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Brief Retrospect on the Use of Photobiomodulation (PBM) Therapy for Augmented Bone Regeneration (ABR)

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As technology advances at a rapid rate, innovations in regenerative medicine will eventually include the use of energy-based therapeutics, such as low intensity-pulsed ultrasound stimulation (LIPUs), pulsed electromagnetic field stimulation (PMFs), and low-level laser/light therapy (LLLT) or photobiomodulation therapy (PBMt). Among these treatments, LLLT/PBMt attracted significant attention by the turn of the century, as evidenced by the numerous publications compared to LIPUs and PMFs, particularly for augmented bone regeneration (ABR). This is a testament of how the maturation of technology and scientific knowledge leads to latent compounded applications, even when the value of a technique is reliant on empirical data. This article reviews some of the notable investigations using LLLT/PBMt for bone regeneration published in the past decade, focusing on how this type of therapy has been utilized together with the existing regenerative medicine landscape.

Key words

Low-level laser/light therapy; Photobiomodulation therapy; Laser therapy; Augmented bone regeneration

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INTRODUCTION

Bone defects, either fractures or lack thereof, are among the most common disorders encountered in the medical field. This condition can be brought about by numerous conditions such as injuries, cancer (and related treatments), surgery, infectious and autoimmune diseases, and even genetics. Variations with regards to cause of different bone defects also equates disparities between appropriate treatments. Decades of research have already contributed to the development of ever more advancing therapeutics seeking one vital purpose—guided bone regeneration (GBR). Although it is well known that bone can regenerate like any other tissue in the human body, bone requires a particular set of conditions to proceed. It follows an extended scheme of regeneration that involves several overlapping processes.¹ Since bone tissue is the main support structure that influences stability of almost all surrounding soft tissue, it's crucial that bone heals according to its form and associated function.

Stabilization of bone fractures is one of the most important considerations when addressing bone defects. Callus formation in broken bones progress slowly and only occurs within a very short range of distance.¹ Minimizing the distance and mobility of the fractured bone tissue limits the occurrence of non-union. This has led medical and clinical scientists to develop different devices and techniques for fracture immobilization with the aim of GBR.

Aside from immobilization, another aspect to be considered is proper ossification. Bone is a hard tissue which contains high amounts of minerals compared to other soft tissues. This necessitates the presence of a mineral source to support calcification of the newly formed dense tissue. Hence, this led to medical and material scientists to examine biomaterials not only as immediate mineral source for tissue calcification but as proper tissue scaffolds mimicking the stability and structural form of bone tissue. Copious implantable materials for GBR based on natural sources (demineralized/acellular bone), synthetic materials (polymers/mineral-based/metals), and related composites have already been successfully utilized as viable medical products.

Biological mechanisms have also been elucidated with the aim of using cells and exploiting biomolecular pathways to improve previously developed techniques for GBR. The introduction of cell, protein, and genetic-based biomolecular analyses was accompanied by enormous interest in using biological molecules to promote augmented bone regeneration (ABR). Notwithstanding the advancements in GBR generated from recent investiga-

tions, the use of energy-based medical therapeutics such as pulsed electromagnetic field stimulation, ultrasound stimulation, and laser application for ABR has garnered traction lately.

Initial studies mainly utilized these aforementioned energy-based technologies for the purpose of observation and visualization of organs and tissues. Early investigations regarding the use of energy for tissue regeneration have been scarce and far in between. This could possibly be due to the persistent changes in understanding the fundamental nature of the different forms of energy. Unlike biomaterials and biologics, energy not only exists in different forms but also in a broad spectrum and is highly transferrable across various states of matter. This complicates not only the direct application of energy for therapeutic purposes but also imposes the promotion of proper safety precautions for both the practitioner and patient alike. In addition to this, technological advancements in the form of hardware capable of measuring, generating, and harnessing the potential of different forms of energy became a limiting factor in pursuing energy-based therapeutics early on. Nevertheless, the knowledge, policies, and machinery/devices have already reached the level of maturity enough to merit investigations several energy-based technologies for regenerative applications.

As previously mentioned, pulsed magnetic field stimulation (PMFs) is one of the energy-based therapy that is currently being investigated for ABR. Initial studies attributed the efficacy of PMFs to the two factors; the fast-tracked synthesis of bone matrix thru the induced weak electric currents;² and the subsequent bone loss matrix downregulation.^{3,4} Later studies have revamped this theory by suggesting that PMFs boosts cell proliferation and step-up the osteogenic process.^{5,6} This led to the approval of PMFs for supplementing post-osteotomy recovery⁷ and as treatment for both osteoarthritis and pseudoarthrosis.^{8,9}

Low intensity pulsed ultrasound stimulation (LIPUs) similarly went through the same inquiries concerning its potential for ABR using animal models¹⁰ and through clinical studies alike.^{11,12} A number of studies delving into the mechanism by which LIPUs leads to ABR had reported that ultrasound induction influences the c-fos, cyclooxygenase-2, prostaglandin-2, nitric oxide (NO), osteocalcin, and osteopontin levels in osteoblasts as a result of amplified calcium influx into the osteoblasts.^{13,14} This occurs through signal transduction across the cytoskeleton proteins, actin filaments, and extracellular matrix connected via adhesive contacts during LIPUs. Ultrasound stimuli travels between adherent cells setting off stretch-

activated calcium channels; this in turn increases cell surface expression of integrins leading to formation of stress fibers via reorganization of actin cytoskeleton.¹⁵⁻¹⁷

Likewise, Low-level Laser therapy (LLLt); the use of non-ionizing light energy for regenerative medicine, has also been a prominent topic for ABR as of late. Compared to PMFs and LIPUs, application of LLLt for bone regeneration is a more recent and pervasive topic that picked up greater traction by the end of the 20th century. Based on current publication search, information regarding the use of PMFs and LIPUs dates back as far as mid 1970s and has relatively fewer number of publications compared to LLLt, this indicative of the major interest and relative greater potential of using lasers for bone regeneration therapy. Thus, this article will be a retrospect on select publications with notable developments concerning the use of LLLt for bone regeneration in the past decade.

PHOTOBIMODULATION THERAPY (PBMt) FOR BONE REGENERATION

Low-level laser/light therapy entails exposure of cells and tissues to light energy ranging within the red and near-infrared (600-1070 nm) wavelength of the electromagnetic spectrum.¹⁸ The presence of chromophores like hemoglobin and melanin, which have effective absorption below 600 nm, can be efficiently utilized to treat superficial tissues while longer wavelength ranging from 780-950 nm are used for addressing deeper tissues like bone.¹⁸ This energy-based therapy is delivered in lower power density need to generate heat thus the term "cold laser" became associated with LLLt.¹⁹

In fact, a recent publication concerning naming scheme for the said procedure have led to the promotion of "Photobiomodulation therapy" (PBMt) as an alternative term for LLLt.²⁰ This was to improve consolidation of published articles making use of low-level/low-power laser/light treatments that do not induce ionizing or thermal effects on cells and tissues nonetheless stimulate certain biological response. The term "photobiostimulation" was derived from the photochemical effect resulting from the absorption of light energy promoting certain chemical changes that affect biological processes in living organisms. Thus, for the remainder of this article, LLLt will be referred to as PBMt.

Although abundant studies have been conducted regarding the use of PBMt for regenerative purposes, the mechanism by which it enhances the recovery of damaged tissue is yet to be fully elucidated. Based on existing literature, improvement on bone regeneration through

PBMt is attributed to at least two modes of action. The first mechanism is ascribed to the absorption of the light energy by the respiratory chain terminal enzyme-cytochrome C oxidase leading to the increase of mitochondrial membrane potential which consequently elevates adenosine triphosphate, cyclic adenosine monophosphate, NO, and reactive oxygen species levels.²¹ This increased mitochondrial activity causes interactions with the cell nucleus that translating to modifications in gene expression related to dense tissue formation and ossification.^{21,22} Through this effect, PBMt has been known to influence not only cell viability but also the expression of collagen 1, osteocalcin, bone morphogenetic protein-2, alkaline phosphatase, bone sialoprotein in osteoblasts.²³⁻²⁵ The second mechanism relates to the effect of PBMt on macrophage polarization where in the same alteration in mitochondrial activity affects the proinflammatory and anti-inflammatory protein expressions in macrophage cells. Studies have shown that PBMt is capable favoring the transformation of macrophages into M2 phenotype which alleviate inflammation and promotes tissue repair and remodeling.^{1,26}

Current literature regarding the use of PBMt for bone regeneration is mainly sourced from orthodontic applications reporting the suitability of the procedure for reducing pain and inflammation,^{26,27} periodontitis management,^{26,28} and bone remodeling during tooth movement.^{29,30} However, independent studies are still being conducted regarding the use of PBMt for regenerating critical sized bone defects in animal models,³¹⁻³³ enhancing results of distraction osteogenesis,^{34,35} regenerating irradiated bone,³⁶ repair bone lesions,³⁷ manage osteoporosis,^{38,39} and resolve osteonecrosis.⁴⁰⁻⁴²

PBMt COMBINED WITH OTHER ENERGY BASED THERAPEUTICS

Studies regarding the use of PBMt in conjunction with other energy-based therapy have also been conducted for ABR to a limited extent. The concept of combined energy-based therapeutics mimics the trend in biomedical material development in which combinations thereof or composites are tested to determine possible advantages within the same context. For the most part, PBMt is paired with LIPUs and more commonly compared with PMFs. This is probably due to the fact that PBMt and PMFs are both electromagnetic radiations that both exists in a spectrum although at drastically different wavelengths. On the other hand, LIPUs is high frequency vibrations that travel across tissues and does not carry photon

energy, making it a suitable complementary physical stimulation for tissues and cells.

The combination of LIPUs and PBMt have been studied as cumulative alternating treatment for improving bone consolidation during distraction osteogenesis,⁴³ remodeling bone during tooth movement⁴⁴ and post-osteotomy tibial bone regeneration.⁴⁵ These studies primarily concentrate on the synergistic effect of both treatments with LIPUs improving cell infiltration and viability; and PBMt promoting osteogenesis and reducing inflammation.

PBMt COMBINED WITH IMPLANTABLE MATERIALS

Aside from the combined application of PBMt with either LIPUs or PMFs, it has also been tested out together with synthetic and biologically derived implantable materials for bone regeneration. This was brought about by the initial success from the use of PBMt for treating disease and wound in different tissue types. Since the start of the 21st century, PBMt has been applied as a supplementary procedure in some studies that makes use of biomaterials, drugs, grafts, and cell seeded tissue scaffolds for bone regeneration.

Relatively recent publications applying PBMt on bone implants focuses on both the stimulatory effect on the bone defect and the photothermal effect on the implant material. Case in point, the use of magnetic particles (strontium hexaferrite)⁴⁶ and hydrogenated black titanium oxide coating⁴⁷ both improve bone regeneration and simultaneously ablate cancer cells through hyperthermia upon exposure to near-infrared laser. Under this context the researchers makes use of a non-ionizing light en-

ergy to promote bone tissue repair whilst killing tumor cells with heated implanted biomaterial. The use of black phosphorous together with PBMt as bone implants has also been investigated. Subsequent publications have reported the usability of near-infrared light not only as stimulation for tissue repair but also as a photothermal release mechanism for strontium chloride⁴⁸ and microsphere drug carriers⁴⁹ for bone regeneration.

Osteoporosis treatment through use of simvastatin and alendronate have also been tested together with PBMt where in reports indicated enhanced cell viability and bone formation.^{50,51} Similarly, studies about post-surgery PBMt of bone defects implanted with autogenous bone grafts,⁵² non-autogenous bone^{53,54} implants, and fibrin sealants^{55,56} confirm the benefits of the said treatment in terms of bone regeneration and implant integration.

The use of biologics such as stem cells^{39,57} and platelet concentrate alongside PBMt were also explored for ABR in independent studies. The observed increased bone regeneration benefited from PBMt enhancing stem cell viability whilst improving anti-inflammatory response in animals treated with platelet concentrate respectively.

FUTURE OF LLLT/PBMt FOR AUGMENTED BONE REGENERATION

The considerable number of studies conducted using PBMt has expanded the coverage of this energy-based therapeutic to include bone tissue. Fig. 1 summarizes the notable treatments combined with PBMt for augmented bone regeneration. However, the abundant investigations appear to symptomatic of several issues that still needs to be addressed within the experimental framework of using

Fig. 1. Schematic diagram showing the several notable treatments/approach for bone regeneration in combination with photobiomodulation therapy (PBMt) and the resulting effect. LLLt, low-level laser/light therapy.

PBMt for regenerative medicine. This becomes particularly noticeable with regards to examining factors such as light/laser wavelength, dosimetry, and hardware used for PBMt. Possessing a wide-range tunable laser would be ideal for verifying the effects of the different laser/light wavelengths at specific doses but then again this would probably significantly raise the cost of conducting such experiments. This is probably why this type of definitive investigation is yet to be conducted. As a result, the parameters for assessing the PBMt is yet to be established and until then investigators would be limited to relying on existing literature to pick out experimental settings. In addition, corroborating the results of independent studies is also rather complicated since the efficacy of PBMt is chiefly reinforced by empirical/observational data. Granting that probable mechanisms have been proposed as to how PBMt enhances tissue regeneration, these investigations will remain handicapped until a more conclusive intracellular process can be directly linked PBMt. Even so, the extensive queries regarding the added value of using red to infrared spectrum of photonic energy for regenerative purposes will continue to grow with biomaterials, pharmaceuticals, and treatment technique further develop. As technology mature and hardware for energy-based therapeutics become more available, widespread adaptation of these types of treatments for regeneration is inevitable even for deep seated hard tissue like bone.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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