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Molecular impacts of photobiomodulation on bone regeneration: A systematic review

Sepanta Hosseinpour [a b], Reza Fekrazad [b c], Praveen R. Arany [d], Qingsong Ye [a]

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Abstract

Photobiomodulation (PBM) encompasses a light application aimed to increase healing process, tissue regeneration, and reducing inflammation and pain. PBM is specifically aimed to modify the expression of cellular molecules; however, PBM impacts on cellular and molecular pathways especially in bone regenerative medicine have been investigated in scattered different studies. The purpose of the current study is to systematically review evidence on molecular impact of PBM on bone regeneration. A comprehensive electronic search in Medline, Scopus, EMBASE, EBSCO, Cochrane library, web of science, and google scholar was conducted from January 1975 to October 2018 limited to English language publications on administrations of photobiomodulation for bone regeneration which evaluated biological factors. In addition, hand search of selected journals was done to retrieve all articles. This systematic review was performed based on PRISMA guideline. Among these studies, five articles reported *in vitro* results, twelve articles were *in vivo*, and three of them were clinical trials. The data tabulated according to the type of

markers (osteogenic markers, angiogenic markers, growth factors, and inflammation mediators). PBM's effects depend on many parameters which energy density is more important than the others. PBM can significantly enhance expression of osteocalcin, collagen, RUNX-2, vascular endothelial growth factor, bone morphogenic proteins, and COX-2. Although since the heterogeneity of the studies and their limitations, an evidence-based decision for definite therapeutic application of PBM is still unattainable, the findings of our review can help other researchers to ameliorate their study design and elect more efficient approach for their investigation.

Introduction

Photobiomodulation (PBM) encompasses a light application aimed to increase healing process (Posten et al., 2005), tissue regeneration (da Silva et al., 2010), reducing inflammation and pain (Woodruff et al., 2004), and alteration in immunologic activity (Dostalova et al., 2017). Nowadays, PBM as a noninvasive therapeutic approach applied for wide medical purposes from nerve injuries (Sene et al., 2013) and wound healing (Ustaoglu et al., 2017) to osteoarthritis treatment (Huang et al., 2015). PBM commonly consist of low level laser therapy, red/infrared coherent or LED non coherent light which provides lower (1–500 mW) output power in comparison to other laser treatment methods (AlGhamdi et al., 2012). Hence, not only this treatment modality is not harmful due to lack of any thermal effects (Basford, 1995), but also it can stimulate some beneficial photochemical reactions that affect cellular metabolism.

In vivo investigations have shown that PBM can stimulate mesenchymal stem cells (MSCs) proliferation by potential changes in gene expressions and activations (Peat et al., 2018, Schneede et al., 1988, Wu et al., 2012). Funk et al. represented that cytokine release will alter after PBM via He – Ne laser (Funk et al., 1992). In addition, there are many studies reported beneficial impacts of PBM on wound healing and tissue repair which have been suggested to cause by modulating of inflammation mediators like interleukin (IL) −1, interferon–γ (Deng et al.), and tumor necrosis factor (TNF) –α, and increasing of growth factor secretion such as fibroblast growth factor (FGF), platelet derived growth factor (PDGF), and transforming growth factor (TGF) (Al-Watban and Zhang, 2004, Enwemeka et al., 2004, Neiburger, 1999, Safavi et al., 2008). PBM induces new bone formation with enhancing osteoblastic activity and reducing osteoclastic activity

(Ninomiya et al., 2007). It has been shown that laser therapy can increase bone regeneration via affecting regulatory factors in bone matrix (Ueda and Shimizu, 2003). Moreover, PBM is able to increase the expression of bone morphogenic protein-4 (BMP-4) and activation of transcription factors such as Runt-related transcription factor −2 (RUNX-2) genes during bone healing process in animal model (Fávaro–Pípi et al., 2011). There are several proposed molecular mechanism for explaining PBM's effects such as affecting beta catenin pathway, cyclinD1 pathway, and mitogen activated protein kinase pathway (de Freitas and Hamblin, 2016). PBM can increase intracellular adenosine triphosphate (ATP) which plays a major role in cellular signaling (Farivar et al., 2014). It has been seen that Calcium concentration increased after PBM application (Santulli and R Marks, 2015). Thereby, Calcium-sensitive signaling pathways can be triggered by laser irradiation (Sharma et al., 2011, Wu et al., 2010).

Although one of the goals of PBM is to modify the expression of cellular molecules, the molecular mechanisms especially in bone regenerative medicine have been investigated in various scattered studies and are not precisely understood. The current study aims to systematically review the available literature on molecular impact of PBM on bone regeneration.

Section snippets

Protocol

This review is organized and followed PRISMA guidelines (Moher et al., 2015) for systematic reviews.…

Eligibility criteria

Types of studies: All clinical investigations (clinical trials, case-controls, and case series), *in vitro* and *in vivo* investigations, which administrated level laser therapy, red/infrared coherent or LED non-coherent light (photobiomodulation) for bone regenerative investigations on cell lines, humans and animal models were included. Case reports, systematic and literature reviews, letter to…

Study selection

Fig. 1 illustrated the PRISMA flow diagram of search strategy used in this study. 2873 articles were retrieved from the databases and one article from other sources and two studies from hand search. A total of 2876 articles were initially screened by two independent reviewers and 2781 studies were excluded due to duplication and un related keywords according to our study design. After exclusion of non-relevant articles, the records of 95 studies were evaluated. Within these studies, four of…

Discussion

PBM has been applied in various field of medicine such as promoting tissue healing (Posten et al., 2005) and repair (da Silva et al., 2010), analgesic and anti-inflammatory effects(Woodruff et al., 2004), and acceleration of regenerative processes (Posten et al., 2005) for the last decades. Previous studies demonstrated that PBM inducing mitochondrial respiration (Karu et al., 1999), promoting cell proliferation, and altering cellular regulatory proteins (Buravlev et al., 2015, Stein et al.,…

Conclusions

Based on the studies evaluated here, PBM administration demonstrated promising results for bone tissue regenerating processes. PBM can up regulate numerous osteogenic factors, angiogenic factors, growth factors, and inflammation mediators that facilitate bone formation. PBM significantly increased the expression of OCN, RUNX-2, BMP-2, -9, COX-2 via 830 nm, Ga—Al—As laser. In addition, 635 nm, Ga—Al—As laser and 809 nm, Ga—Al—As laser induced significantly higher expression of OCN, Collagen type I,…

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Acknowledgements

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Recommended articles

References (98)

M. Bayat *et al.*
Comparison of the in vitro effects of low-level laser therapy and low-intensity pulsed ultrasound therapy on bony cells and stem cells
Prog. Biophys. Mol. Biol. (2018 Mar 1)

C.H. Chen *et al.*
Low power laser irradiation and human adipose-derived stem cell treatments promote bone regeneration of critical-sized calvarial defects in rats
Annals of Physical and Rehabilitation Medicine (2018)

V. Cury *et al.*
Low level laser therapy increases angiogenesis in a model of ischemic skin flap in rats mediated by VEGF, HIF-1alpha and MMP-2
J. Photochem. Photobiol., B (2013)

P. Ducy *et al.*
Osf2/Cbfa1: a transcriptional activator of osteoblast differentiation
Cell (1997)

E.M. El-Maghraby *et al.*
Assessment of the effect of low-energy diode laser irradiation on gamma irradiated rats' mandibles

Arch. Oral Biol. (2013)

R. Fekrazad *et al.*
The effects of combined low level laser therapy and mesenchymal stem cells on bone regeneration in rabbit calvarial defects
J. Photochem. Photobiol. B Biol. (2015)

A.M. Ferreira *et al.*
Collagen for bone tissue regeneration
Acta Biomater. (2012)

J.O. Funk *et al.*
Cytokine production after helium neon laser irradiation in cultures of human peripheral blood mononuclear cells
J. Photochem. Photobiol. B Biol. (1992)

F. Gomes *et al.*
Low-level laser therapy improves peri-implant bone formation: resonance frequency, electron microscopy, and stereology findings in a rabbit model
Int. J. Oral Maxillofac. Surg. (2015)

K.D. Hankenson *et al.*
Angiogenesis in bone regeneration
Injury (2011)

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Cited by (51)

Exploring the biphasic dose-response effects of photobiomodulation on the viability, migration, and extracellular vesicle secretion of human adipose mesenchymal stem cells
2024, Journal of Photochemistry and Photobiology B: Biology

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The role of photobiomodulation in accelerating bone repair

2024, Progress in Biophysics and Molecular Biology

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Photobiomodulation in dental extraction therapy: Postsurgical pain reduction and wound healing

2023, Journal of the American Dental Association

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Angiogenetic and anti-inflammatory effects of photobiomodulation on bone regeneration in rat: A histopathological, immunohistochemical, and molecular analysis

2023, Journal of Photochemistry and Photobiology B: Biology

> *Citation Excerpt :*
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> …It is noteworthy that PBMT can increase bone regeneration by increasing the activity of osteoblasts, decreasing the activity of osteoclasts, and affecting regulatory factors in the bone matrix. In addition, PBM can express bone morphogenic protein-4 (BMP-4) and activate transcription factors like Runt-related transcription factor 2 (RUNX-2) genes [16]. Accordingly, all these processes can initiate and improve bone healing [17,18]….

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