon laser improved viability of osteoporotic bone marrow-derived mesenchymal stem cells from ovariectomy-induced osteoporotic rats.

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The purpose of this study was to evaluate the influences of helium–neon (He–Ne) and infrared (IR) lasers on the viability and proliferation rate of healthy and ovariectomy-induced osteoporotic (OVX) bone marrow mesenchymal stem cells (BMMSCs) in vitro. MSCs harvested from the BM of healthy and OVX rats were culture expanded. He–Ne and IR lasers were applied three times at energy densities of 0.6, 1.2, and 2.4??J/cm2 for BMMSCs. BMMSCs viability and proliferation rate were evaluated by MTT assay on days 2, 4, 6, 14, and 21. The results showed that healthy BMMSCs responded optimally to 0.6??J/cm2 using an IR laser after three times of laser radiation. Moreover, it was found that OVX-BMMSCs responded optimally to 0.6??J/cm2 with He–Ne laser and one-time laser radiation. It is concluded that the low-level laser therapy (LLLT) effect depends on the physiological state of the BMMSCs, type of the laser, wavelength, and number of laser sessions. The biostimulation efficiency of LLLT also depends on the delivered energy density. LLLT can enhance the viability and proliferation rate of healthy and especially osteoporotic autologous BMMSCs, which could be very useful in regenerative medicine.

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Photobiomodulation (blue and green light) encourages osteoblastic-differentiation of human adipose-derived stem cells: role of intracellular calcium and light-gated ion channels.

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RUNX2, osterix, and the osteoblast protein, osteocalcin. The 420 nm and 540 nm wavelengths were more effective in stimulating osteoblast differentiation compared to 660 nm and 810 nm. Intracellular calcium was higher after 420 nm and 540 nm, and could be inhibited by capsazepine and SKF96365, which also inhibited osteogenic differentiation. We hypothesize that activation of light-gated calcium ion channels by blue and green light could explain our results.

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Low-Level Laser Irradiation Precondition for Cardiac Regenerative Therapy.

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OBJECTIVE: The purpose of this article was to review the molecular mechanisms of low-level laser irradiation (LLLI) preconditioning for heart cell therapy. BACKGROUND DATA: Stem cell transplantation appears to offer a better alternative to cardiac regenerative therapy. Previous studies have confirmed that the application of LLLI plays a positive role in regulating stem cell proliferation and in remodeling the hostile milieu of infarcted myocardium. Greater understanding of LLLI's underlying mechanisms would be helpful in translating cell transplantation therapy into the clinic. METHODS: Studies investigating LLLI preconditioning for cardiac regenerative therapy published up to 2015 were retrieved from library sources and Pubmed databases. RESULTS: LLLI preconditioning stimulates proliferation and differentiation of stem cells through activation of cell proliferation signaling pathways and alteration of microRNA expression. It also could stimulate paracrine secretion of stem cells and alter cardiac cytokine expression in infarcted myocardium. CONCLUSIONS: LLLI preconditioning provides a promising approach to maximize the efficacy of cardiac cell-based therapy. Although many studies have reported possible molecular mechanisms involved in LLLI preconditioning, the exact mechanisms are still not clearly understood.

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Effects of low-level laser therapy on stem cells from human exfoliated deciduous teeth.

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OBJECTIVE: This study aimed to evaluate the influence of different laser therapy energy densities on SHED viability and proliferation. MATERIAL AND METHODS: SHED were irradiated according to the groups: I (1.2 J/cm2 - 0.5 mW - 10 s), II (2.5 J/cm2 - 10 mW - 10 s), III (3.7 J/cm2 - 15 mW - 10 s), IV (5.0 J/cm2 - 20 mW - 10 s), V (6.2 J/cm2 - 25 mW - 10 s), and VI (not irradiated - control group). Cell viability was assessed 6 and 24 h after irradiation measuring the mitochondrial activity and using the Crystal Violet assay. Cell proliferation was assessed after 24, 48, and 72 h of irradiation by SRB assay. RESULTS: MTT assay demonstrated differences from 6 to 24 hours after irradiation. After 24 h, groups I and IV showed higher absorbance values than those of control group. Crystal Violet assay showed statistically differences in the absorbance rate from 6 to 24 h after irradiation for groups III and VI. At 24 h after irradiation, Group III absorbance rate was greater than that of groups I, II, and IV. Group VI absorbance rate was greater than that of groups I and IV. SRB assay showed that the group I had higher rates than those of groups II, III, V, and VI, at 24 h after irradiation. After 48 h, group I exhibited the greatest cell proliferation rate followed by groups III, V, and VI. After 72 h, group III exhibited the lowest cell proliferation rate than those of groups II, IV, and V. CONCLUSIONS: The Low-Level Laser Therapy energy densities used in this study did not cause loss of cell viability and stimulated SHED proliferation within the parameters described in this study.

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Effect of low-level laser irradiation on proliferation of human dental mesenchymal stem cells; a systemic review.

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CONTEXT: Identification of factors that enhance the proliferation of human dental mesenchymal stem cells (DMSCs) is vital to facilitate tissue regeneration. The role of low-level laser irradiation (LLLI) on proliferation of human DMSCs has not been well established. OBJECTIVE: To assess the effect of LLLI on proliferation of human DMSCs when applied in-vitro. DATA SOURCES: Electronic search of literature was conducted (2000-2016) on PubMed, Web of Science, and Scopus databases. Search terms included low-level light therapy, low-level laser irradiation, low-level light irradiation, LLLT, humans, adolescent, adult, cells, cultured, periodontal ligament, dental pulp, stem cells, dental pulp stem cells, mesenchymal stem cells, periodontal ligament stem cell, deciduous teeth, cell proliferation, adult stem cells, radiation, and proliferation. RESULTS: The literature search identified 165 studies with 6 being eligible for inclusion; all used diode lasers; 5 studies used InGaAIP diode lasers; 4 used 660nm, and the other two applied 810nm or 980nm wavelength LLLI. The distance between the DMSCs and the laser spot ranged between 0.5mm to 2mm. The time intervals of cell proliferation analysis ranged from 0h to 7days after LLLI. After 660nm LLLI, an increase in the DMSC's proliferation was reported [DMSCs extracted from dental pulp of deciduous teeth (two irradiations, 3J/cm2, 20mW was more effective than 40mW), adult teeth (two irradiations, 0.5 and 1.0J/cm2, 30mW), and from adult periodontal ligament (two irradiations, 1.0J/cm2 was more effective than 0.5J/cm2, 30mW)]. Similarly, an increase in the proliferation of DMSCs extracted from dental pulp of adult teeth was reported after 810nm LLLI (7 irradiations in 7days, 0.1 and 0.2J/cm2, 60mW) or 980nm LLLI (single irradiation, 3J/cm2, 100mW). However, 660nm LLLI in one study did not increase the proliferation of DMSCs (single irradiation, energy densities of 0.05, 0.30, 7, and 42J/cm2, 28mW). CONCLUSION: There is limited evidence that in-vitro LLLI (660/810/980nm, with energy densities of 0.1-3J/cm2) increases the proliferation of DMSCs. Considering the limited evidence and their method heterogeneity it is difficult to reach a firm conclusion. Further research is necessary to identify the optimal characteristics of the LLLI setting (wave length, energy density, power output, frequency/duration of irradiations, distance between the cells and the laser spot/probe) to increase proliferation of DMSCs, and assess its impact on replicative senescence, as well as determine feasibility of the use in the clinical setting.

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Noninvasive low-level laser therapy for thrombocytopenia.

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Thrombocytopenia is a common hematologic disorder that is managed primarily by platelet transfusions. We report here that noninvasive whole-body illumination with a special near-infrared laser cures acute thrombocytopenia triggered by γ-irradiation within 2 weeks in mice, as opposed to a 5-week recovery time required in controls. The low-level laser (LLL) also greatly accelerated platelet regeneration in the presence of anti-CD41 antibody that binds and depletes platelets, and prevented a severe drop in platelet count caused by a common chemotherapeutic drug. Mechanistically, LLL stimulated mitochondrial biogenesis specifically in megakaryocytes owing to polyploidy of the cells. LLL also protected megakaryocytes from mitochondrial injury and apoptosis under stress. The multifaceted effects of LLL on mitochondria bolstered megakaryocyte maturation; facilitated elongation, branching, and formation of proplatelets; and doubled the number of platelets generated from individual megakaryocytes in mice. LLL-mediated platelet biogenesis depended on megakaryopoiesis and was inversely correlated with platelet counts, which kept platelet biogenesis in check and effectively averted thrombosis even after repeated uses, in sharp contrast to all current agents that stimulate the differentiation of megakaryocyte progenitors from hematopoietic stem cells independently of platelet counts. This safe, drug-free, donor-independent modality represents a paradigm shift in the prophylaxis and treatment of thrombocytopenia.

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Angiogenic Synergistic Effect of Adipose-Derived Stromal Cell Spheroids with Low-Level Light Therapy in a Model of Acute Skin Flap Ischemia.

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Human adipose-derived mesenchymal stem cells (hASCs) are an attractive cell source for tissue engineering. However, one obstacle to this approach is that the transplanted hASC population can decline rapidly in the recipient tissue. The aim of this study was to investigate the effects of low-level light therapy (LLLT) on transplanted spheroid hASCs in skin flaps of mice. hASCs were cultured in monolayers or spheroids. LLLT, hASCs, spheroids and spheroids transplanted with LLLT were applied to the skin flaps. Healing of the skin flaps was assessed by gross evaluation and by hematoxylin and eosin staining and elastin van Gieson staining. Compared with the spheroid group, skin flap healing was enhanced in the spheroid + LLLT group, including the neovascularization and regeneration of skin appendages. The survival of hASCs was enhanced by decreased apoptosis of hASCs in the skin flaps of the spheroid + LLLT group. The secretion of growth factors was stimulated in the spheroid + LLLT group compared with the ASC and spheroid groups. These data suggest that LLLT was an effective biostimulator of spheroid hASCs in the skin flaps, enhancing the survival of hASCs and stimulating the secretion of growth factors.

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Low-Level Laser Therapy to the Bone Marrow Ameliorates Neurodegenerative Disease Progression in a Mouse Model of Alzheimer's Disease: A Minireview.

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OBJECTIVE: This communication reviews the ability of low-level laser therapy (LLLT) to stimulate mesenchymal stem cells (MSCs) in autologous bone marrow (BM) to enhance the capacity of MSCs to infiltrate the brain, clear beta-amyloid, and improve cognition. BACKGROUND: We recently reported that LLLT applied to the BM enhanced the proliferation of MSCs and their mobilization toward the ischemic heart region, suggesting a possible application of this approach in regenerative medicine and neurodegenerative diseases. It was also shown that circulating monocytes can infiltrate the brain and reduce brain amyloid load in an Alzheimer's disease (AD) mouse model. METHODS AND RESULTS: MSCs from wild-type mice stimulated with LLLT demonstrated an increased ability to maturate toward a monocyte lineage and to increase phagocytosis of soluble Abeta in vitro. Furthermore, weekly LLLT for 2 months to the BM, starting at 4 months of age (progressive stage of the disease in these 5XFAD transgenic male mice), improved memory and spatial learning, compared to a sham-treated AD mouse model. Histology revealed a significant reduction in Abeta brain burden in the laser-treated mice compared to the nonlaser-treated ones. CONCLUSIONS: The application of LLLT to the BM is suggested as a therapeutic approach in progressive stages of AD, and its potential role in mediating MSC therapy in brain amyloidogenic disease is implied.

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Low-intensity laser phototherapy enhances the proliferation of dental pulp stem cells under nutritional deficiency.

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Dental trauma in immature permanent teeth can damage pulp vascularization, which leads to necrosis and cessation of apexogenesis. Studies on tissue engineering using stem cells from human exfoliated deciduous teeth (SHEDs) have yielded promising results. Laser phototherapy (LPT) is able to influence the proliferation and differentiation of these cells, which could improve tissue engineering. SHEDs (eighth passage) were seeded into 96-well culture plates (103 cells/well) and were grown in culture medium supplemented with 15% defined fetal bovine serum (FBS) for 12 h. After determining the appropriate nutrition deficiency status (5% FBS), the cells were assigned into four groups: 1) G1 - 15% FBS (positive control); 2) G2 - 5% FBS (negative control); 3) G3 - 5% FBS +LPT 3 J/cm2; and 4) G4 - 5% FBS+LPT 5 J/cm2. For the LPT groups, two laser irradiations at 6 h intervals were performed using a continuous wave InGaAlP diode laser (660 nm, with a spot size of 0.028 cm2, 10 mW) in punctual and contact mode. Cell viability was assessed via an MTT reduction assay immediately after the second laser irradiation (0 h) and 24, 48, and 72 h later. We found that G3 and G4 presented a significantly higher cell growth rate when compared with G2 ($p < 0.01$). Moreover, G4 exhibited a similar cell growth rate as G1 throughout the entire experiment ($p > 0.05$). These findings indicate that LPT with 5 J/cm2 can enhance the growth of SHEDs during situations of nutritional deficiency. Therefore, LPT could be a valuable adjunct treatment in tissue engineering when using stem cells derived from the dental pulp of primary teeth.

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Mesenchymal Stem Cells Synergize with 635, 532, and 405 nm Laser Wavelengths in Renal Fibrosis: A Pilot Study.

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Chronic kidney disease is a global health problem with only 20% receiving care worldwide. Kidneys with compromised function have ongoing inflammation, including increased oxidative stress and apoptosis, peritubular capillary loss, tubular atrophy, and tubulointerstitial fibrosis. Promising studies have highlighted the significant potential of MSC-based strategies to mitigate fibrosis; however, reversal of established fibrosis has been problematic, suggesting that methods to potentiate MSC effects require further development. Laser treatments at visible wavelengths have been reported to enhance mitochondrial potential and available cellular ATP, facilitate proliferation, and inhibit apoptosis. We hypothesized that laser-delivered energy might provide wavelength-specific effects in the fibrotic kidney and enhance MSC responses.

Renal fibrosis, established in C57BL6 mice following 21 days of unilateral ureter obstruction (UUO), was treated with one of three wavelengths alone or with autologous MSC. Mitochondrial activity, cell proliferation, apoptosis, and cytokines were measured 24 h later.

Wavelengths 405, 532, and 635 nm all significantly synergized with MSC to enhance mitochondrial activity and reduce apoptosis. Proliferative activity was observed in the renal cortices following combined treatment with the 532 nm laser and MSC; endothelial proliferation increased in response to the 635 nm laser alone and to the combined effects of MSC and the 405 nm wavelength. Reductions of transforming growth factor-β were observed with 532 nm alone and when combined with MSC.

Specific wavelengths of laser energy appear to induce different responses in renal fibrotic tissue. These findings support further study in the development of a customized laser therapy program of combined wavelengths to optimize MSC effects in the treatment of renal fibrosis.

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[The influence of continuous low-intensity laser radiation at the red (635 nm) and green (525 nm) wavelengths on the human mesenchymal stem cells in vitro: a review of the literature and original investigations].

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Low-intensity laser radiation can be used as one of the methods for the non-specific regulation of the human mesenchymal stem cell (MSC) activity at the preliminary stage of their in vitro cultivation. The objective of the present study was to estimate the influence of the limiting regimes of continuous low-intensity laser radiation (CLIR) of red (635 nm) and green (525 nm) spectra. MATERIAL AND METHODS: The adhesive culture of human mesenchymal stem cells obtained from a donor's umbilical cord tissue was used in the experiments (following 4 passages). They were irradiated using a Lazmik-VLOK laser therapeutic device equipped with the KLO-635-40 (635 nm, 4,9 mW/cm2) and KLO-525-50 (525 nm, 5,4 mW/cm2) laser diode emitting heads operating in a continuous mode. A special nozzle (jar) for laser and vacuum massage (KB-5, 35 cm in diameter) was employed to fix the heads. The exposure time in all the irradiation regimes was 5 minutes. CONCLUSION: The study has demonstrated that neither the morphological features nor the viability of mesenchymal stem cells was altered under the influence of laser irradiation at the aforementioned energy and time parameters. The data obtained indicate that laser irradiation with the limiting levels of the chosen energy parameters produces no positive effect on the cell proliferative activity; more than that, it may cause its inhibition.

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Hypoxia and laser enhance expression of SDF-1 in muscles cells.

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Targeted homing of transplanted mesenchymal stem cells (MSCs) is a decades old discussion in regenerative medicine. It has been proved that stromal cell-derived factor-1 (SDF-1alpha) is a potent chemoattractant of MSCs. Therefore, different strategies have been used to increase secretion of SDF-1alpha in damaged tissues to elevate targeted homing of MSCs. Previous studies have revealed that increased SDF-1alpha expression in hypoxic necrotic tissues and also low-level laser exposure enhanced angiogenesis in injured tissues. Herein, human skeletal and cardiac muscle cells (HSKM and HCM) were treated with hypoxia and low level laser to see their effects on expression of SDF-1alpha and on MSCs migration towards these treated cells. The optimal treatment conditions were determined by investigating the cellular viability after treatment. Real-Time PCR and Western blot analysis were done to study the expression of SDF-1alpha in treated cells. Migration potential of MSCs toward hypoxic and laser treated cells was investigated via migration assay. MTT assay revealed that laser and hypoxia treatment had no effect on the viability of HCM, HSKM compared with Glioblastoma cells. Real-Time PCR showed 16- and 90-fold elevation in mRNA of SDF-1alpha in HSKM and HCM cells, respectively, in laser treated with 12 J/cm2 intensity. In these two groups, selected as optimal conditions, HIF-1alpha expression showed maximum fold changes that might be partly because of response to treatments help to SDF-1alpha expression. It can be concluded that hypoxia and laser treatments may recruit MSCs and applied as a useful strategy for the further targeted stem cell homing.

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Effect of Photobiomodulation on Mesenchymal Stem Cells.

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The effects of coherent and noncoherent light sources such as low-level lasers and light-emitting diodes (LEDs) on cells and tissues, known as PBM, form the basis of photomedicine. This treatment technique effects cell function, proliferation, and migration, and plays an important role in tissue regeneration. Stem cells have been found to be helpful elements in tissue regeneration, and the combination of stem cell therapy and laser therapy appears to positively affect treatment results.

An electronic search in PubMed was conducted of publications from the previous 12 years. English language articles related to the subject were found using selected key words. The full texts of potentially suitable articles were assessed according to inclusion and exclusion criteria.

After evaluation, 30 articles were deemed relevant according to the inclusion criteria. The energy density of the laser was 0.7-9 J/cm 2. The power used for visible light was 30-110 mW and that used for infrared light was 50 -800 mW. Nearly all studies showed that low-level laser therapy had a positive effect on cell proliferation. Similar outcomes were found for LED; however, some studies suggest that the laser alone is not effective, and should be used as an adjunct tool.

PBM has positive effects on MSCs. This review concluded that doses of 0.7-4 J/cm 2 and wavelengths of 600-700 nm are appropriate for light therapy. The results were dependent upon different parameters; therefore, optimization of parameters used in light therapy to obtain favorable results is required to provide more accurate comparison.

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Photobiomodulation of Dental Derived Mesenchymal Stem Cells: A Systematic Review.

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Systematic reviews provide the best evidence on the effectiveness of a procedure and permit investigation of factors that may influence the performance of a method. To the best of our knowledge, no previous systematic review has evaluated the effects of PBM only on ddMSCs.

The search was conducted in PubMed /MEDLINE ®, Scopus and Web of Science databases, and reported according to the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA Statement). Original research articles investigating the effects of PBM therapy on ddMSCs, published from 2000 to August 2015, were retrieved and used for this review according to the following eligibility criteria: evaluating PBM therapy, assessing stem cells of dentoalveolar origin, published in English, dealing with cells characterized as stem cells, and using light that did not need external chromophores.

From the initial 3467 potentially relevant articles identified, 6 were excluded because they were duplicates, and 3453 were considered ineligible based on the inclusion criteria. Therefore, eight articles remained, and these were fully analyzed in order to closely check exclusion criteria items. Only one of them was excluded because the cultured cells studied were not characterized as stem cells. Finally, seven articles served as the basis for this systematic review.

PBM therapy has no deleterious effects on ddMSCs. Although no other clear conclusion was obtained because of the scarce number of publications, the results of these studies are pointing to an important tendency of PBM therapy to improve ddMSCs' viability and proliferation.

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Effects of Photobiomodulation and Mesenchymal Stem Cells on Articular Cartilage Defects in a Rabbit Model.

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For healing of the articular cartilage defects, although positive effects of BMSCs and LLLT have been demonstrated, their combination effect is still unknown; therefore, we investigated combining these two techniques has a synergistic effect.

After bone marrow aspiration from 10 rabbits, BMSCs were isolated, cultured in monolayer, suspended on a type I collagen scaffold and then implanted onto a full-thickness osteochondral defect (4 mm in diameter), artificially made on the patellar groove of both knees in the same rabbits. Then a knee was selected randomly in each rabbit as the experimental group, and subjected to Ga-Al-As (810 nm) laser irradiation with energy density of 4 J/cm 2 every other day for 3 weeks. As the control group, the other knee did not receive LLLT. After this period, animals were euthanized and osteochondral defects were evaluated by histomorphometric methods.

No significant difference in new cartilage formation and inflammation was found between the groups (p > 0.05). However, there was significantly more new bone formation in the experimental group (p < 0.05).

In terms of our research, although better healing in osteochondral defects was seen when combining BMSCs and LLLT compared with the use of BMSCs alone, this improvement was predominantly caused by new bone formation rather than new cartilage formation.

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Combined effects of low-level laser therapy and human bone marrow mesenchymal stem cell conditioned medium on viability of human dermal fibroblasts cultured in a high-glucose medium.

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Low-level laser therapy (LLLT) exhibited biostimulatory effects on fibroblasts viability. Secretomes can be administered to culture mediums by using bone marrow mesenchymal stem cells conditioned medium (BM-MSCs CM). This study investigated the combined effects of LLLT and human bone marrow mesenchymal stem cell conditioned medium (hBM-MSCs CM) on the cellular viability of human dermal fibroblasts (HDFs), which was cultured in a high-glucose (HG) concentration medium. The HDFs were cultured either in a concentration of physiologic (normal) glucose (NG; 5.5 mM/l) or in HG media (15 mM/l) for 4 days. LLLT was performed with a continuous-wave helium-neon laser (632.8 nm, power density of 0.00185 W/cm2 and energy densities of 0.5, 1, and 2 J/cm2). About 10 % of hBM-MSCs CM was added to the HG HDF culture medium. The viability of HDFs was evaluated using dimethylthiazol-diphenyltetrazolium bromide (MTT) assay. A significantly higher cell viability was observed when laser of either 0.5 or 1 J/cm2 was used to treat HG HDFs, compared to the control groups. The cellular viability of HG-treated HDFs was significantly lower compared to the LLLT + HG HDFs, hBM-MSCs CM-treated HG HDFs, and LLLT + hBM-MSCs CM-treated HG HDFs. In conclusion, hBM-MSCs CM or LLLT alone increased the survival of HG HDFs cells. However, the combination of hBM-MSCs CM and LLLT improved these results in comparison to the conditioned medium.

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Tenogenic induction of equine mesenchymal stem cells by means of growth factors and low-level laser technology.

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Tendons regenerate poorly due to a dense extracellular matrix and low cellularity. Cellular therapies aim to improve tendon repair using mesenchymal stem cells and tenocytes; however, a current limitation is the low proliferative potential of tenocytes in cases of severe trauma. The purpose of this study was to develop a method useful in veterinary medicine to improve the differentiation of Peripheral Blood equine mesenchymal stem cells (PB-MSCs) into tenocytes. PB-MSCs were used to study the effects of the addition of some growth factors (GFs) as TGFbeta3 (transforming growth factor), EGF2 (Epidermal growth factor), bFGF2 (Fibroblast growth factor) and IGF -1 (insulin-like growth factor) in presence or without Low Level Laser Technology (LLLT) on the mRNA expression levels of genes important in the tenogenic induction as Early Growth Response Protein-1 (EGR1), Tenascin (TNC) and Decorin (DCN). The singular addition of GFs did not show any influence on the mRNA expression of tenogenic genes whereas the specific combinations that arrested cell proliferation in favour of differentiation were the following: bFGF2 + TGFbeta3 and bFGF2 + TGFbeta3 + LLLT. Indeed, the supplement of bFGF2 and TGFbeta3 significantly upregulated the expression of Early Growth Response Protein-1 and Decorin, while the use of LLLT induced a significant increase of Tenascin C levels. In conclusion, the present study might furnish significant suggestions for developing an efficient approach for tenocyte induction since the external administration of bFGF2 and TGFbeta3, along with LLLT, influences the differentiation of PB-MSCs towards the tenogenic fate.

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Osteogenic differentiation and gene expression of dental pulp stem cells under low-level laser irradiation: a good promise for tissue engineering.

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The effects of low-level laser therapy (LLLT) has been the focus of recent studies as being assumed responsible for promoting photostimulatory and photobiomodulatory effects in vivo and in vitro, increasing cell metabolism, improving cell regeneration and invoking an anti-inflammatory response. A positive effect of LLLT on the bone proliferation of some cell types has been observed, but little is known about its effect on dental pulp stem cells (DPSCs). Here, we accurately describe the technical procedure to isolate mesenchymal DPSCs, and assay their osteogenic capacity when irradiated with an LLLT source. These preliminary results show that LLLT irradiation influences the in vitro proliferation of DPSCs and increases the expression of essential proteins for bone formation, although it is necessary to carry out further experiments on other cell types and to uniform the methodological designs.

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Low-Level Laser Therapy to the Bone Marrow Reduces Scarring and Improves Heart Function Post-Acute Myocardial Infarction in the Pig.

Blatt A, Elbaz-Greener GA, Tuby H, Maltz L, Siman-Tov Y, Ben-Aharon G, Copel L, Eisenberg I, Efrati S, Jonas M, Vered Z, Tal S, Goitien O, Oron U

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OBJECTIVE: Cell therapy for myocardial repair is one of the most intensely investigated strategies for treating acute myocardial infarction (MI). The aim of the present study was to determine whether low-level laser therapy (LLLT) application to stem cells in the bone marrow (BM) could affect the infarcted porcine heart and reduce scarring following MI. METHODS: MI was induced in farm pigs by percutaneous balloon inflation in the left coronary artery for 90 min. Laser was applied to the tibia and iliac bones 30 min, and 2 and 7 days post-induction of MI. Pigs were euthanized 90 days post-MI. The extent of scarring was analyzed by histology and MRI, and heart function was analyzed by echocardiography. RESULTS: The number of c-kit+ cells (stem cells) in the circulating blood of the laser-treated (LT) pigs was 2.62- and 2.4-fold higher than in the non-laser-treated (NLT) pigs 24 and 48 h post-MI, respectively. The infarct size [% of scar tissue out of the left ventricle (LV) volume as measured from histology] in the LT pigs was 3.2 +/- 0.82%, significantly lower, 68% ($p < 0.05$), than that (16.6 +/- 3.7%) in the NLT pigs. The mean density of small blood vessels in the infarcted area was significantly higher [6.5-fold ($p < 0.025$)], in the LT pigs than in the NLT ones. Echocardiography (ECHO) analysis for heart function revealed the left ventricular ejection fraction in the LT pigs to be significantly higher than in the NLT ones. CONCLUSIONS: LLLT application to BM in the porcine model for MI caused a significant reduction in scarring, enhanced angiogenesis and functional improvement both in the acute and long term phase post-MI.

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Low Intensity Laser Irradiation at 636 nm Induces Increased Viability and Proliferation in Isolated Lung Cancer Stem Cells.

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OBJECTIVE: The purpose of this in vitro study was to evaluate the effects of low-intensity laser irradiation (LILI) on isolated lung cancer stem cells (CSCs) after several time intervals, using a wavelength of 636 nm and fluences between 5 and 20 J/cm2. BACKGROUND DATA: LILI has been proven to have a biomodulatory effect on various diseased conditions. A number of studies have been conducted on CSCs. METHODS: Lung CSCs were isolated from lung cancer cells (A549), using cell surface marker CD 133. Isolated lung CSCs were divided into four groups: group 1 consisted of control cells receiving no irradiation; groups 2, 3, and 4 were exposed to laser irradiation at fluences of 5, 10, and 20 J/cm2, respectively. LILI was performed using a 636 nm diode laser with a power output of +/-85 mW. Cellular responses were evaluated after 24, 48, or 72 h, and included cell morphology, viability, and proliferation. RESULTS: Cellular morphology indicated an increase in cell density caused by cell proliferation over time. Biostimulatory effects were achieved in lung CSCs when examining viability and proliferation. CONCLUSIONS: It should, therefore, be noted that a low wavelength of 636 nm at various fluences induces biostimulation, which may have detrimental effects when using LILI as a form of regeneration.

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Differentiation Potential of Adipose-Derived Stem Cells When Cocultured with Smooth Muscle Cells, and the Role of Low-Intensity Laser Irradiation.

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OBJECTIVE: The aim of the study was to investigate the differentiation potential of adipose-derived stem cells (ADSCs) when cocultured with smooth muscle cells (SMCs), and to determine the role of low-intensity laser irradiation (LILI). BACKGROUND DATA: ADSCs isolated from adipose tissue are isolated with ease and in large amounts. SMCs constitute most parts of the intestinal, urinary, reproductive, and cardiovascular systems. LILI has been found to have positive effects on different cell types, including ADSCs. METHODS: The study used ADSCs (Stempro Adipose Derived Stem Cells-R7788-115) and SMCs (SKU-T-1 American Type Culture Collection HTB -114) cell lines. These cell lines were cocultured in a 1:1 ratio with and without growth factors and then exposed to LILI using 636 nm at 5 J/cm2. RESULTS: Cell viability and proliferation increased significantly in the cocultured groups that were exposed to LILI alone, as well as in combination with growth factors. Further, there was a significant decrease in the expression of stem cell markers with a concomitant increase in SMC markers. CONCLUSIONS: These results suggest that ADSCs have the ability to differentiate into SMCs when cocultured with SMCs, whereas LILI potentially augments the differentiation potential and need. This further highlights the significant role that LILI has to offer ADSC therapy in regenerative medicine.

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Evaluation of the Proliferative Effects Induced by Low-Level Laser Therapy in Bone Marrow Stem Cell Culture.

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OBJECTIVE: The objective of this study was to evaluate the effect of laser irradiation on dog bone marrow stem cells. BACKGROUND DATA: Low doses of low-level red laser positively affect the viability of mesenchymal stem cells, and also increase proliferation. METHODS: Low-level laser (wavelength, 660 nm; power output, 50 mW), was applied to dog bone marrow stem cell cultures (DBMSC). The energy densities delivered varied from 1 to 12J/cm2. The effect of the laser irradiation was evaluated on cell proliferation measured with the MTT colorimetric test, cell cycle phase, and on lipidic peroxidation (free radical production). RESULTS: The results indicate that laser irradiation to DBMSC did not change the morphology of the cells, but significantly increased their viability and the number of cells at the G2/M phase with 6, 10, and 12 J/cm2. On the other hand, malonaldehyde production was significantly enhanced with 8 J/cm2. CONCLUSIONS: The parameters used to irradiate DBMSC increased significantly proliferation without producing high levels of reactive oxygen species (ROS).

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Bioactive glass plus laser phototherapy as promise candidates for dentine hypersensitivity treatment.

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Treatments for dentine hypersensitivity (DH) may produce positive effects, though do not have lasting results. We investigated the reparative potential of stem cells derived from deciduous teeth (SHEDs) in response to components delivered from substances used in the treatment of the DH, associated or not to laser phototherapy (LPT), to stimulate dentine formation. SHEDs were submitted to substances delivered from a laboratorial P-rich bioactive glass [57SiO2 -26CaO-17P2 O5 (wt %)] or a commercially available desensitizer (Gluma(R) Desensitizer), associated (or not) to LPT (InGAlP diode laser, 660 nm, 0.028 cm2 , 20 mW, 5 J/cm2 , 7 s, contact mode). Biomaterial characterization was performed by X-ray diffraction, scanning electron microscopy and the particle size was evaluated by dynamic light scattering. SHEDs proliferation and differentiation were analyzed by MTT and Alizarin Red staining, respectively. The conditioned media used in these tests were evaluated regarding their pH and the ionic concentration changes due to ions leached from the bioactive glass (BG). BG majority presented a non-crystalline solid structure and mixed particle sizes characterized by the agglomeration of nanoparticles. Cultures treated with BG alone or in association to LPT showed improved cell growth in relation to Gluma(R) ($p < 0.05$). Gluma(R) was cytotoxic in all tested conditions, regardless irradiated or not. BG associated to LPT induced intense mineral matrix formation. In conclusion, BG releases ionic dissolution products able to promote SHEDs differentiation. BG associated to LPT improves SHEDs proliferation and differentiation in vitro, and may be a promise therapeutic approach for the DH treatment. (c) 2015 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2015.

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Effects of low-level laser irradiation on proliferation and functional protein expression in human RPE cells.

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Low-level laser irradiation (LLLI) modulates a set of biological effects in many cell types such as fibroblasts, keratinocytes, and stem cells. However, no study to date has reported the effects of LLLI on retinal pigment epithelia (RPE) cells. The aim of this study was to investigate whether LLLI could enhance the proliferation of RPE cells and increase the expression of RPE functional genes/proteins. Human ARPE-19 cells were seeded overnight and treated with 8 J/cm(2) of LLLI. Cell proliferation was measured by CCK8 assay and cell cycle distribution was evaluated by FACS. The transcription of cell cycle-specific genes and RPE functional genes was quantified by RT-PCR. Moreover, the expression of ZO-1 and CRALBP were evaluated by immunostaining. A dose of 8 J/cm(2) of LLLI significantly increased proliferation and promoted cell cycle progression while upregulating the transcription of CDK4 and CCND1 and decreasing the transcription of CDKN2A, CDKN2C, and CDKN1B in human ARPE-19 cells. Additionally, LLLI enhanced the expression of ZO-1 and CRALBP in human ARPE-19 cells. In conclusion, LLLI could enhance the proliferative ability of human ARPE-19 cells by modulating cyclin D1, CDK4, and a group of cyclin-dependent kinase inhibitors. It also could increase the expression of RPE-specific proteins. Thus, LLLI may be a potential approach for the treatment of RPE degenerative diseases.

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Normal and aging hair biology and structure 'aging and hair'.

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Much like an individual's hairstyle, hair fibers along the scalp see a number of changes over the course of one's lifetime. As the decades pass, the shine and volume synonymous with youthful hair may give way to thin, dull, and brittle hair commonly associated with aging. These changes are a result of a compilation of genetic and environmental elements influencing the cells of the hair follicle, specifically the hair follicle stem cells and melanocytes. Telomere shortening, decrease in cell numbers, and particular transcription factors have all been implicated in this process. In turn, these molecular alterations lead to structural modifications of the hair fiber, decrease in melanin production, and lengthening of the telogen phase of the hair cycle. Despite this inevitable progression with aging, there exists an array of treatments such as light therapy, minoxidil, and finasteride which have been designed to mitigate the effects of aging, particularly balding and thinning hair. Although each works through a different mechanism, all aim to maintain or potentially restore the youthful quality of hair.

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Effect of low-level laser irradiation on proliferation and viability of human dental pulp stem cells.

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A positive effect of low-level laser irradiation (LLLI) on the proliferation of some cell types has been observed, but little is known about its effect on dental pulp stem cells (DPSCs). The aim of this study was to identify the lowest energy density able to promote the proliferation of DPSCs and to maintain cell viability. Human DPSCs were isolated from two healthy third molars. In the third passage, the cells were irradiated or not (control) with an InGaAlP diode laser at 0 and 48 h using two different energy densities (0.5 and 1.0 J/cm(2)). Cell proliferation and viability and mitochondrial activity were evaluated at intervals of 24, 48, 72, and 96 h after the first laser application. Apoptosis- and cell cycle-related events were analyzed by flow cytometry. The group irradiated with an energy density of 1.0 J/cm(2) exhibited an increase of cell proliferation, with a statistically significant difference ($p < 0.05$) compared to the control group at 72 and 96 h. No significant changes in cell viability were observed throughout the experiment. The distribution of cells in the cell cycle phases was consistent with proliferating cells in all three groups. We concluded that LLLI, particularly a dose of 1.0 J/cm(2), contributed to the growth of DPSCs and maintenance of its viability. This fact indicates this therapy to be an important future tool for tissue engineering and regenerative medicine involving stem cells.

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Dose-responses of Stem Cells from Human Exfoliated Teeth to Infrared LED Irradiation.

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Despite several reports regarding tissue regeneration, including pulp repair induced by different light sources, only limited data have been reported concerning the effects of light-emitting diodes (LED) on stem cells from human exfoliated deciduous teeth (SHEDs). The aim of this study was to evaluate the effects of different energy densities of infrared LED on the cell viability, number of cells and mineralized tissue production by SHEDs. SHEDs were obtained from near-exfoliation primary teeth (n=3), seeded in plain DMEM (104 cells/cm2), and irradiated by a LED prototype (LEDTable 850 nm, 40 mW/cm2) delivering 0 (control), 2, 4, 8, 15 or 30 J/cm2 (n=9). Cell viability (MTT assay), cell proliferation (trypan blue assay), and mineralized nodule (MN) formation (alizarin red stain) were assessed 12 and 72 h post-irradiation. Data were subjected to Kruskal-Wallis and Mann-Whitney tests (alpha=0.05). Cells irradiated with 2 or 4 J/cm2 exhibited higher metabolism at 72 h, and all energy densities provided increase in cell proliferation after 12 h. Regarding MN formation, the best results were observed at 72 h after SHED irradiation with 8 and 15 J/cm2. It was concluded that the cell viability, cell number and MN formation by pulp cells are enhanced after exposure to infrared LED irradiation. Overall, the greatest SHED biostimulation was obtained with 4 and 8 J/cm2.

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The effects of combined low level laser therapy and mesenchymal stem cells on bone regeneration in rabbit calvarial defects.

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Although several studies evaluated the effects of MSCs and LLLT, there is little information available regarding in vivo application of LLLT in conjunction with MSCs.
Forty-eight circular bone defects (6mm in diameter) were prepared in the calvaria of 12 New-Zealand white rabbits. The defects of each animal were randomly assigned to 4 groups: (C) no treatment; (L) applying LLLT; (SC) filled with MSCs; (SCL) application of both MSCs and LLLT. LLL was applied on alternate days at wavelength of 810 nm, power density of 0.2 W/cm(2) and a fluency of 4 J/cm(2) using a Gallium-Aluminum-Arsenide (GaAlAs) diode laser. The animals were sacrificed after 3 weeks and then histological samples were evaluated to determine the amount of new bone formation and the remaining scaffold and inflammation.
The histological evaluation showed a statistically significant increase in new bone formation of LLLT group relative to the control and the other two experimental groups (p<0.05). There was no significant difference in bone formation of the control group compared to experimental groups filled with MSCs. Laser irradiation had no significant effect on resorption of the scaffold material. In addition, inflammation was significantly reduced in LLLT group compared to the control defects and the other two experimental groups.
Low level laser therapy could be effective in bone regeneration but there is no evidence of a synergistic effect when applied in conjunction with MSCs.

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Low Reactive Level Laser Therapy for Mesenchymal Stromal Cells Therapies.

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Low reactive level laser therapy (LLLT) is mainly focused on the activation of intracellular or extracellular chromophore and the initiation of cellular signaling by using low power lasers. Over the past forty years, it was realized that the laser therapy had the potential to improve wound healing and reduce pain and inflammation. In recent years, the term LLLT has become widely recognized in the field of regenerative medicine. In this review, we will describe the mechanisms of action of LLLT at a cellular level and introduce the application to mesenchymal stem cells and mesenchymal stromal cells (MSCs) therapies. Finally, our recent research results that LLLT enhanced the MSCs differentiation to osteoblast will also be described.

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Effect of Low-Level Laser Therapy on Human Adipose-Derived Stem Cells: In Vitro and In Vivo Studies.

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BACKGROUND: Low-level laser therapy (LLLT) continues to receive much attention in many clinical fields. Also, LLLT has been used to enhance the proliferation of various cell lines, including stem cells. This study investigated the effect of LLLT on human adipose-derived stem cells (ADSCs) through in vitro and in vivo studies. METHODS: Low-level laser irradiation of cultured ADSCs was performed using a 830 nm Ga-Al-As (gallium-aluminum-arsenide) laser. Then, proliferation of ADSCs was quantified by a cell counting kit-8. In the in vivo study, irradiated ADSCs or non-irradiated ADSCs were transplanted, and then, low-level laser irradiation of each rat was performed as per the protocol. Cell viability was quantified by immunofluorescent staining using the human mitochondria antibody. RESULTS: In the in vitro study, the laser-irradiated groups showed an increase in absorbance compared to the control group. Also, in the in vivo study, there was a significant increase in the number of human ADSCs in the laser-irradiated groups compared to the control group ($p < 0.001$). CONCLUSIONS: Our study showed that LLLT could enhance the proliferation and viability of ADSCs. The ADSCs enhanced by LLLT could be applied in various clinical fields. With the use of LLLT, the proliferation and viability of various cells can be enhanced, besides ADSCs. NO LEVEL ASSIGNED: This journal requires that authors assign a level of evidence to each submission to which Evidence-Based Medicine rankings are applicable. This excludes Review Articles, Book Reviews, and manuscripts that concern Basic Science, Animal Studies, Cadaver Studies, and Experimental Studies. For a full description of these Evidence-Based Medicine ratings, please refer to the Table of Contents or the online Instructions to Authors http://www.springer.com/00266 .

Aesthetic Plast Surg 2015 Jul 17

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Photoactivation of ROS Production In Situ Transiently Activates Cell Proliferation in Mouse Skin and in the Hair Follicle Stem Cell Niche Promoting Hair Growth and Wound Healing.

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The role of reactive oxygen species (ROS) in the regulation of hair follicle (HF) cycle and skin homeostasis is poorly characterized. ROS have been traditionally linked to human disease and aging, but recent findings suggest that they can also have beneficial physiological functions in vivo in mammals. To test this hypothesis, we transiently switched on in situ ROS production in mouse skin. This process activated cell proliferation in the tissue and, interestingly, in the bulge region of the HF, a major reservoir of epidermal stem cells, promoting hair growth, as well as stimulating tissue repair after severe burn injury. We further show that these effects were associated with a transient Src kinase phosphorylation at Tyr416 and with a strong transcriptional activation of the prolactin family 2 subfamily c of growth factors. Our results point to potentially relevant modes of skin homeostasis regulation and demonstrate that a local and transient ROS production can regulate stem cell and tissue function in the whole organism.

J Invest Dermatol 2015 Jul 2

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Enhancement of Ischemic Wound Healing by Spheroid Grafting of Human Adipose-Derived Stem Cells Treated with Low-Level Light Irradiation.

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We investigated whether low-level light irradiation prior to transplantation of adipose-derived stromal cell (ASC) spheroids in an animal skin wound model stimulated angiogenesis and tissue regeneration to improve functional recovery of skin tissue. The spheroid, composed of hASCs, was irradiated with low-level light and expressed angiogenic factors, including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and hepatocyte growth factor (HGF). Immunochemical staining analysis revealed that the spheroid of the hASCs was CD31+, KDR+, and CD34+. On the other hand, monolayer-cultured hASCs were negative for these markers. PBS, human adipose tissue-derived stromal cells, and the ASC spheroid were transplanted into a wound bed in athymic mice to evaluate the therapeutic effects of the ASC spheroid in vivo. The ASC spheroid transplanted into the wound bed differentiated into endothelial cells and remained differentiated. The density of vascular formations increased as a result of the angiogenic factors released by the wound bed and enhanced tissue regeneration at the lesion site. These results indicate that the transplantation of the ASC spheroid significantly improved functional recovery relative to both ASC transplantation and PBS treatment. These findings suggest that transplantation of an ASC spheroid treated with low-level light may be an effective form of stem cell therapy for treatment of a wound bed.

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Adipose-derived stromal cell cluster with light therapy enhance angiogenesis and skin wound healing in mice.

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Human adipose-derived mesenchymal stem cells (hASCs) are attractive cell source for skin tissue engineering. The aim of this study was to investigate the effects of low-level light therapy (LLLT) on transplanted cluster hASC in a skin wound animal model. The hASCs were cultured in monolayer or clusters. The LLLT, hASCs, hASC clusters, and hASC clusters transplantation with LLLT (cluster + LLLT) were applied to the wound bed in athymic mice. Wound healing was assessed by gross evaluation and by hematoxylin and eosin staining, and elastin van gieson histochemistry. The survival, differentiation, and secretion of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) of the cluster ASC were evaluated by immunohistochemistry and Western blotting. The cluster + LLLT group enhanced the wound healing, including neovascularization and regeneration of skin appendages, compared with the cluster group. The secretion of growth factors was stimulated in the cluster + LLLT group compared with the ASCs and cluster group. These data suggest that LLLT is an effective biostimulator of cluster hASCs in wound healing that enhances the survival of hASCs and stimulates the secretion of growth factors in the wound bed.

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Laser phototherapy enhances mesenchymal stem cells survival in response to the dental adhesives.

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Background. We investigated the influence of laser phototherapy (LPT) on the survival of human mesenchymal stem cells (MSCs) submitted to substances leached from dental adhesives. Method. MSCs were isolated and characterized. Oral mucosa fibroblasts and osteoblast-like cells were used as comparative controls. Cultured medium conditioned with two adhesive systems was applied to the cultures. Cell monolayers were exposed or not to LPT. Laser irradiations were performed using a red laser (GaAlAs, 780 nm, 0.04 cm(2), 40 mW, 1 W/cm(2), 0.4 J, 10 seconds, 1 point, 10 J/cm(2)). After 24 h, cell viability was assessed by the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide reduction assay. Data were statistically compared by ANOVA followed by Tukey's test ($P < 0.05$). Results. Different cell types showed different viabilities in response to the same materials. Substances leached from adhesives were less cytotoxic to MSCs than to other cell types. Substances leached from Clearfil SE Bond were highly cytotoxic to all cell types tested, except to the MSCs when applied polymerized and in association with LPT. LPT was unable to significantly increase the cell viability of fibroblasts and osteoblast-like cells submitted to the dental adhesives. Conclusion. LPT enhances mesenchymal stem cells survival in response to substances leached from dental adhesives.

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Visible red and infrared light alters gene expression in human marrow stromal fibroblast cells.

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Primary cultures of isolated human bone marrow stem cells (hBMSC) were exposed to visible red (VR, 633 nm) and infrared (IR, 830 nm) radiation wavelengths from a light emitting diode (LED) over a range of energy densities (0.5, 1.0, 1.5, and 2.0 Joules/cm2) Cultured cells were assayed for cell proliferation, osteogenic potential, adipogenesis, mRNA and protein content. mRNA was analyzed by microarray and compared among different wavelengths and energy densities. Mesenchymal and epithelial cell responses were compared to determine whether responses were cell type specific. Protein array analysis was used to further analyze key pathways identified by microarrays.

Different wavelengths and energy densities produced unique sets of genes identified by microarray analysis. Pathway analysis pointed to TGF-beta 1 in the visible red and Akt 1 in the infrared wavelengths as key pathways to study. TGF-beta protein arrays suggested switching from canonical to non-canonical TGF-beta pathways with increases to longer IR wavelengths. Microarrays suggest RANKL and MMP 10 followed IR energy density dose-response curves. Epithelial and mesenchymal cells respond differently to stimulation by light suggesting cell type-specific response is possible.

These studies demonstrate differential gene expression with different wavelengths, energy densities and cell types. These differences in gene expression have the potential to be exploited for therapeutic purposes and can help explain contradictory results in the literature when wavelengths, energy densities and cell types differ.

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Effect of low-level laser therapy on mesenchymal stem cell proliferation: a systematic review.

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Low-level laser therapy (LLLT) has been used in several in vitro experiments in order to stimulate cell proliferation. Cells such as fibroblasts, keratinocytes, lymphocytes, and osteoblasts have shown increased proliferation when submitted to laser irradiation, although little is known about the effects of LLLT on stem cells. This study aims to assess, through a systematic literature review, the effects of LLLT on the in vitro proliferation of mesenchymal stem cells. Using six different terms, we conducted an electronic search in PubMed/Medline database for articles published in the last twelve years. From 463 references obtained, only 19 papers met the search criteria and were included in this review. The analysis of the papers showed a concentration of experiments using LLLT on stem cells derived from bone marrow, dental pulp, periodontal ligament, and adipose tissue. Several protocols were used to irradiate the cells, with variations on wavelength, power density, radiation time, and state of light polarization. Most studies demonstrated an increase in the proliferation rate of the irradiated cells. It can be concluded that the laser therapy positively influences the in vitro proliferation of stem cells studied, being necessary to carry out further experiments on other cell types and to uniform the methodological designs.

Lasers Med Sci 2015 Mar 13

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[The influence of pulsed low-intensity laser radiation of the red (635 nm) and infrared (904 nm) spectra on the human mesenchymal stem cells in vitro].

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INTRODUCTION: Mesenchymal stem cells (MSC) have for a long time been an object of investigation with a view to elucidating the prospects for their application in clinical medicine and cosmetology. One of the approaches to the non-specific regulation of the activity of these cells at the stage of preliminary in vitro combination is the treatment with low-intensity laser radiation (LILR). The objective of the present study was to evaluate the possibility of using pulsed LILR of the infrared and red spectra for this purpose. MATERIAL AND METHODS: We used the 4th passage adhesive MSC cultures based at the umbilical tissue of a donor who gave the informed consent to participate in the study. The source of illumination was a Lazmik-VLOK laser therapeutic apparatus (RU No RZN 2014/1410 dated 06.02.2014) with the matrix laser infrared radiation heads (wavelength 904 nm, light pulse length 108 ns, frequency 1500 Hz). The apparatus was operated either in the multi-frequency Lazmik regime [Moskvin S.V., 2014] with mean power density 0.05 and 0.14 mW/cm2 and the red spectrum (wavelength 635 nm, light pulse length 144 ns, frequency 1500 Hz) or in the multi-frequency Lazmik regime [Moskvin S.V., 2014] with mean power density 0.03 and 0.12. The exposition was 5 min in both regimes. CONCLUSION: The study has demonstrated that neither the morphological structure nor the viability of mesenchymal stem cells changed under the influence of energy and time parameters used in experiments. The number of cells was shown to slightly increase in comparison with control. The most pronounced effect was documented after illumination with pulse infrared (904 nm) LILR in the multi-frequency Lazmik regime. The maximum effect was observed during a period between days 1 and 3 of cultivation.

Vopr Kurortol Fizioter Lech Fiz Kult 2014 Nov-Dec (6) 40-7

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Photomodulation of proliferation and differentiation of stem cells by the visible and infrared light.

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OBJECTIVE: The aim of this article is to review experimental studies of visible and infrared light irradiation of human and animal stem cells (SCs) in vitro and in vivo to assess photobiomodulation effects on their proliferation and differentiation. BACKGROUND DATA: The clinical application of light irradiation remains controversial, primarily because of the complexity of the rational choice of irradiation parameters. In laboratories, the theoretical justification underlying the choice of irradiation parameters also remains a challenge. METHODS: A systematic review was completed of original research articles that investigated the effects of light irradiation on human and animal SCs in vitro and in vivo (to June 2014). Relevant articles were sourced from PubMed and MEDLINE((R)). The search terms were laser (light) therapy (irradiation), stem cells, and phototherapy, stem cells. RESULTS: The analysis revealed the importance of cell type when choosing the cell irradiation parameters. The influence of wavelength on the SC proliferation rate seemed to be nonsignificant. The high values of increased proliferation or differentiation were obtained using high power density, low energy density, and short exposure time. SC exposure to light without inducers did not lead to their differentiation. The maximum differentiation was achieved using irradiation parameters different from the ones needed to achieve the maximum proliferation of the same cells. CONCLUSIONS: Increased power density and reduced energy density were needed to increase the SC response. Based on the analysis, we have presented a graph of the cell response to generalized photostimulus, and introduced the concepts of "photostress" and "photoshock" to describe the stages of this response.

Photomed Laser Surg 2015 Mar 33(3) 164-74

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Drug discovery for alopecia: gone today, hair tomorrow.

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In this article, the authors review the biology of hair, hair follicle (HF) cycling, stem cells and signaling pathways. AGA, due to dihydrotesterone, is treated by 5-α reductase inhibitors, androgen receptor blockers and ATP-sensitive potassium channel-openers. AA, which involves attack by CD8(+)NK group 2D-positive (NKG2D(+)) T cells, is treated with immunosuppressives, biologics and JAK inhibitors. Meanwhile, CIA is treated by apoptosis inhibitors, cytokines and topical immunotherapy.

The desire to treat alopecia with an easy topical preparation is expected to grow with time, particularly with an increasing aging population. The discovery of epidermal stem cells in the HF has given new life to the search for a cure for baldness. Drug discovery efforts are being increasingly centered on these stem cells, boosting the hair cycle and reversing miniaturization of HF. Better understanding of the molecular mechanisms underlying the immune attack in AA will yield new drugs. New discoveries in HF neogenesis and low-level light therapy will undoubtedly have a role to play.

Expert Opin Drug Discov 2015 Mar 10(3) 269-92

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Near infrared laser stimulation of human neural stem cells into neurons on graphene nanomesh semiconductors.

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Reduced graphene oxide nanomeshes (rGONMs), as p-type semiconductors with band-gap energy of ~ 1 eV, were developed and applied in near infrared (NIR) laser stimulation of human neural stem cells (hNSCs) into neurons. The biocompatibility of the rGONMs in growth of hNSCs was found similar to that of the graphene oxide (GO) sheets. Proliferation of the hNSCs on the GONMs was assigned to the excess oxygen functional groups formed on edge defects of the GONMs, resulting in superhydrophilicity of the surface. Under NIR laser stimulation, the graphene layers (especially the rGONMs) exhibited significant cell differentiations, including more elongations of the cells and higher differentiation of neurons than glia. The higher hNSC differentiation on the rGONM than the reduced GO (rGO) was assigned to the stimulation effects of the low-energy photoexcited electrons injected from the rGONM semiconductors into the cells, while the high-energy photoelectrons of the rGO (as a zero band-gap semiconductor) could suppress the cell proliferation and/or even cause cell damages. Using conventional heating of the culture media up to ~ 43 °C (the temperature typically reached under the laser irradiation), no significant differentiation was observed in dark. This further confirmed the role of photoelectrons in the hNSC differentiation.

Colloids Surf B Biointerfaces 2015 Feb 1 126 313-21

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Vascular regeneration effect of adipose-derived stem cells with light-emitting diode phototherapy in ischemic tissue.

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The objective of this study was to investigate the effects on the vascular regeneration of adipose-derived stem cells (ASCs) by using red light-emitting diode (LED) irradiation in ischemic hind limbs. Low-level light therapy (LLLT) has been shown to enhance proliferation and cytokine secretion of a number of cells. ASCs are an attractive cell source for vascular tissue engineering. This approach is hindered because transplanted ASCs decline rapidly in the recipient tissue. Ischemic hind limbs were treated with LLLT from an LED array (660 nm) at an irradiance of 50 mW/cm2 and a radiant exposure of 30 J/cm2. LLLT, ASC transplantation, and ASC transplantation with LLLT (ASC + LLLT) were applied to ischemic limbs, and cell survival and differentiation, and secretion of vascular endothelial growth factor and basic fibroblast growth factor of the ASCs were evaluated by immunostaining and Western blot analyses. Vascular regeneration was assessed by immunostaining and hematoxylin and eosin staining. In the ASC + LLLT group, the survival of ASCs was increased due to the decreased apoptosis of ASCs. The secretion of growth factors was stimulated in this group compared with ASCs alone. The ASC + LLLT group displayed improved treatment efficacy including neovascularization and tissue regeneration compared with ASCs alone. In particular, quantitative analysis of laser Doppler blood perfusion image ratio showed that blood perfusion was enhanced significantly ($p < 0.05$) by ASC + LLLT treatment. These data suggest that LLLT is an effective biostimulator of ASCs in vascular regeneration, which enhances the survival of ASCs and stimulates the secretion of growth factors in ischemic limbs.

Lasers Med Sci 2015 Jan 8

https://pubmed.ncbi.nlm.nih.gov/25567209

Autologous bone-marrow stem cells stimulation reverses post-ischemic-reperfusion kidney injury in rats.

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BACKGROUND/AIMS: Low-level laser therapy (LLLT) has been found to modulate biological activity. The aim of the present study was to investigate the possible beneficial effects of LLLT application to stem cells in the bone marrow (BM), on the kidneys of rats that had undergone acute ischemia-reperfusion injury (IRI). METHODS: Injury to the kidneys was induced by the excision of the left kidney and 60 min of IRI to the right kidney in each rat. Rats were then divided randomly into 2 groups: non-laser-treated and laser-treated. LLLT was applied to the BM 10 min and 24 h post-IRI and rats were sacrificed 4 days post-IRI. Blood was collected before the sacrifice and the kidney processed for histology. RESULTS: Histological evaluation of kidney sections revealed the restored structural integrity of the renal tubules, and a significant reduction of 66% of pathological score in the laser-treated rats as compared to the non-laser-treated ones. C-kit positive cell density in kidneys post-IRI and laser-treatment was ($p = 0.05$) 2.4-fold higher compared to that of the non-laser treated group. Creatinine, blood urea nitrogen, and cystatin-C levels were significantly 55, 48, and 25% lower respectively in the laser-treated rats as compared to non-treated ones. CONCLUSION: LLLT application to the BM causes induction of stem cells, which subsequently migrate and home in on the injured kidney. Consequently, a significant reduction in pathological features and improved kidney function post-IRI are evident. The results demonstrate a novel approach in cell-based therapy for acute ischemic injured kidneys. (c) 2014 S. Karger AG, Basel.

Am J Nephrol 2014 40(5) 425-33

https://pubmed.ncbi.nlm.nih.gov/25413586

Scientists use laser and stem cells to repair teeth. Groundbreaking advances in dental treatment could regenerate teeth rather than replace them.

not listed,

Duke Med Health News 2014 Sep 20(9) 7

https://pubmed.ncbi.nlm.nih.gov/25362737

660 nm red light-enhanced bone marrow mesenchymal stem cell transplantation for hypoxic-ischemic brain damage treatment.

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Bone marrow mesenchymal stem cell transplantation is an effective treatment for neonatal hypoxic-ischemic brain damage. However, the in vivo transplantation effects are poor and their survival, colonization and differentiation efficiencies are relatively low. Red or near-infrared light from 600-1,000 nm promotes cellular migration and prevents apoptosis. Thus, we hypothesized that the combination of red light with bone marrow mesenchymal stem cell transplantation would be effective for the treatment of hypoxic-ischemic brain damage. In this study, the migration and colonization of cultured bone marrow mesenchymal stem cells on primary neurons after oxygen-glucose deprivation were detected using Transwell assay. The results showed that, after a 40-hour irradiation under red light-emitting diodes at 660 nm and 60 mW/cm(2), an increasing number of green fluorescence-labeled bone marrow mesenchymal stem cells migrated towards hypoxic-ischemic damaged primary neurons. Meanwhile, neonatal rats with hypoxic-ischemic brain damage were given an intraperitoneal injection of 1 x 10(6) bone marrow mesenchymal stem cells, followed by irradiation under red light-emitting diodes at 660 nm and 60 mW/cm(2) for 7 successive days. Shuttle box test results showed that, after phototherapy and bone marrow mesenchymal stem cell transplantation, the active avoidance response rate of hypoxic-ischemic brain damage rats was significantly increased, which was higher than that after bone marrow mesenchymal stem cell transplantation alone. Experimental findings indicate that 660 nm red light emitting diode irradiation promotes the migration of bone marrow mesenchymal stem cells, thereby enhancing the contribution of cell transplantation in the treatment of hypoxic-ischemic brain damage.

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Effects of low level laser therapy on attachment, proliferation, and gene expression of VEGF and VEGF receptor 2 of adipocyte-derived mesenchymal stem cells cultivated under nutritional deficiency.

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Low-level laser therapy (LLLT) has been shown to increase the proliferation of several cell types. We evaluated the effects of LLLT on adhesion, proliferation, and gene expression of vascular endothelial growth factor (VEGF) and type 2 receptor of VEGF (VEGFR2) at mesenchymal stem cells (MSCs) from human (hMSCs) and rat (rMSCs) adipose tissues on nutritional deficiencies. A dose-response curve was performed with cells treated with laser Ga-Al-As (660 nm, 30 mW) at energy of 0.7 to 9 J. Cell adhesion and proliferation were quantified 20, 40, and 60 min after LLLT and 24, 72, and 120 h after cultivation. Gene expression was verified by RT-PCR after 2 h of LLLT. A minor nutritional support caused a significant decrease in proliferation and adhesion of hMSCs and rMSCs. However, at the lowest LLLT dose (0.7 J), we observed a higher proliferation in hMSCs at standard condition shortly after irradiation (24 h). Adhesion was higher in hMSCs cultivated in controlled conditions at higher LLLT doses (3 and 9 J), and rMSCs show a reduction in the adhesion on 1.5 to 9 J. On nutritional deprivation, a 9 J dose was shown to reduce proliferation with 24 h and adhesion to all culture times in rMSCs. VEGF and VEGFR2 were increased after LLLT in both cell types. However, hMSCs under nutritional deprivation showed higher expression of VEGF and its receptor after irradiation with other laser doses. In conclusion, LLLT on human and rat MSCs might upregulate VEGF messenger RNA (mRNA) expression and modulate cell adhesion and proliferation distinctively.

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Enhanced angiogenic effect of adipose-derived stromal cell spheroid with low-level light therapy in hind limb ischemia mice.

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The aim of this study was to investigate the effects of low-level laser therapy (LLLT) on transplanted human adipose-derived mesenchymal stem cells (hASCs) spheroid in a hind limb ischemia animal model. LLLT, hASCs spheroid and hASCs spheroid transplantation with LLLT (spheroid + LLLT) were applied to the ischemic hind limbs in athymic mice. The survival, differentiation and secretion of vascular endothelial growth factor (VEGF), basic fibroblast growth factor (FGF), and hepatocyte growth factor (HGF) of the spheroid ASCs were evaluated by immunohistochemistry and western blots. Spheroid + LLLT group had enhanced the tissue regeneration, including angiogenesis, compared with the ASC group. The spheroid ASCs contributed to tissue regeneration via differentiation and secretion of growth factors. In the spheroid + LLLT group, the survival of spheroid hASCs increased with a concomitant decrease in apoptosis of spheroid hASCs in the ischemic hind limb. The secretion of growth factors was stimulated in the spheroid + LLLT group compared with the ASCs and spheroid group. These data suggested that LLLT is an effective biostimulator of spheroid hASCs in tissue regeneration that enhanced the survival of ASCs and stimulated the secretion of growth factors in the ischemic hind limb.

Biomaterials 2014 Nov 35(34) 9280-9

https://pubmed.ncbi.nlm.nih.gov/25132605

Light coaxes stem cells to repair teeth.

not listed,

Dent Today 2014 Jul 33(7) 40, 43

https://pubmed.ncbi.nlm.nih.gov/25118519

Phototherapy up-regulates dentin matrix proteins expression and synthesis by stem cells from human-exfoliated deciduous teeth.

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OBJECTIVES: The aim of this study was to evaluate the effects of infrared LED (850nm) irradiation on dentin matrix proteins expression and synthesis by cultured stem cells from human exfoliated deciduous teeth (SHED). METHODS: Near-exfoliation primary teeth were extracted (n=3), and SHED cultures were characterized by immunofluorescence using STRO-1, CD44, CD146, Nanog and OCT3/4 antibodies, before experimental protocol. The SHEDs were seeded (3x104 cells/cm2) with DMEM containing 10% FBS. After 24-h incubation, the culture medium was replaced by osteogenic differentiation medium, and the cells were irradiated with LED light at energy densities (EDs) of 0 (control), 2, or 4J/cm2 (n=8). The irradiated SHEDs were then evaluated for alkaline phosphatase (ALP) activity, total protein (TP) production, and collagen synthesis (SIRCOL Assay), as well as ALP, collagen type I (Col I), dentin sialophosphoprotein (DSPP), and dentin matrix acidic phosphoprotein (DMP-1) gene expression (qPCR). Data were analyzed by Kruskal-Wallis and Mann-Whitney tests (alpha=0.05). RESULTS: Increased ALP activity and collagen synthesis, as well as gene expression of DSPP and ALP, were observed for both EDs compared with non-irradiated cells. The ED of 4J/cm2 also increased gene expression of COL I and DMP-1. CONCLUSIONS: In conclusion, infrared LED irradiation was capable of biostimulating SHEDs by increasing the expression and synthesis of proteins related with mineralized tissue formation, with overall better results for the energy dose of 4J/cm2. CLINICAL SIGNIFICANCE: Phototherapy is an additional approach for the clinical application of LED in Restorative Dentistry. Infrared LED irradiation of the cavity's floor could biostimulate subjacent pulp cells, improving local tissue healing.

J Dent 2014 Jul 24

https://pubmed.ncbi.nlm.nih.gov/25064041

Low-Level Laser Therapy Ameliorates Disease Progression in a Mouse Model of Alzheimer's Disease.

Farfara D, Tuby H, Trudler D, Doron-Mandel E, Maltz L, Vassar RJ, Frenkel D, Oron U

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Low-level laser therapy (LLLT) has been used to treat inflammation, tissue healing, and repair processes. We recently reported that LLLT to the bone marrow (BM) led to proliferation of mesenchymal stem cells (MSCs) and their homing in the ischemic heart suggesting its role in regenerative medicine. The aim of the present study was to investigate the ability of LLLT to stimulate MSCs of autologous BM in order to affect neurological behavior and beta-amyloid burden in progressive stages of Alzheimer's disease (AD) mouse model. MSCs from wild-type mice stimulated with LLLT showed to increase their ability to maturate towards a monocyte lineage and to increase phagocytosis activity towards soluble amyloid beta (Abeta). Furthermore, weekly LLLT to BM of AD mice for 2 months, starting at 4 months of age (progressive stage of AD), improved cognitive capacity and spatial learning, as compared to sham-treated AD mice. Histology revealed a significant reduction in Abeta brain burden. Our results suggest the use of LLLT as a therapeutic application in progressive stages of AD and imply its role in mediating MSC therapy in brain amyloidogenic diseases.

J Mol Neurosci 2014 Jul 4

https://pubmed.ncbi.nlm.nih.gov/24994540

Photoactivation of Endogenous Latent Transforming Growth Factor-beta1 Directs Dental Stem Cell Differentiation for Regeneration.

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Rapid advancements in the field of stem cell biology have led to many current efforts to exploit stem cells as therapeutic agents in regenerative medicine. However, current ex vivo cell manipulations common to most regenerative approaches create a variety of technical and regulatory hurdles to their clinical translation, and even simpler approaches that use exogenous factors to differentiate tissue-resident stem cells carry significant off-target side effects. We show that non-ionizing, low-power laser (LPL) treatment can instead be used as a minimally invasive tool to activate an endogenous latent growth factor complex, transforming growth factor-β1 (TGF-β1), that subsequently differentiates host stem cells to promote tissue regeneration. LPL treatment induced reactive oxygen species (ROS) in a dose-dependent manner, which, in turn, activated latent TGF-β1 (LTGF-β1) via a specific methionine residue (at position 253 on LAP). Laser-activated TGF-β1 was capable of differentiating human dental stem cells in vitro. Further, an in vivo pulp capping model in rat teeth demonstrated significant increase in dentin regeneration after LPL treatment. These in vivo effects were abrogated in TGF-β receptor II (TGF-βRII) conditional knockout (DSPP(Cre)TGF-βRII(fl/fl)) mice or when wild-type mice were given a TGF-βRI inhibitor. These findings indicate a pivotal role for TGF-β in mediating LPL-induced dental tissue regeneration. More broadly, this work outlines a mechanistic basis for harnessing resident stem cells with a light-activated endogenous cue for clinical regenerative applications.

Sci Transl Med 2014 May 28 6(238) 238ra69

Low-level laser irradiation induces in vitro proliferation of mesenchymal stem cells.

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Objective : To evaluate the effect of low-level laser irradiation on the proliferation and possible nuclear morphological changes of mouse mesenchymal stem cells. Methods : Mesenchymal stem cells derived from bone marrow and adipose tissue were submitted to two applications (T0 and T48 hours) of low-level laser irradiation (660nm; doses of 0.5 and 1.0J/cm2). The trypan blue assay was used to evaluate cell viability, and growth curves were used to analyze proliferation at zero, 24, 48, and 72 hours. Nuclear alterations were evaluated by staining with DAPI (4'-6-diamidino-2-phenylindole) at 72 hours. Results : Bone marrow-derived mesenchymal stem cells responded to laser therapy in a dose-dependent manner. Higher cell growth was observed when the cells were irradiated with a dose of 1.0J/cm2, especially after 24 hours ($p<0.01$). Adipose-derived mesenchymal stem cells responded better to a dose of 1.0J/cm2, but higher cell proliferation was observed after 48 hours ($p<0.05$) and 72 hours ($p<0.01$). Neither nuclear alterations nor a significant change in cell viability was detected in the studied groups. Conclusion : Low-level laser irradiation stimulated the proliferation of mouse mesenchymal stem cells without causing nuclear alterations. The biostimulation of mesenchymal stem cells using laser therapy might be an important tool for regenerative therapy and tissue engineering.

Einstein (Sao Paulo) 2014 Mar 12(1) 75-81

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Helium-Neon Laser Irradiation Promotes the Proliferation and Migration of Human Epidermal Stem Cells In Vitro: Proposed Mechanism for Enhanced Wound Re-epithelialization.

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Abstract Objective: The present study was conducted to investigate the effects of helium-neon (He-Ne) laser irradiation on the proliferation, migration, and differentiation of cultured human epidermal stem cells (ESCs). Background data: A He-Ne laser with a wavelength of 632.8 nm is known to have photobiological effects, and is widely used for accelerating wound healing; however, the cellular mechanisms involved have not been completely understood. Methods: The ESCs were prepared from human foreskin, and irradiated by using He-Ne laser at 632.8 nm with 2 J/cm(2). The ESC proliferation, migration, and differentiation were examined by using XTT assay, scratch assay, and flow cytometry technology, respectively. The phosphorylation of extracellular signal-regulated kinases (ERK) was analyzed by using Western blotting. Results: He-Ne laser irradiation markedly promoted cell proliferation and migration accompanied by an increase in the phosphorylation of ERK, but did not significantly influence cell differentiation. Conclusion: Our data indicated that photostimulation with a He-Ne laser resulted in a significant increase in human ESC proliferation and migration in vitro, which might contribute, at least partially, to accelerated wound re-epithelialization by low-level laser therapy.

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https://pubmed.ncbi.nlm.nih.gov/24661127

Effects of low level light irradiation on the migration of mesenchymal stem cells derived from rat bone marrow.

Li WT, Chen CW, Huang PY

Low level light irradiation (LLLI) was found to exert positive effects on various cells in vitro. The aim of this study was to investigate the effect of LLLI on the migration of rat bone marrow mesenchymal stem cells (rbMSCs). Light irradiation was applied at the energy density of 4 J/cm(2) using red (630 nm) and near infrared (NIR, 850 nm) light emitting diodes (LEDs). Wound healing assay showed both red and NIR light irradiation increased cell mobility. Red and NIR light enhanced transmembrane migration of rbMSCs up to 292.9% and 263.6% accordingly. This agreed with enzymatic activities of MMP-2 and MMP-9 enhanced by irradiation. F-actin accumulation and distribution correlated to increased migration in light-irradiated MSCs. Reactive oxygen species production as well as the expression of pFAK and pNF-small ka, CyrillicB were elevated after red and NIR LLLI. The study demonstrated that red and NIR LLLI increased rbMSCs migration and identified the phosphorylation of FAK and NF-small ka, CyrillicB as critical steps for the elevated cell migration upon LLLI.

Conf Proc IEEE Eng Med Biol Soc 2013 Jul 2013 4121-4

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Low-level laser (light) therapy (LLLT) in skin: stimulating, healing, restoring.

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Low-level laser (light) therapy (LLLT) is a fast-growing technology used to treat a multitude of conditions that require stimulation of healing, relief of pain and inflammation, and restoration of function. Although skin is naturally exposed to light more than any other organ, it still responds well to red and near-infrared wavelengths. The photons are absorbed by mitochondrial chromophores in skin cells. Consequently, electron transport, adenosine triphosphate nitric oxide release, blood flow, reactive oxygen species increase, and diverse signaling pathways are activated. Stem cells can be activated, allowing increased tissue repair and healing. In dermatology, LLLT has beneficial effects on wrinkles, acne scars, hypertrophic scars, and healing of burns. LLLT can reduce UV damage both as a treatment and as a prophylactic measure. In pigmentary disorders such as vitiligo, LLLT can increase pigmentation by stimulating melanocyte proliferation and reduce depigmentation by inhibiting autoimmunity. Inflammatory diseases such as psoriasis and acne can also be managed. The noninvasive nature and almost complete absence of side effects encourage further testing in dermatology.

Semin Cutan Med Surg 2013 Mar 32(1) 41-52

https://pubmed.ncbi.nlm.nih.gov/24049929

Effects of laser therapy on the proliferation of human periodontal ligament stem cells.

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Low-level laser irradiation (LLLI) stimulates the proliferation of a variety of cell types. However, very little is known about the effect of laser therapy on dental stem cells. The aim of the present study was to evaluate the effect of LLLI (660 nm, 30 mW) on the proliferation rate of human periodontal ligament stem cells (hPDLSC), obtained from two healthy permanent third molars extracted due to surgical indication. Culture cells were either irradiated or not (control) with an InGaAlP diode laser at 0 and 48 h, using two different energy densities (0.5 J/cm(2), 16 s and 1.0 J/cm(2), 33 s). Cell proliferation was evaluated by the Trypan blue exclusion method and by measuring mitochondrial activity using the MTT-based cytotoxicity assay at intervals of 0, 24, 48, and 72 h after the first laser application. An energy density of 1.0 J/cm(2) improved the cell proliferation in comparison to the other groups (control and laser 0.5 J/cm(2)) at 48 and 72 h. The group irradiated with 1.0 J/cm(2) presented significantly higher MTT activity at 48 and 72 h when compared to the energy density of 0.5 J/cm(2). It can be concluded that LLLI using infrared light and an energy density of 1.0 J/cm(2) has a positive stimulatory effect on the proliferation of hPDLSC.

Lasers Med Sci 2013 Sep 7

https://pubmed.ncbi.nlm.nih.gov/24013624

Low-level laser (light) therapy (LLLT) for treatment of hair loss.

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Searches of PubMed and Google Scholar were carried out using keywords alopecia, hair loss, LLLT, photobiomodulation.

Studies have shown that LLLT stimulated hair growth in mice subjected to chemotherapy-induced alopecia and also in alopecia areata. Controlled clinical trials demonstrated that LLLT stimulated hair growth in both men and women. Among various mechanisms, the main mechanism is hypothesized to be stimulation of epidermal stem cells in the hair follicle bulge and shifting the follicles into anagen phase.

LLLT for hair growth in both men and women appears to be both safe and effective. The optimum wavelength, coherence and dosimetric parameters remain to be determined.

Lasers Surg Med 2013 Aug 23

https://pubmed.ncbi.nlm.nih.gov/23970445

Periodontal effects with self ligating appliances and laser biostimulation.

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BACKGROUND: Recently, various biostimulation's effects of low energy laser irradiation have been reported. The present study was designed to examine the effects of low-energy laser irradiation on alveolar bone remodelling during orthodontic tooth movement and finally on formation of new keratinized gingiva. MATERIALS AND METHODS: 22 patients and 27 teeth in vestibular mucosal without keratinized gingiva were selected. Every patient was treated with self ligating appliances. In every orthodontic session the patient was treated with Diode laser biostimulation. At the moment of debonding, 27 teeth involved in the research were evaluated in terms of quality and quantity of attached gingiva. BOP and CAL loss were investigated. RESULTS: EVERY TOOTH CONSIDERED AT THE END OF ORTHODONTIC TREATMENT SHOWED AN ATTACHED GINGIVA AROUND THE CROWN: The average of keratinized gingiva at the end of the study was 3.10 mm and the mean increasing at each month was 0,49 mm. CONCLUSIONS: The combination between self ligating appliances and laser's biostimulation could improve the differentiation of periodontal ligaments stem cells in fibroblasts, able to promote attached gingiva around the crown of the teeth erupted in oral vestibular mucosa.

Dent Res J (Isfahan) 2012 Dec 9(Suppl 2) S186-91

https://pubmed.ncbi.nlm.nih.gov/23814581

Long-Term Safety of Low-Level Laser Therapy at Different Power Densities and Single or Multiple Applications to the Bone Marrow in Mice.

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Abstract Objective: The purpose of this study was to determine the long-term safety effect of low-level laser therapy (LLLT) to the bone marrow (BM) in mice. Background data: LLLT has been shown to have a photobiostimulatory effect on various cellular processes and on stem cells. It was recently shown that applying LLLT to BM in rats post-myocardial infarction caused a marked reduction of scar tissue formation in the heart. Methods: Eighty-three mice were divided into five groups: control sham-treated and laser-treated at measured density of either 4, 10, 18, or 40 mW/cm2 at the BM level. The laser was applied to the exposed flat medial part of the tibia 8 mm from the knee joint for 100 sec. Mice were monitored for 8 months and then killed, and histopathology was performed on various organs. Results: No histological differences were observed in the liver, kidneys, brain or BM of the laser-treated mice as compared with the sham-treated, control mice. Moreover, no neoplasmic response in the tissues was observed in the laser-treated groups as compared with the control, sham-treated mice. There were no significant histopathological differences among the same organs under different laser treatment regimes in response to the BM-derived mesenchymal stem cell proliferation following LLLT to the BM. Conclusions: LLLT applied multiple times either at the optimal dose (which induces photobiostimulation of stem cells in the BM), or at a higher dose (such as five times the optimal dose), does not cause histopathological changes or neoplasmic response in various organs in mice, as examined over a period of 8 months.

Photomed Laser Surg 2013 May 15

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Low-level laser (light) therapy (LLLT) on muscle tissue: performance, fatigue and repair benefited by the power of light.

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The use of low level laser (light) therapy (LLLT) has recently expanded to cover areas of medicine that were not previously thought of as the usual applications such as wound healing and inflammatory orthopedic conditions. One of these novel application areas is LLLT for muscle fatigue and muscle injury. Since it is becoming agreed that mitochondria are the principal photoacceptors present inside cells, and it is known that muscle cells are exceptionally rich in mitochondria, this suggests that LLLT should be highly beneficial in muscle injuries. The ability of LLLT to stimulate stem cells and progenitor cells means that muscle satellite cells may respond well to LLLT and help muscle repair. Furthermore the ability of LLLT to reduce inflammation and lessen oxidative stress is also beneficial in cases of muscle fatigue and injury. This review covers the literature relating to LLLT and muscles in both preclinical animal experiments and human clinical studies. Athletes, people with injured muscles, and patients with Duchenne muscular dystrophy may all benefit.

Photonics Lasers Med 2012 Nov 1 1(4) 267-286

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Enhancement of bone consolidation in mandibular distraction osteogenesis: A contemporary review of experimental studies involving adjuvant therapies.

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BACKGROUND: One of the major disadvantages of mandibular distraction osteogenesis (MDO) is the prolonged time required for consolidation of the regenerate bone. The objective of the present study is to perform a contemporary review of various adjuvant therapies to enhance bone consolidation in MDO. METHODS: A PubMed search for articles related to MDO, along with the references of those articles, was performed. Inclusion and exclusion criteria were applied to all experimental studies assessing adjuvant therapies to enhance bone consolidation. RESULTS: A total of 1414 titles and abstracts were initially reviewed; 61 studies were included for full review. Many studies involved growth factors, hormones, pharmacological agents, gene therapy, and stem cells. Other adjuvant therapies included mechanical stimulation, laser therapy, and hyperbaric oxygen. Majority of the studies demonstrated positive bone healing effects and thus adjuvant therapies remain a viable strategy to enhance and hasten the consolidation period. CONCLUSION: Although most studies have demonstrated promising results, many questions still remain, such as optimal amount, timing, and delivery methods required to stimulate the most favorable bone regeneration. As well, further studies comparing various adjuvant therapies and documentation of long-term adverse effects are required prior to clinical application.

J Plast Reconstr Aesthet Surg 2013 Apr 17

https://pubmed.ncbi.nlm.nih.gov/23602673

Low-level laser therapy promotes the osteogenic potential of adipose-derived mesenchymal stem cells seeded on an acellular dermal matrix.

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This study investigates the feasibility of using an adipose-derived mesenchymal stem cell (ASC)-seeded acellular dermal matrix (ADM) along with low-level laser therapy (LLLT) to repair bone defect in athymic nude mice. Critical-sized calvarial defects were treated either with ADM, ADM/LLLT, ADM/ASCs, or ADM/ASCs/LLLT. In micro-computed tomography scans, the ADM/ASCs and the ADM/ASCs/LLLT groups showed remarkable bone formation after 14 days. Additionally, bone regeneration in the ADM/ASCs/LLLT group was obvious at 28 days, but in the ADM/ASCs group at 56 days. Bone mineral density and bone tissue volume in the ADM/ASCs/LLLT group significantly increased after 7 days, but in the ADM/ASCs group after 14 days. Histological analysis revealed that the defects were repaired in the ADM/ASCs and the ADM/ASCs/LLLT group, while the defects in the ADM and the ADM/LLLT groups exhibited few bone islands at 28 and 56 days. The successful seeding of ASCs onto ADM was confirmed, and LLLT enhanced the proliferation and the survival of ASCs at 14 days. Our results indicate that ASC-seeded grafts promote bone regeneration, and the application of LLLT on ASC-seeded ADM results in rapid bone formation. The implantation of an ASC-seeded ADM combined with LLLT may be used effectively for bone regeneration. (c) 2013 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater, 2013.

J Biomed Mater Res B Appl Biomater 2013 Mar 26

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Synergistic effects of low-level laser and mesenchymal stem cells on functional recovery in rats with crushed sciatic nerves.

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Transplantation of mesenchymal stem cells (MSCs) has been proposed to exert beneficial effects on peripheral nerve regeneration after a peripheral nerve injury, but the functional recovery in the denervated limb is still limited. In this study, we used low-level laser therapy (LLLT) as an adjunct therapy for MSC transplantation on the functional recovery of crushed sciatic nerve in rats. Peripheral nerve injury was induced in 48 Sprague-Dawley rats by crushing the unilateral sciatic nerve, using a vessel clamp. The animals with crushed injury were randomly divided into four groups: control group, with no treatment; MSC group, treated with MSC alone; LLLT group, treated with LLLT alone; and MSCLLLT group, treated with a combination of MSC and LLLT. The sciatic function index (SFI), vertical activity of locomotion (VA) and ankle angle (AA) of rats were examined for functional assessments after treatment. Electrophysiological, morphological and S100 immunohistochemical studies were also conducted. The MSCLLLT group showed a greater recovery in SFI, VA and AA, with significant difference from MSC, LLLT and control groups ($p < 0.05$). Moreover, markedly enhanced electrophysiological function and expression of S100 immunoreactivity, as well as fewer inflammatory cells and less vacuole formation were also demonstrated after nerve crush injury in the MSCLLLT group when compared with the groups receiving a single treatment ($p < 0.05$). MSC transplantation combined with LLLT could achieve better results in functional recovery than a conventional treatment of MSC or LLLT alone. LLLT has a synergistic effect in providing greater functional recovery with MSC transplantation after nerve crush injury. Copyright (c) 2013 John Wiley & Sons, Ltd.

J Tissue Eng Regen Med 2013 Mar 7

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Low-Power Laser Irradiation Suppresses Inflammatory Response of Human Adipose-Derived Stem Cells by Modulating Intracellular Cyclic AMP Level and NF-kappaB Activity.

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Mesenchymal stem cell (MSC)-based tissue regeneration is a promising therapeutic strategy for treating damaged tissues. However, the inflammatory microenvironment that exists at a local injury site might restrict reconstruction. Low-power laser irradiation (LPLI) has been widely applied to retard the inflammatory reaction. The purpose of this study was to investigate the anti-inflammatory effect of LPLI on human adipose-derived stem cells (hADSCs) in an inflammatory environment. We showed that the hADSCs expressed Toll-like Receptors (TLR) 1, TLR2, TLR3, TLR4, and TLR6 and that lipopolysaccharide (LPS) significantly induced the production of pro-inflammatory cytokines (Cyclooxygenase-2 (Cox-2), Interleukin-1beta (IL-1beta), Interleukin-6 (IL-6), and Interleukin-8 (IL-8)). LPLI markedly inhibited LPS-induced, pro-inflammatory cytokine expression at an optimal dose of 8 J/cm(2). The inhibitory effect triggered by LPLI might occur through an increase in the intracellular level of cyclic AMP (cAMP), which acts to down-regulate nuclear factor kappa B (NF-kappaB) transcriptional activity. These data collectively provide insight for further investigations of the potential application of anti-inflammatory treatment followed by stem cell therapy.

PLoS One 2013 8(1) e54067

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The influence of low-intensity laser therapy on bone healing.

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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.

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Regenerative medicine, stem cells, and low-level laser therapy: future directives.

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Photomed Laser Surg 2012 Dec 30(12) 681-2

https://pubmed.ncbi.nlm.nih.gov/23140266

Enhanced wound healing effect of canine adipose-derived mesenchymal stem cells with low-level laser therapy in athymic mice.

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BACKGROUND: Adipose-derived mesenchymal stem cells (ASCs) are attractive cell source for skin tissue engineering. However, one obstacle to this approach is that the transplanted ASC population can decline rapidly in the recipient tissue. OBJECTIVE: The aim of this study was to investigate the effects of low-level laser therapy (LLLT) on transplanted canine ASCs in a skin wound animal model. METHODS: LLLT, ASC transplantation (ASCs) and ASC transplantation with LLLT (ASCs+LLLT) were applied to the wound bed in athymic mice. Wound healing was assessed by gross evaluation and by hematoxylin and eosin staining. The survival, differentiation and secretion of vascular endothelial growth factor and basic fibroblast growth factor of the ASCs were evaluated by immunohistochemistry and Western blotting. RESULTS: The ASCs and ASCs+LLLT groups stimulated wound closure and histological skin regeneration. The ASCs+LLLT group enhanced the wound healing, including neovascularization and regeneration of skin appendages, compared with the ASCs group. The ASCs contributed skin regeneration via differentiation and secretion of growth factors. In the ASCs+LLLT group, the survival of ASCs was increased by the decreased apoptosis of ASCs in the wound bed. The secretion of growth factors was stimulated in the ASCs+LLLT group compared with the ASCs group. CONCLUSION: These data suggest that LLLT is an effective biostimulator of ASCs in wound healing that enhances the survival of ASCs and stimulates the secretion of growth factors in the wound bed.

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Visible 532 nm laser irradiation of human adipose tissue-derived stem cells: Effect on proliferation rates, mitochondria membrane potential and autofluorescence.

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BACKGROUND AND OBJECTIVE: The photobiological effect of laser light on cells and tissues originates from light absorption by endogenous chromophores and hence it depends on the wavelength of light source and cell type. Earlier studies regarding the biostimulation effects of green laser light investigated a wide variety of cells but not adipose tissue-derived stem cells (ADSCS). In this study we reported the in vitro effect of 532-nm Nd:YAG laser on proliferation, mitochondrial activity of these mesenchymal stem cells (MSCs) on the autofluorescence emission at wavelengths associated with nicotinamide adenine dinucleotide (NADH) and flavoproteins. MATERIALS AND METHODS: ADSCS were exposed to 532 nm second harmonic generation laser light at moderate power density (0.153 W/cm(2)) for periods of 30, 45, 60, 180, and 300 seconds. Mitochondrial membrane potential was measured using JC1 stain and confocal laser scanning microscopy, cell proliferation rates, and cellular autofluorescence emission at 450 and 540 nm wavelengths were measured using micro plate spectrofluorometer 48 hours after irradiation. RESULTS: Shorter (30-60 seconds) exposure times led to significantly increased proliferation, attributed to increased mitochondrial activity ($P < 0.05$). At longer exposures we observed a significant decrease in proliferation and autofluorescence ($P < 0.05$). Strong correlation was observed between proliferation rates of cells and autofluorescence intensity. CONCLUSION: Our results show that autofluorescence of the respiratory chain components and key autofluorescent metabolites offers a non-invasive method to quantify cellular response to laser irradiation. Lasers Surg. Med. 44: 769-778, 2012. (c) 2012 Wiley Periodicals, Inc.

Lasers Surg Med 2012 Nov 44(9) 769-78

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Low-level visible light (LLVL) irradiation promotes proliferation of mesenchymal stem cells.

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Low-level visible light irradiation was found to stimulate proliferation potential of various types of cells in vitro. Stem cells in general are of significance for implantation in regenerative medicine. The aim of the present study was to investigate the effect of low-level light irradiation on the proliferation of mesenchymal stem cells (MSCs). MSCs were isolated from the bone marrow, and light irradiation was applied at energy densities of 2.4, 4.8, and 7.2 J/cm(2). Illumination of the MSCs resulted in almost twofold increase in cell number as compared to controls. Elevated reactive oxygen species and nitric oxide production was also observed in MSCs cultures following illumination with broadband visible light. The present study clearly demonstrates the ability of broadband visible light illumination to promote proliferation of MSCs in vitro. These results may have an important impact on wound healing.

Lasers Med Sci 2012 Sep 25

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Photobiostimulation and Tissue Engineering process on wound healing treatment by ClAlPc-nanoemulsion from a multiple-wavelength portable light source on a 3D-human stem cell dermal equivalent.

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This research evaluated the effect of multiple-wave lasertherapy on the healing process of surgical wounds based on in vitro models denominated stem-dermal equivalents. These human skin models were obtained from a co-culture of dermal cells and bone marrow mesenchymal stem cells. The experimental tests were carried out using a LED portable to multiple waves (operating at 660 nm and 810 nm) at different doses to induce photobiostimulation (10 to 70 mJ.cm-2). What is more, a photosensitizer drug was employed as a new advanced designed nanomaterial, being a nanoemulsion with biopolymers to obtain an efficient drug delivery system to release lipophilic compounds. The studies were performed considering the light combination application monitoring the kinetic contraction of the dermal equivalent model and the quantification of important macromolecules (as metaloproteases derivatives), related directly with wound healing process. Results showed that an appropriate photomodulation using the combination of both wavelengths (in the red and infrared range) is possible, such that it can contribute to wound healing therapy and/or other pathological skin disease treatment.

Curr Med Chem 2012 Aug 16

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Effects of red light-emitting diode irradiation on dental pulp cells.

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Light irradiation activates a range of cellular processes in a variety of cell types, including stem cells, and can promote tissue repair. This study investigated the effects of light-emitting diode (LED) exposure on dental pulp cells (DPCs). Dose response analysis at 20-second intervals up to 120 seconds demonstrated that a LED array emitting 653-nm red light stimulated significantly increased cell growth at 3 and 7 days post-irradiation with 40 (149 mJ/cm (2)) and 60 (224 mJ/cm(2)) seconds of radiant exposure. Double-dosing cells at days 1 and 4 of a 7-day culture period with 60-second (224 mJ/cm(2)) LED exposure significantly increased cell growth compared with a single dosing regime. BrdU analysis demonstrated significantly increased proliferation rates associated with significantly increased ATP, nitric oxide (NO), and mitochondrial metabolic activity. LED-stimulated NO levels were not reduced by inhibition of NO-synthase activity. Light exposure also rescued the inhibition of mitochondrial dysfunction and increased levels of in vitro mineralization compared with control. Media exchange experiments indicated that autocrine signaling was not likely responsible for red-light-induced DPC activity. In conclusion, data analysis indicated that 653-nm LED irradiation promoted DPC responses relevant to tissue repair, and this is likely mediated by increased mitochondrial activity.

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Laser irradiation did not increase the proliferation or the differentiation of stem cells from normal and inflamed dental pulp.

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OBJECTIVE: Low-level laser therapy (LLLT) has been reported to be responsible for promoting photostimulatory and photobiomodulatory effects in vivo and in vitro, stimulating cell growth, increasing cell metabolism, improving cell regeneration and invoking an anti-inflammatory response. This study was performed in order to investigate whether low-level laser therapy could increase the proliferation and differentiation potentials of hDPSC isolated from healthy dental pulps and from inflamed pulps. DESIGN: Human dental pulp stem cells (hDPSC) were isolated from normal and inflamed dental pulps from different patients. STRO-1-positive cells were isolated and irradiated with a red low-level laser (660nm) in four different energy fluences (0.05, 0.30, 7 and 42J/cm(2)); the authors hypothesized that the first three fluences would promote biostimulatory effects, whereas the highest dose would induce antiproliferative effects. The two lower fluences were produced by irradiating the two higher fluences through a dentine disc, which was used to simulate a clinical condition. The proliferation and the cell odonto-osteogenic differentiation competence were compared. RESULTS: No statistically significant differences were observed between the proliferation rates and the relative productions of mineralized nodules compared to the respective controls, either for hDPSC from normal or inflamed dental pulps. CONCLUSIONS: The irradiation with low-level InGaAlP red low-level laser (660nm) in four different energy fluences (0.05, 0.30, 7 and 42J/cm(2)) potentiated neither proliferation nor odonto-osteogenic differentiation of hDPSC isolated from patients with normal and inflamed pulps.

Arch Oral Biol 2012 Mar 31

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Effects of low-level laser irradiation on proliferation and osteoblastic differentiation of human mesenchymal stem cells seeded on a three-dimensional biomatrix: in vitro pilot study.

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Mesenchymal stem cells (MSCs) from bone marrow are a recent source for tissue engineering. Several studies have shown that low-level laser irradiation has numerous biostimulating effects. The purpose of this trial was to evaluate the effects of Nd:Yag laser irradiation on proliferation and differentiation of MSCs induced into the osteoblastic lineage. MSCs were collected from adult human bone marrow, isolated, and cultured in complete medium (alpha-MEM). Subsequently, they were treated with osteogenic medium, seeded in three-dimensional collagen scaffolds, and incubated. We used six scaffolds, equally divided into three groups: two of these were irradiated with Nd:Yag laser at different power levels (15 Hz, 100 mJ, 1.5 W, and one with a power level of 15 Hz, 150 mJ, 2.25 W), and one was left untreated (control group). Evaluations with specific staining were performed at 7 and 14 days. After 7 days, proliferation was significantly increased in scaffolds treated with laser, compared with the control scaffold. After 14 days, however, laser irradiation did not appear to have any further effect on cell proliferation. As concerns differentiation, an exponential increase was observed after 14 days of laser irradiation, with respect to the control group. However, this was a pilot study with very limited sample size, we conclude, that low-level laser irradiation might lead to a reduction in healing times and potentially reduces risks of failure.

Lasers Med Sci 2012 Mar 25

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miRNA-193 pro-proliferation effects for bone mesenchymal stem cells after low-level laser irradiation treatment through ING5.

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Enhanced proliferation of mesenchymal stem cells (MSCs) can be helpful for the clinical translation of cell therapy. Low-level laser irradiation (LLLI) has been demonstrated to regulate MSC proliferation. MiRNAs are involved in various pathophysiologic processes in stem cells, but the role of miRNAs in LLLI-based promotion of MSC proliferation remains unclear. We found that the proliferation level and cell cycle-associated genes in MSCs were increased after LLLI treatment in a time-dependent manner. Microarray assays revealed subsets of miRNAs to be differentially regulated, and that these dynamic changes were confirmed by qRT-PCR after LLLI. MiR-193 was the most highly upregulated miRNA, and the change in it was related with the proliferation level. Gain-loss function experiments demonstrated miR-193 could regulate the proliferation of MSCs including human's and rat's, but could not affect apoptosis and differentiation level. Blockade of miR-193 repressed the MSC proliferation induced by LLLI. By qRT-PCR we found that miR-193 in particular regulated CDK2 expression. Bioinformatic analyses and luciferase reporter assays revealed that ING5 could be the best target of miR-193 to functionally regulate proliferation and CDK2 activity, and the mRNA and protein level of ING5 was regulated by miR-193. Furthermore, inhibited ING5 by siRNA could up-regulate proliferation of MSCs and the expression of CDK2. Taken together, these results strongly suggest that miR-193 plays a critical part in MSC proliferation in response to LLLI stimulation, which is potentially amenable to therapeutic manipulation for clinical application.

Stem Cells Dev 2012 Mar 2

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Low-Level Laser Irradiation Affects the Release of Basic Fibroblast Growth Factor (bFGF), Insulin-Like Growth Factor-I (IGF-I), and Receptor of IGF-I (IGFBP3) from Osteoblasts.

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Abstract Objective: It was the aim of the present study to evaluate whether the laser irradiation of osteoblasts could enhance the release of growth factors including basic fibroblast growth factor (bFGF), insulin-like growth factor-I (IGF-I), and receptor of IGF-I (IGFBP3). Background data: Low-level laser therapy (LLLT) has been shown to have biostimulatory effects on various cell types by enhancing production of some cytokines and growth factors. Materials and methods: Human mesenchymal stem cells (MSCs) were seeded in osteogenic medium and differentiated into osteoblasts. Three groups were formed: in the first group (single dose group), osteoblasts were irradiated with laser (685 nm, 25 mW, 14.3 mW/cm(2), 140 sec, 2 J/cm(2)) for one time; and in the second group, energy at the same dose was applied for 2 consecutive days (double dose group). The third group was not irradiated with laser and served as the control group. Proliferation, viability, bFGF, IGF-I, and IGFBP3 levels were compared between groups. Results: Both of the irradiated groups revealed higher proliferation, viability, bFGF, IGF-I, and IGFBP3 expressions than did the nonirradiated control group. There was increase in bFGF and IGF-I expressions and decrease in IGFBP3 in the double dose group compared to single dose group. Conclusions: The results of the present study indicate that LLLT increases the proliferation of osteoblast cells and stimulates the release of bFGF, IGF-I, and IGFBP3 from these cells. The biostimulatory effect of LLLT may be related to the enhanced production of the growth factors.

Photomed Laser Surg 2012 Jan 11

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Laser biomodulation of normal and neoplastic cells.

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This study was designed to determine the laser dose for the stimulation, zero-bioactivation, and inhibition of normal and neoplastic cells in vitro. The medical use of laser biomodulation has been occurring for decades in the area of tissue healing and inflammatory conditions. The potential to modulate the regeneration and differentiation of early cellular precursors by laser photons is a valuable endeavor searching for novel and efficient methods. A 35-mW HeNe (632.8-nm) laser and power density of 1.25 mW/cm(2) was used to irradiate tissue culture dishes seeded with 400 cells/dish of normal cells (CHO, CCL-226, 3 T3, and HSF) and neoplastic cells (EMT-6 and RIF-1). All cell lines were cultured using DMEM supplemented with 10% and 5% FBS, 2 mM glutamine and 100 U pen-strep antibiotic. Irradiation times of 16, 32, 48, 64, 80, 96, 112, 128, 144, and 160 s for three consecutive days to deliver cumulative doses of 60, 120, 180, 240, 300, 360, 420, 480, 540, and 600 mJ/cm(2) were done, respectively. Cell cultures were stained and colony-forming efficiency was determined. Data analysis was done using Student's t test, alpha = 0.05. A trend of stimulation, zero-bioactivation, and inhibition in all cell lines was observed except for CCL-226 which gave a pattern of inhibition, zero-bioactivation, and inhibition. The optimum biostimulatory dose was at 180 mJ/cm(2) and bioinhibitory doses were from 420-600 mJ/cm(2) cumulative doses. This study established the dose-dependency of cell growth to laser treatments, that the extent of cellular proliferation is influenced by the type of cells involved, and the risk when laser irradiation is performed on patients with undiagnosed neoplasms and during pregnancy. On the other hand, the ability of laser irradiation to regulate embryonic fibroblasts and human skin fibroblast in vitro suggests possible laser biomodulatory effects on embryonic and adult stem cells directed for tissue regeneration. Studies on the effects of light treatments exploring different laser parameters for the clonal expansion and differentiation of stem cells are recommended.

Lasers Med Sci 2011 Dec 29

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Induction of primitive pigment cell differentiation by visible light (helium-neon laser): a photoacceptor-specific response not replicable by UVB irradiation.

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Solar lights encompass ultraviolet (UV), visible, and infrared spectrum. Most previous studies focused on the harmful UV effects, and the biologic effects of lights at other spectrums remained unclear. Recently, lights at visible region have been used for regenerative purposes. Using the process of vitiligo repigmentation as a research model, we focused on elucidating the pro-differentiation effects induced by visible light. We first showed that helium-neon (He-Ne) laser (632.8 nm) irradiation stimulated differentiation of primitive pigment cells, an effect not replicable by UVB treatment even at high and damaging doses. In addition, significant increases of mitochondrial DNA copy number and the regulatory genes for mitochondrial biogenesis were induced by He-Ne laser irradiation. Mechanistically, we demonstrated that He-Ne laser initiated mitochondrial retrograde signaling via a Ca(2+)-dependent cascade. The impact on cytochrome c oxidase within the mitochondria is responsible for the efficacy of He-Ne laser in promoting melanoblast differentiation. Taken together, we propose that visible lights from the sun provide important environmental cues for the relatively quiescent stem or primitive cells to differentiate. In addition, our results also indicate that visible light may be used for regenerative medical purposes involving stem cells.

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The effect of noncoherent red light irradiation on proliferation and osteogenic differentiation of bone marrow mesenchymal stem cells.

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Mesenchymal stem cells (MSCs) are promising for use in regenerative medicine. Low-level light irradiation (LLLI) has been shown to modulate various processes in different biological systems. The aim of our study was to investigate the effect of red light emitted from a light-emitting diode (LED) on bone marrow MSCs with or without osteogenic supplements. MSCs both with and without osteogenic supplements were divided into four groups, and each group was irradiated at doses of 0, 1, 2 and 4 J/cm(2). Cellular proliferation was evaluated using WST-8 and 5-ethynyl-2'-deoxyuridine (EdU) fluorescence staining. The alkaline phosphatase activity, mineralization, and expression of osteoblast master genes (Col1alpha1, Alpl, Bglap and Runx2) were monitored as indicators of MSC differentiation towards osteoblasts. In groups without osteogenic supplements, red light at all doses significantly stimulated cellular proliferation, whereas the osteogenic phenotype of the MSCs was not enhanced. In groups with osteogenic supplements, red light increased alkaline phosphatase activity and mineralized nodule formation, and stimulated the expression of Bglap and Runx2, but decreased cellular proliferation. In conclusion, nonconherent red light can promote proliferation but cannot induce osteogenic differentiation of MSCs in normal media, while it enhances osteogenic differentiation and decreases proliferation of MSCs in media with osteogenic supplements.

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Effects of low-level laser irradiation on mesenchymal stem cell proliferation: a microarray analysis.

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Increased proliferation after low-level laser irradiation (LLLI) has been well demonstrated in many cell types including mesenchymal stem cells (MSCs), but the exact molecular mechanisms involved remain poorly understood. The aim of this study was to investigate the change in mRNA expression in rat MSCs after LLLI and to reveal the associated molecular mechanisms. MSCs were exposed to a diode laser (635 nm) as the irradiated group. Cells undergoing the same procedure without LLLI served as the control group. Proliferation was evaluated using the MTS assay. Differences in the gene expression profiles between irradiated and control MSCs at 4 days after LLLI were analyzed using a cDNA microarray. Gene ontology and pathway analysis were used to find the key regulating genes followed by real-time PCR to validate seven representative genes from the microarray assays. This procedure identified 119 differentially expressed genes. Real-time PCR confirmed that the expression levels of v-akt murine thymoma viral oncogene homolog 1 (Akt1), the cyclin D1 gene (Ccnd1) and the phosphatidylinositol 3-kinase, catalytic alpha polypeptide gene (Pik3ca) were upregulated after LLLI, whereas those of protein tyrosine phosphatase non-receptor type 6 (Ptpn6) and serine/threonine kinase 17b (Stk17b) were downregulated. cDNA microarray analysis revealed that after LLLI the expression levels of various genes involved in cell proliferation, apoptosis and the cell cycle were affected. Five genes, including Akt1, Ptpn6, Stk17b, Ccnd1 and Pik3ca, were confirmed and the PI3K/Akt/mTOR/eIF4E pathway was identified as possibly playing an important role in mediating the effects of LLLI on the proliferation of MSCs.

Lasers Med Sci 2011 Sep 29

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Osteoblast differentiation of amniotic fluid-derived stem cells irradiated with visible light.

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The effect of visible light irradiation on the expression of pluripotent genes (Oct-4, Sox2, and Nanog) in amniotic fluid-derived stem cells (AFSCs) and on the osteogenic differentiation ability of AFSCs was investigated using light-emitting diodes (LEDs) at 0-2 mW/cm(2) in various wavelengths: [blue (470 nm), green (525 nm), yellow (600 nm), and red (630 nm)]. Pluripotent gene expression in AFSCs was up-regulated by visible light irradiation from a LED for more than 6 h. Green light irradiation of AFSCs up-regulated the expression of pluripotent genes more significantly than irradiation with other light. The osteogenic differentiation of AFSCs was facilitated by green and blue light irradiation. Facilitated differentiation into osteogenic cells by visible light irradiation was not mediated by reactive oxygen species (ROS); alkaline phosphatase activity (a marker of early osteogenic differentiation) and gene expression of osteopontin (a marker of late osteogenic differentiation) did not change significantly between AFSCs in differentiation medium with or without a ROS scavenger (vitamin C). The mitogen-activated protein kinase/extracellular signal-regulated protein kinase pathway, as well as other unknown signaling pathways, may be responsible for the activation of signaling pathways that facilitate the differentiation of AFSCs into osteogenic cells on light irradiation.

Tissue Eng Part A 2011 Nov 17(21-22) 2593-602

https://pubmed.ncbi.nlm.nih.gov/21774692

In Vitro Evaluation of Chloroaluminum Phthalocyanine Nanoemulsion and Low-Level Laser Therapy on Human Skin Dermal Equivalents and Bone Marrow Mesenchymal Stem Cells.

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Nanotechnology and tissue engineering are promising scientific fields in the development of advanced materials useful to human health. This article describes the preparation of a nanocarrier for the controlled release of a photosensitizer compound associated with low-level light therapy for skin wound healing treatment and applicable to other skin diseases. A biological model was used as an in vitro skin equivalent based on a three-dimensional culture of fibroblasts and mesenchymal stem cells and denominated by dermal equivalent (DE). Results show that it is possible to use the photomodulation process to control the wound healing in a scratching process and to induce the biomolecules release, both of which are related with the inflammatory wound healing process. In the studies, the MMP-2 and MMP-9 expression from zymography analyses were evaluated. All results showed a dependence on enzymatic activity relating to lowlevel laser applications which indicates a potential application in wound healing processes based on phototherapy and nanotechnology.

Curr Med Chem 2011 Jul 4

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Induction of autologous mesenchymal stem cells in the bone marrow by low-level laser therapy has profound beneficial effects on the infarcted rat heart.

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BACKGROUND AND OBJECTIVES: The adult mammalian heart is known to have a very limited regenerative capacity following acute ischemia. In this study we investigated the hypothesis that photobiostimulation of autologous bone-marrow-derived mesenchymal stem cells (MSCs) by low-level laser therapy (LLLT) applied to the bone marrow (BM), may migrate to the infarcted area and thus attenuate the scarring processes following myocardial infarction (MI). MATERIALS AND METHODS: Sprague-Dawley rats underwent experimental MI. LLLT (Ga-Al-As diode laser, power density 10 mW/cm(2) , for 100 seconds) was then applied to the BM of the exposed tibia at different time intervals post-MI (20 minutes and 4 hours). Sham-operated infarcted rats served as control. RESULTS: Infarct size and ventricular dilatation were significantly reduced (76% and 75%, respectively) in the laser-treated rats 20 minutes post-MI as compared to the control-non-treated rats at 3 weeks post-MI. There was also a significant 25-fold increase in cell density of c-kit+ cells in the infarcted area of the laser-treated rats (20 minutes post-MI) as compared to the non-laser-treated controls. CONCLUSION: The application of LLLT to autologous BM of rats post-MI offers a novel approach to induce BM-derived MSCs, which are consequently recruited from the circulation to the infarcted heart and markedly attenuate the scarring process post-MI. Lasers Surg. Med. 43:401-409, 2011. (c) 2011 Wiley-Liss, Inc.

Lasers Surg Med 2011 Jul 43(5) 401-9

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The effects of low-level laser irradiation on differentiation and proliferation of human bone marrow mesenchymal stem cells into neurons and osteoblasts-an in vitro study.

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Bone marrow-derived mesenchymal stem cells (BMSCs) are promising for use in regenerative medicine. Several studies have shown that low-level laser irradiation (LLLI) could affect the differentiation and proliferation of MSCs. The aim of this study was to examine the influence of LLLI at different energy densities on BMSCs differentiation into neuron and osteoblast. Human BMSCs were cultured and induced to differentiate to either neuron or osteoblast in the absence or presence of LLLI. Gallium aluminum arsenide (GaAlAs) laser irradiation (810 nm) was applied at days 1, 3, and 5 of differentiation process at energy densities of 3 or 6 J/cm(2) for BMSCs being induced to neurons, and 2 or 4 J/cm(2) for BMSCs being induced to osteoblasts. BMSCs proliferation was evaluated by MTT assay on the seventh day of differentiation. BMSCs differentiation to neurons was assessed by immunocytochemical analysis of neuron-specific enolase on the seventh day of differentiation. BMSCs differentiation to osteoblast was tested on the second, fifth, seventh, and tenth day of differentiation via analysis of alkaline phosphatase (ALP) activity. LLLI promoted BMSCs proliferation significantly at all energy densities except for 6 J/cm(2) in comparison to control groups on the seventh day of differentiation. LLLI at energy densities of 3 and 6 J/cm(2) dramatically facilitated the differentiation of BMSCs into neurons ($p < 0.001$). Also, ALP activity was significantly enhanced in irradiated BMSCs differentiated to osteoblast on the second, fifth, seventh, and tenth day of differentiation ($p < 0.001$ except for the second day). Using LLLI at 810 nm wavelength enhances BMSCs differentiation into neuron and osteoblast in the range of 2-6 J/cm(2), and at the same time increases BMSCs proliferation (except for 6 J/cm(2)). The effect of LLLI on differentiation and proliferation of BMSCs is dose-dependent. Considering these findings, LLLI could improve current in vitro methods of differentiating BMSCs prior to transplantation.

Lasers Med Sci 2011 May 20

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Influence of Low Intensity Laser Irradiation on Isolated Human Adipose Derived Stem Cells Over 72 Hours and Their Differentiation Potential into Smooth Muscle Cells Using Retinoic Acid.

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INTRODUCTION: Human adipose derived stem cells (hADSCs), with their impressive differentiation potential, may be used in autologous cell therapy or grafting to replace damaged tissues. Low intensity laser irradiation (LILI) has been shown to influence the behaviour of various cells, including stem cells. AIMS: This study aimed to investigate the effect of LILI on hADSCs 24, 48 or 72 h post-irradiation and their differentiation potential into smooth muscle cells (SMCs). METHODOLOGY: hADSCs were exposed to a 636 nm diode laser at a fluence of 5 J/cm(2). hADSCs were differentiated into SMCs using retinoic acid (RA). Morphology was assessed by inverted light and differential interference contrast (DIC) microscopy. Proliferation and viability of hADSCs was assessed by optical density (OD), Trypan blue staining and adenosine triphosphate (ATP) luminescence. Expression of stem cell markers, beta1-integrin and Thy-1, and SMC markers, smooth muscle alpha actin (SM-alphaa), desmin, smooth muscle myosin heavy chain (SM-MHC) and smoothelin, was assessed by immunofluorescent staining and real-time reverse transcriptase polymerase chain reaction (RT-PCR). RESULTS: Morphologically, hADSCs did not show any differences and there was an increase in viability and proliferation post-irradiation. Immunofluorescent staining showed expression of beta1-integrin and Thy-1 72 h post-irradiation. RT-PCR results showed a down regulation of Thy-1 48 h post-irradiation. Differentiated SMCs were confirmed by morphology and expression of SMC markers. CONCLUSION: LILI at a wavelength of 636 nm and a fluence of 5 J/cm(2) does not induce differentiation of isolated hADSCs over a 72 h period, and increases cellular viability and proliferation. hADSCs can be differentiated into SMCs within 14 days using RA.

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Low-level laser therapy: a useful technique for enhancing the proliferation of various cultured cells.

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The aim of this work is to review the available literature on the details of low-level laser therapy (LLLT) use for the enhancement of the proliferation of various cultured cell lines including stem cells. A cell culture is one of the most useful techniques in science, particularly in the production of viral vaccines and hybrid cell lines. However, the growth rate of some of the much-needed mammalian cells is slow. LLLT can enhance the proliferation rate of various cell lines. Literature review from 1923 to 2010. By investigating the outcome of LLLT on cell cultures, many articles report that it produces higher rates of ATP, RNA, and DNA synthesis in stem cells and other cell lines. Thus, LLLT improves the proliferation of the cells without causing any cytotoxic effects. Mainly, helium neon and gallium-aluminum-arsenide (Ga-Al-As) lasers are used for LLLT on cultured cells. The results of LLLT also vary according to the applied energy density and wavelengths to which the target cells are subjected. This review suggests that an energy density value of 0.5 to 4.0 J/cm(2) and a visible spectrum ranging from 600 to 700 nm of LLLT are very helpful in enhancing the proliferation rate of various cell lines. With the appropriate use of LLLT, the proliferation rate of cultured cells, including stem cells, can be increased, which would be very useful in tissue engineering and regenerative medicine.

Lasers Med Sci 2011 Jan 28

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Increased mobility and stem-cell proliferation rate in Dugesia tigrina induced by 880nm light emitting diode.

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The therapeutic effects elicited by photobiostimulation in the near infrared range may be associated with increased proliferation rate of particular cell-types. The present study utilized commercial light emitting diodes to investigate the effects of low-level near-infrared radiation on the proliferation rate of stem cells in amputated planarian. Whole and amputated animals were exposed to either ambient diurnal lighting, darkness, white light, red light, or near-infrared (880nm) light. Irradiation was consistent for the duration of the experiments and was provided using commercial 5mm light emitting diodes (approximately 1.0mW/m(2) in power density and approximately 0.01J/cm (2) in radiant exposure). Compared to other groups amputated planarian exposed to near-infrared displayed increased mobility by the 3rd day of exposure (F((4,26))=4.31, p<0.04, eta(2)=41%). Higher densities of stem cells were measured in these worms 84h post injury (F((4,72))=4.78, p<0.01, eta(2)=21%). These findings suggest that non-coherent light sources with power-densities about 1000 times lower than contemporary low-power laser settings remain effective in generating photobiostimulation effects and warrants further investigation on stem-cell proliferation induced by near-infrared light emitting diodes.

J Photochem Photobiol B 2010 Nov 24

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Enhanced liver regeneration following acute hepatectomy by low-level laser therapy.

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OBJECTIVE: The aim of the present study was to investigate the effect of low-level laser therapy (LLLT) on liver regeneration following hepatectomy. Background: LLLT has been found to modulate various biological processes. MATERIALS AND METHODS: Twelve mature male rats were used. The liver was exposed, and 70% of it was excised. The rats were assigned randomly to two groups: control, non-laser treated, and experimental, laser-treated (diode [Ga-Al-As] laser 804 nm) group. For determination of newly formed blood vessels and proliferating cells, 5-Bromo-2'deoxyuridine (BrdU) was injected intraperitoneally. The rats were sacrificed 2 d post hepatectomy, and histological sections from each liver were processed for analysis of new blood-vessel formation using BrdU immunostaining kit. Mesenchymal stem cells (MSCs) were assessed using c-kit immunostaining. BrdU-labeled cells were counted as for estimation of newly formed hepatic cells. RESULTS: It was found that the number of proliferating cells (BrdU positive cells) per area in the regenerating regions of the livers were significantly ($p < 0.01$) 2.6-fold higher in the laser-treated rats than in the control non-laser-treated rats. The density of the newly formed blood vessels and c-kit immunopositive cells in the regenerating area of the laser-treated livers was significantly ($p < 0.01$) 3.3- and 2.3-fold respectively higher than the control non-laser treated livers. CONCLUSION: It is concluded that LLLT following acute hepatectomy most probably stimulates a significant enhancement of liver regeneration conducive to both the formation of new hepatocytes and MSCs and angiogenesis in the regenerating liver.

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Red-light light-emitting diode irradiation increases the proliferation and osteogenic differentiation of rat bone marrow mesenchymal stem cells.

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OBJECTIVE: The objective of this study was to investigate the effects on the proliferation and osteogenic differentiation of rat mesenchymal stem cells (MSCs) by using red-light light-emitting diode (LED) irradiation. BACKGROUND DATA: Low-level light irradiation (LLLI) has been shown to enhance proliferation and cytokine secretion of a number of cells. MSCs are capable of regenerating various mesenchymal tissues and are essential in supporting the growth and differentiation of hematopoietic stem cells within the bone marrow. MATERIALS AND METHODS: Rat bone marrow MSCs were treated with single or multiple doses of LLLI from an LED array (630 nm) at the irradiances of 5 and 15 mW/cm(2), and radiant exposures of 2 and 4 J/cm(2). The proliferation, clonogenic potential, and osteogenic differentiation of MSCs were evaluated after illumination. RESULTS: The growth of MSCs was enhanced by red-light LLLI, and the effect became more obvious at low cell density. A single dose of LLLI led only to a short-term increase in MSCs proliferation. A maximal increase in cell proliferation was observed with multiple exposures of LLLI at 15 mW/cm(2) and 4 J/cm(2). The number of colony-forming unit fibroblasts increased when cells were illuminated under the optimal parameter. During osteogenesis, significant increases ($p < 0.01$) in both alkaline phosphatase and osteocalcin expressions were found in the MSCs that received light irradiation. CONCLUSION: Our data demonstrated that MSCs proliferation was enhanced by multiple exposures to LLLI from 630-nm LEDs, and cell growth depended on the plating density. Furthermore, multiple dose of LLLI could enhance the osteogenic potential of rat MSCs.

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In vitro effect of carboplatin, cytarabine, paclitaxel, vincristine, and low-power laser irradiation on murine mesenchymal stem cells.

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BACKGROUND AND OBJECTIVES: Mesenchymal stem cells (MSCs) are promising for use in regenerative medicine. Cytostatics can decrease, but low-power laser irradiation (LPLI) can increase the growth of MSCs. The interaction of LPLI, MSCs and cytostatics is not known. This study investigated the effect of four cytostatics (carboplatin, cytarabine, paclitaxel, vincristine), LPLI, and combination of a cytostatic drug and LPLI on murine MSCs (mMSCs). STUDY DESIGN/MATERIALS AND METHODS: MMSCs were exposed to LPLI (660 nm diode laser; 60 mW output power; range of power density: 76-156 mW/cm(2); range of energy density: 1.9-11.7 J/cm(2)) and/or a cytostatic drug (carboplatin: 2, 10, 50; cytarabine: 0.4, 10, 50; paclitaxel: 0.4, 2, 10; vincristine: 0.02, 0.1, 0.5 microg/ml, respectively). Cell proliferation was measured after 24, 48, or 72 hours incubation. RESULTS: LPLI at 1.9 J/cm(2) dose increased the proliferation rate with 41% after 48 hours. However, 11.7 J/cm(2) LPLI caused 42% inhibition and cytostasis was still detectable after 72 hours. LPLI caused equivalent stimulation in single or in divided doses (3.8 vs. double 1.9 J/cm(2) in a 24-hour period). The cytotoxicity of 50 microg/ml carboplatin was eliminated, the inhibitory power of 0.1 microg/ml vincristine was attenuated by 1.9 J/cm(2) LPLI even 3 days post-treatment (attenuation >10%). The 11.7 J/cm(2) LPLI enhanced the cytotoxicity of 50 microg/ml cytarabine (from 48% to 73%) and 10 microg/ml paclitaxel (from 37% to 78%). Combination of the ineffective 0.4 microg/ml cytarabine or paclitaxel with the inhibitory 11.7 J/cm(2) LPLI exhibited stronger inhibition than the 11.7 J/cm(2) LPLI alone (69% and 69% vs. 42%). CONCLUSIONS: Low energy density of LPLI increases and high energy density of LPLI decreases the proliferation of mMSCs. Furthermore, LPLI can prevent or attenuate some drug's cytotoxicity and amplify others'. The result depends on the applied energy density, on the type and concentration of the cytostatics.

Lasers Surg Med 2009 Aug 41(6) 463-9

https://pubmed.ncbi.nlm.nih.gov/19588531

Implantation of low-level laser irradiated mesenchymal stem cells into the infarcted rat heart is associated with reduction in infarct size and enhanced angiogenesis.

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OBJECTIVE: The aim of the present study was to evaluate the possible beneficial effects of implantation of laser-irradiated mesenchymal stem cells (MSCs) into the infarcted rat heart. BACKGROUND DATA: It was demonstrated that low-level laser therapy (LLLT) upregulates cytoprotective factors in ischemic tissues. MATERIALS AND METHODS: MSCs were isolated from rat bone marrow and grown in culture. The cells were laser irradiated with a Ga-Al-As laser (810 nm wavelength), labeled with 5-bromo-2'deoxyuridine (BrdU), and then implanted into infarcted rat hearts. Non-irradiated cells were similarly labeled and acted as controls. Hearts were excised 3 wk later and cells were stained for BrdU and c-kit immunoreactivity. RESULTS: Infarcted hearts that were implanted with laser-treated cells showed a significant reduction of 53% in infarct size compared to hearts that were implanted with non-laser-treated cells. The hearts implanted with laser-treated cells prior to implantation demonstrated a 5- and 6.3-fold significant increase in cell density that positively immunoreacted to BrdU and c-kit, respectively, as compared to hearts implanted with non-laser-treated cells. A significantly 1.4- and 2-fold higher level of angiogenesis and vascular endothelial growth factor, respectively, were observed in infarcted hearts that were implanted with laser-treated cells compared to non-laser-treated implanted cells. CONCLUSION: The findings of the present study provide the first evidence that LLLT can significantly increase survival and/or proliferation of MSCs post-implantation into the ischemic/infarcted heart, followed by a marked reduction of scarring and enhanced angiogenesis. The mechanisms associated with this phenomenon remain to be elucidated in further studies.

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Effects of low-level laser therapy on proliferation and differentiation of murine bone marrow cells into osteoblasts and osteoclasts.

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BACKGROUND AND OBJECTIVE: Low-Level Laser Therapy (LLLT) has been suggested to improve bone tissue healing. The cellular and molecular mechanisms involved in this effect are still unclear but bone cell proliferation and differentiation alteration have been proposed. The aim of the present study was to investigate, in vitro, the effect of LLLT on bone cell proliferation, osteoblastic and osteoclastic differentiation, both involved in bone remodeling and regeneration. STUDY DESIGN/MATERIALS AND METHODS: Murine bone marrow cells, which contain both osteoblast and osteoclast progenitors, were cultured and induced to differentiate in the absence or in the presence of LLLT. Laser exposition parameters were determined using a powermeter and consisted in an 808 nm infrared wavelength laser light in continuous mode, with an energy density of 4 J/cm(2) administered three times a week. Cell proliferation and differentiation were assessed after specific staining and microscopic analysis of the cultures after various times, as well as by quantitative RT-PCR analysis of a panel of osteoblast and osteoclast markers after nucleic acid extraction. RESULTS: The use of a powermeter revealed that the power emitted by the optical fiber of the laser device was markedly reduced compared to the displayed power. This allowed to adjust the LLLT parameters to a final energy density exposure of 4 J/cm(2). In these conditions, proliferation of bone marrow mesenchymal stem cells as well as osteoclast or osteoblast differentiation of the corresponding progenitors were found similar in control and LLLT conditions. CONCLUSION: Using the present experimental protocol, we concluded that an 808 nm wavelength infrared LLLT does not alter murine bone progenitor cell proliferation and differentiation. Moreover our results confirm the necessary use of a powermeter to fix LLLT protocol parameters.

Lasers Surg Med 2009 Apr 41(4) 291-7

https://pubmed.ncbi.nlm.nih.gov/19347941

Effect of low-level laser irradiation and epidermal growth factor on adult human adipose-derived stem cells.

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The study investigated the effects of low-level laser radiation and epidermal growth factor (EGF) on adult adipose-derived stem cells (ADSCs) isolated from human adipose tissue. Isolated cells were cultured to semi-confluence, and the monolayers of ADSCs were exposed to low-level laser at 5 J/cm(2) using 636 nm diode laser. Cell viability and proliferation were monitored using adenosine triphosphate (ATP) luminescence and optical density at 0 h, 24 h and 48 h after irradiation. Application of low-level laser irradiation at 5 J/cm(2) on human ADSCs cultured with EGF increased the viability and proliferation of these cells. The results indicate that low-level laser irradiation in combination with EGF enhances the proliferation and maintenance of ADSCs in vitro.

Lasers Med Sci 2010 Jan 25(1) 33-9

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In vitro effects of low-level laser irradiation for bone marrow mesenchymal stem cells: proliferation, growth factors secretion and myogenic differentiation.

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BACKGROUND AND OBJECTIVES: Bone marrow derived mesenchymal stem cells (BMSCs) have shown to be an appealing source for cell therapy and tissue engineering. Previous studies have confirmed that the application of low-level laser irradiation (LLLI) could affect the cellular process. However, little is known about the effects of LLLI on BMSCs. The aim of this study was designed to investigate the influence of LLLI at different energy densities on BMSCs proliferation, secretion and myogenic differentiation. STUDY DESIGN/MATERIALS AND METHODS: BMSCs were harvested from rat fresh bone marrow and exposed to a 635 nm diode laser (60 mW; 0, 0.5, 1.0, 2.0, or 5.0 J/cm(2)). The lactate dehydrogenase (LDH) release was used to assess the cytotoxicity of LLLI at different energy densities. Cell proliferation was evaluated by using 3-(4, 5-dimethylithiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) and 5-bromo-2'-deoxyuridine (BrdU) assay. Production of vascular endothelial growth factor (VEGF) and nerve growth factor (NGF) were measured by enzyme-linked immunosorbent assay (ELISA). Myogenic differentiation, induced by 5-azacytidine (5-aza), was assessed by using immunocytochemical staining for the expression of sarcomeric alpha-actin and desmin. RESULTS: Cytotoxicity assay showed no significant difference between the non-irradiated group and irradiated groups. LLLI significantly stimulated BMSCs proliferation and 0.5 J/cm(2) was found to be an optimal energy density. VEGF and NGF were identified and LLLI at 5.0 J/cm(2) significantly stimulated the secretion. After 5-aza induction, myogenic differentiation was observed in all groups and LLLI at 5.0 J/cm(2) dramatically facilitated the differentiation. CONCLUSIONS: LLLI stimulates proliferation, increases growth factors secretion and facilitates myogenic differentiation of BMSCs. Therefore, LLLI may provide a novel approach for the preconditioning of BMSCs in vitro prior to transplantation.

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Stem cell proliferation under low intensity laser irradiation: a preliminary study.

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BACKGROUND AND OBJECTIVES: Phototherapy with low intensity laser irradiation has shown to be effective in promoting the proliferation of different cells. The aim of this in vitro study was to evaluate the potential effect of laser phototherapy (660 nm) on human dental pulp stem cell (hDPSC) proliferation. STUDY DESIGN/MATERIALS AND METHODS: The hDPSC cell strain was used. Cells cultured under nutritional deficit (10% FBS) were either irradiated or not (control) using two different power settings (20 mW/6 seconds to 40 mW/3 seconds), with an InGaAIP diode laser. The cell growth was indirectly assessed by measuring the cell mitochondrial activity through the MTT reduction-based cytotoxicity assay. RESULTS: The group irradiated with the 20 mW setting presented significantly higher MTT activity at 72 hours than the other two groups (negative control--10% FBS--and lased 40 mW with 3 seconds exposure time). After 24 hours of the first irradiation, cultures grown under nutritional deficit (10% FBS) and irradiated presented significantly higher viable cells than the non-irradiated cultures grown under the same nutritional conditions. CONCLUSIONS: Under the conditions of this study it was possible to conclude that the cell strain hDPSC responds positively to laser phototherapy by improving the cell growth when cultured under nutritional deficit conditions. Thus, the association of laser phototherapy and hDPSC cells could be of importance for future tissue engineering and regenerative medicine. Moreover, it opens the possibility of using laser phototherapy for improving the cell growth of other types of stem cells.

Lasers Surg Med 2008 Aug 40(6) 433-8

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Treatment of tendinopathy: what works, what does not, and what is on the horizon.

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Tendinopathy is a broad term encompassing painful conditions occurring in and around tendons in response to overuse. Recent basic science research suggests little or no inflammation is present in these conditions. Thus, traditional treatment modalities aimed at controlling inflammation such as corticosteroid injections and nonsteroidal antiinflammatory medications (NSAIDS) may not be the most effective options. We performed a systematic review of the literature to determine the best treatment options for tendinopathy. We evaluated the effectiveness of NSAIDS, corticosteroid injections, exercise-based physical therapy, physical therapy modalities, shock wave therapy, sclerotherapy, nitric oxide patches, surgery, growth factors, and stem cell treatment. NSAIDS and corticosteroids appear to provide pain relief in the short term, but their effectiveness in the long term has not been demonstrated. We identified inconsistent results with shock wave therapy and physical therapy modalities such as ultrasound, iontophoresis and low-level laser therapy. Current data support the use of eccentric strengthening protocols, sclerotherapy, and nitric oxide patches, but larger, multicenter trials are needed to confirm the early results with these treatments. Preliminary work with growth factors and stem cells is promising, but further study is required in these fields. Surgery remains the last option due to the morbidity and inconsistent outcomes. The ideal treatment for tendinopathy remains unclear. LEVEL OF EVIDENCE: Level II, systematic review.

Clin Orthop Relat Res 2008 Jul 466(7) 1539-54

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Red light of 647 nm enhances osteogenic differentiation in mesenchymal stem cells.

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The use of light for medical treatment has been studied previously. In this study, we examined the effect of light from a red light-emitting diode on osteogenic differentiation of mouse mesenchymal stem cells (D1 cells) which were cultured in the presence of osteogenic differentiation medium (ODM) for 3 days, then exposed to a red light-emitting diode (LED) light of 647 nm wavelength once for 10 s, 30 s or 90 s with radiation energies of 0.093 J, 0.279 J and 0.836 J, respectively. D1 cells in the presence of ODM differentiated into osteoblasts, and this process was enhanced on exposure to LED light in ODM medium. This effect was confirmed by increased Alizarin red staining, higher alkaline phosphatase (ALP) activity, higher mRNA expressions of osteocalcin, collagen type I, osteopontin and Runt-related transcription factor2 (Runx2), and higher levels by reverse transcriptase-polymerase chain reaction (RT-PCR) and by increased immunofluorescence staining against cluster of differentiation 44 (CD44) by immunofluorescence microscopy, confocal microscopy and flow cytometric analysis. These data suggest that osteogenic differentiation of mesenchymal stem cells (MSCs) in ODM is enhanced by LED light exposure.

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Primary myogenic cells see the light: improved survival of transplanted myogenic cells following low energy laser irradiation.

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BACKGROUND AND OBJECTIVES: There is a substantial need for finding new avenues to promote muscle recovery when acute skeletal muscle loss extends beyond the natural capacity of the muscle to recover. Maintenance and regeneration of skeletal muscles depend mainly on resident stem cells known as satellite cells. Nevertheless, there are situations in which a significant loss of muscle tissue exhausts the satellite cell pool. For such cases, cell therapy and tissue engineering are becoming promising alternatives. Thus far, attempts to supplement damaged host muscles with donor satellite cells by means of myoblast transplantation therapy were mostly unsuccessful due to massive and rapid loss of donor cells within few hours after transplantation. This study aims at following the effects of low-energy-laser irradiation on the fate of implanted myoblasts. STUDY DESIGN: Primary myogenic cells, harvested from male rat skeletal muscles, were irradiated with low energy laser, seeded on a biodegradable scaffold and expanded in vitro. The scaffold containing cells was transplanted into partially excised muscles of host female rats. Donor cells were identified in the host muscle tissue, using Y-chromosome in situ hybridization. RESULTS: In this study, we show that laser irradiated donor primary myogenic cells not only survive, but also fuse with host myoblasts to form a host-donor syncytium. CONCLUSIONS: Our data show that the use of low energy laser irradiation (LELI), a non-surgical tool, is a promising means to enhance both the survival and functionality of transplanted primary myogenic cells.

Lasers Surg Med 2008 Jan 40(1) 38-45

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Effects of low level red-light irradiation on the proliferation of mesenchymal stem cells derived from rat bone marrow.

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Mesenchymal stem cells (MSCs) are capable of regenerating various mesenchymal tissues and are essential in supporting the growth and differentiation of hematopoietic stem cells within the bone marrow microenvironment in vivo. To achieve clinically meaningful numbers of cells, many approaches have been used to maintain the differentiation potentialities and expand enough cells for clinical treatments. Previously, we have reported that low level light irradiation (LLLI) using 630 nm light emitting diodes (LEDs) could enhance replicative and colony formation potentials of MSCs derived from human bone marrow. The purpose was to study the effect on the proliferation of MSCs derived from the rat bone marrow by red light LLLI (630 nm) under different parameters of irradiation. The irradiance used was 5, 10 or 15 mW/cm2, and the radiant exposure was 2 or 4 J/cm2. Rat MSCs were irradiated at room temperature with single and multiple exposures. The results showed that the proliferation of MSCs plated at the low density (100 cells/well) and high density (1000 cells/well) was enhanced by multiple exposures of red-light LED treatment. The rate of proliferation of MSCs plated at the high density was not as high as those plated at the low density. The optimal parameter for LLLI was at irradiance of 15 mW/cm2, and radiant exposure of 4 J/cm2. The effect on the proliferation of cells by single dose irradiation was temporary. Multiple stimuli may be necessary for the enhancement of cell growth.

Conf Proc IEEE Eng Med Biol Soc 2007 2007 5830-33

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The effect of low level laser irradiation on adult human adipose derived stem cells.

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This study investigated the effect of low level laser irradiation on primary cultures of adult human adipose derived stem cells (ADSC) using a 635-nm diode laser, at 5 J/cm(2) with a power output of 50.2 mW and a power density of 5.5 mW/cm(2). Cellular morphology did not appear to change after irradiation. Using the trypan blue exclusion test, the cellular viability of irradiated cells increased by 1% at 24 h and 1.6% at 48 h but was not statistically significant. However, the increase of cellular viability as measured by ATP luminescence was statistically significant at 48 h ($p < 0.05$). Proliferation of irradiated cells, measured by optical density, resulted in statistically significant increases in values compared to nonirradiated cells ($p < 0.05$) at both time points. Western blot analysis and immunocytochemical labeling indicated an increase in the expression of stem cell marker beta1-integrin after irradiation. These results indicate that 5 J/cm(2) of laser irradiation can positively affect human adipose stem cells by increasing cellular viability, proliferation, and expression of beta1-integrin.

Lasers Med Sci 2008 Jul 23(3) 277-82

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Low-level laser irradiation (LLLI) promotes proliferation of mesenchymal and cardiac stem cells in culture.

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BACKGROUND AND OBJECTIVES: Low-level laser irradiation (LLLI) was found to promote the proliferation of various types of cells in vitro. Stem cells in general are of significance for implantation in regenerative medicine. The aim of the present study was to investigate the effect of LLLI on the proliferation of mesenchymal stem cells (MSCs) and cardiac stem cells (CSCs). STUDY DESIGN/MATERIALS AND METHODS: Isolation of MSCs and CSCs was performed. The cells were cultured and laser irradiation was applied at energy densities of 1 and 3 J/cm(2). RESULTS: The number of MSCs and CSCs up to 2 and 4 weeks respectively, post-LLLI demonstrated a significant increase in the laser-treated cultures as compared to the control. CONCLUSION: The present study clearly demonstrates the ability of LLLI to promote proliferation of MSCs and CSCs in vitro. These results may have an important impact on regenerative medicine.

2014

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Cell biology: Power Games

Lane N

There's a fight going on inside all our cells for each breath of air. Nick Lane sheds therapeutic light on the implications for cancer and degenerative diseases.

Seventy-five years ago, Otto Warburg's star was at its zenith. The pioneering German biochemist delivered his Nobel address in December 1931. He described the ingenious experiments by which he had unmasked the enzyme responsible for the critical step of cell respiration, the process that turns the energy in chemical compounds into energy the cell can use. His work on respiration in the early 1930s nearly earned him a second Nobel, ultimately denied him by Hitler. Then his star began sinking. His ideas on the importance of cell respiration in cancer led many to dismiss him as a crank. And the rise of molecular genetics in the 1960s put such ideas into a far distant orbit.

But now, Warburg's star is rising again. A new generation of researchers is returning to his ideas about respiration in cancer cells. Recent findings suggest that the enzyme he identified, cytochrome oxidase, is a key player in a new understanding of how the cell's energy metabolism affects health and disease. And surprisingly they show that light has a profound effect on how the enzyme works — and could even be used to treat degenerative disease.

To extract energy from molecules, the cell first breaks down glucose into simpler molecules via a process called glycolysis. It then feeds these molecules into energy-producing structures called mitochondria, which strip electrons from them to produce energy with the help of oxygen. As Warburg showed, cytochrome oxidase governs the last reaction in this process.

Perhaps the most surprising aspect of the renaissance of Warburg's ideas is that the methods he used to make this discovery matter again. They exploit two chemical quirks: carbon monoxide (CO) can block respiration by binding to cytochrome oxidase in place of oxygen; and a flash of light can displace it, freeing up the site for oxygen to bind again.

SELF CONTROL By measuring oxygen consumption at different wavelengths of light, Warburg worked out that the enzyme belonged to a group of proteins that include haemoglobin and chlorophyll. But for Warburg, the binding of CO to the enzyme was just an oddity he could put to good use. He had no inkling that biology might use the same trick.

Yet over the past decade, researchers have come to appreciate that cells often use CO, and to an even greater extent NO (nitric oxide), to block respiration. Not only that, but light has striking counter-effects on cytochrome oxidase. And all these suitors to the enzyme turn out to be critical to our understanding not just of cancer, but practically all degenerative diseases.

Nitric oxide is emitted by nerve endings and can act on an enzyme called guanylate cyclase to relax blood vessels — the impotence drug Viagra manipulates this system. For a long time, scientists thought that guanylate cyclase was NO's only target. But in the mid-1990s, they found that the molecule can also bind to cytochrome oxidase and hinder respiration1. What's more, it could do so at levels found in the body's tissues.

The finding that the body could poison one of its own enzymes was initially shrugged off as an imperfection. An example of how evolution cobbles organisms together with no forethought. But a few years later, several groups reported that mitochondria harboured an enzyme that synthesizes NO (ref. 2). Why would cells go out of their way to cook up NO right next to the respiratory enzymes?
According to cell biologist Salvador Moncada of University College London, evolution really has crafted cytochrome oxidase to bind not only oxygen but also NO. "One effect of slowing respiration in some locations is to divert oxygen elsewhere in cells and tissues," he says. This prevents oxygen levels sinking dangerously low. Moncada,for example, has shown that NO blocks respiration in the cells lining blood vessels and that this helps to transfer oxygen into smooth muscle cells in these vessels. Fireflies use a similar trick to flash light (see 'Flashing the gauntlet')

Low level laser irradiation stimulates osteogenic phenotype of mesenchymal stem cells seeded on a three-dimensional biomatrix.

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Mesenchymal stem cells (MSCs) seeded on three-dimensional (3D) coralline (Porites lutea) biomatrices were irradiated with low-level laser irradiation (LLLI). The consequent phenotype modulation and development of MSCs towards ossified tissue was studied in this combined 3D biomatrix/LLLI system and in a control group, which was similarly grown, but was not treated by LLLI. The irradiated and non irradiated MSC were tested at 1-7, 10, 14, 21, 28 days of culturing via analysis of cellular distribution on matrices (trypan blue), calcium incorporation to newly formed tissue (alizarin red), bone nodule formation (von Kossa), fat aggregates formation (oil red O), alkaline phosphatase (ALP) activity, scanning electron microscopy (SEM) and electron dispersive spectrometry (EDS). The results obtained from the irradiated samples showed enhanced tissue formation, appearance of phosphorous peaks and calcium and phosphate incorporation to newly formed tissue. Moreover, in irradiated samples ALP activity was significantly enhanced in early stages and notably reduced in late stages of culturing. These findings of cell and tissue parameters up to 28 days of culture revealed higher ossification levels in irradiated samples compared with the control group. We suggest that both the surface properties of the 3D crystalline biomatrices and the LLLI have biostimulatory effects on the conversion of MSCs into bone-forming cells and on the induction of ex-vivo ossification.

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Low power laser radiation at 685 nm stimulates stem-cell proliferation rate in Dugesia tigrina during regeneration.

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Today's scientific interest in tissue engineering for organ transplantations and regeneration from stem cells, allied with recent observations on biostimulation of tissues and cells by laser radiation, stands as a strong motivation for the present work, in which we examine the effects of the low power laser radiation onto planarians under regenerative process. To investigate those effects, a number of 60 amputated worms were divided in three study groups: a control group and two other groups submitted to daily 1 and 3 min long laser treatment sections at approximately 910 W/m2 power density. A 685 nm diode laser with 35 mW optical power was used. Samples were sent to histological analysis at the 4th, the 7th and the 15th days after amputation. A remarkable increase in stem cells counts for the fourth day of regeneration was observed when the regenerating worms was stimulated by the laser radiation. Our findings encourage further research works on the influence of optical radiation onto stem cells and tissue regeneration.

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Newer options for treating drug-resistant (MDR+) cancer cells using photoradiation therapy.

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Emergence of drug resistance with conventional cytotoxic therapy is a major challenge towards the curability of many cancers, especially in patients undergoing autologous BMT with ex-vivo purged hematopoietic support. We have explored the potential role of photoradiation therapy in purging hematopoietic stem cells of various hematological malignancies. Benzoporphyrin derivative, monoacid ring A (BPD-MA), dihematoporphyrin ether (DHE), and MC-540 were evaluated for the "ex-vivo" purging of residual tumor cells from autologous bone marrow (BM) grafts. BPD-MA and DHE photosensitizing activity was tested against two human large cell lymphoma cell lines and colony forming-unit leukemia (CFU-L) derived from patients with acute myelogenous leukemia (AML). In mixing experiments four log elimination of tumor cell lines was observed after 1 hr of incubation with BPD-MA or DHE followed by white light exposure. By comparison, using the same concentration of BPD-MA or DHE, the mean recovery of normal BM progenitors was 4-5.2% for granulocyte-macrophage colony forming unit (CFU-GM) and 5-9.8% for burst forming unit erythroid (BFU-E). The T lymphoblastic leukemia cell line CEM and its vinblastine (VBL)-resistant subline CEM/VBL100, along with the acute promyelocyte leukemia cell line HL-60 and its vincristine (VCR)-resistant subline HL-60/VCR, were also tested. Our results demonstrated the preferential cytotoxicity of BPD-MA and DHE toward neoplastic cell lines and CFU-L from AML patients. In addition, DHE was slightly more effective in purging tumor cells expressing the p-170 glycoprotein.(ABSTRACT TRUNCATED AT 250 WORDS)

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Increase in colony-forming capacity of the haemopoietic stem cells in the bone marrow exposed to the He-Ne laser radiation in vitro.

Vacek A, Bartonickova A, Vesela Z, Petru F

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Blood pressure controlled by low reactive level diode laser therapy (LLLT)

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The effects of low reactive level laser therapy (LLLT) with an infrared diode laser on blood pressure, particularly the hypotensive effect on hypertension were studied. Essential or primary hypertension is frequently encountered, but its aetiology and consistent control elude present day medicine. Experimental animal studies have shown that hypertension causes destructive changes in the medulla oblongata and in the brain stem: arteriosclerosis, and destructive changes in brain stem cells have been demonstrated in hypertensive human patients. Various biological effects on vascular tissue have been reported for the diode laser, and so the author evaluated the GaAlAs diode laser for the treatment of hypertension by controlling the blood pressure regulatory system, irradiating the area adjacent to the medulla oblongata, Thirty patients were included in the study. Following treatment the results were graded as excellent in 6 patients (20%); good in 11 patients (37%); fair in seven cases (23%), and ineffective in 6 cases (20%), giving an overall effective rate of 80%. In 12 of the 30 patients, whose hypertension had not been effectively controlled by conventional hypotensive treatment, LLLT gave excellent results in 6, good in 5 and fair in 1 patient. In contrast, in a second group of 15 relatively normotensive control patients, there were no excellent or good results, and only 3 fair results, the remainder being graded as ineffective. It was concluded that in general there was no clear-cut hypotensive effect following LLLT with the diode laser, but when applied to the pathological condition known as essential hypertension, LLLT was noticeably effective. These findings warrant further study on this application of LLLT.

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