Biophysical stimulation in the regeneration of musculoskeletal tissue: interesting, but... are we there yet? A narrative review.

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ABSTRACT

Purpose: This paper aims to evaluate the scientific evidence on the role of biophysical stimulation in the regeneration of musculoskeletal tissue and its current clinical applications, and to discuss potential future directions in this field.

Methods: A narrative review of electronic databases was conducted focusing on research articles dealing with biophysical stimulation and regeneration of musculoskeletal tissue published in English within the decade ending 1 February, 2026.

Results: Inclusion and exclusion criteria yielded a final selection of 273 sources: 151 in vitro studies and 122 original articles and clinical trials. The data from these sources are evaluated and discussed, highlighting the main results of a set of the most relevant and representative papers in order to provide an overview of the state of the art on the topic.

Conclusions: Biophysical stimulation, supported by an increasing number of studies that describe its pro-regenerative effects on both skeletal and extra-skeletal tissue, is emerging as a potentially useful therapeutic tool in numerous musculoskeletal disorders. However, examination of the scientific literature shows that in vivo studies on the use of biophysical stimulation for pro-regenerative purposes continue to yield heterogeneous results. Accordingly, biophysical tissue stimulation remains a challenge for the research community and an evolving horizon for the future of regenerative medicine.

KEYWORDS

Biophysical stimulation, regenerative medicine, physical therapy, orthopedic rehabilitation.

Introduction

Biophysical stimulation is a non-invasive therapy involving the delivery of non-ionizing physical energy to a biological system in order to promote anabolic processes and tissue repair. First approved by the FDA in the United States in 1979 for the treatment of delayed fracture healing, this approach has since undergone significant changes driven by substantial technological advances [1]. Growing evidence over the past decades regarding the *in vitro* effects of biophysical stimulation on both skeletal and extra-skeletal tissue has led research to focus on possible new applications in clinical practice, particularly in the context of regenerative medicine, one of the frontiers of future personalized and precision medicine [2]. Various scientific studies have suggested that different physical stimuli, applied under specific biophysical conditions, can promote and direct the differentiation of stem cells toward specific cell lineages. This opens up interesting new perspectives, both in the research setting—where such stimulation may substantially support tissue engineering and nanobiotechnology applications in regenerative medicine—and in future clinical practice in the field of musculoskeletal and joint disorders [3]. These aspects are undoubtedly interesting. Nevertheless, with regard to the objective of biophysical stimulation-driven tissue regeneration, it is now fair and necessary to ask: are we there yet? Has the gap between preclinical and clinical evidence been bridged?

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To address these questions, we conducted a narrative review of the scientific literature on the use of biophysical stimulation for regenerative purposes.

Materials and Methods

A narrative review was conducted, starting with a search of the MEDLINE, PubMed, EMBASE, and Google Scholar databases using the following search strings: "Biophysical Stimulation" [Mesh] OR "Physical Therapeutics" [Mesh] AND "Musculoskeletal Regeneration" [Mesh] OR "Regenerative Medicine" [Mesh] OR "Cartilage Repair" [Mesh] OR "Joint Restoration" [Mesh] OR "Regenerative Rehabilitation" [Mesh]. We considered articles published in English during the decade ending 1 February, 2026. Eligible studies included original articles, trials, case series, reviews, book chapters, and *in vitro* studies addressing the main topic and containing the abovementioned keywords. Commentaries, opinion pa-

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pers, letters to the editor, and editorials were excluded, as were non-English sources and studies for which the full text was not available. The web-based software system RobotAnalyst, an AI tool that combines machine algorithms for contextual organization of references, was first used to pre-screen the articles that met the defined inclusion and exclusion criteria; thereafter, selected articles were screened by the author to confirm eligibility for inclusion in the review and full texts were examined. The data from the sources were then evaluated and discussed, highlighting the main results of a selection of the most relevant and representative papers in order to provide an overview of the state of the art on the topic.

Results

The initial search across the mentioned databases and the preliminary screening using RobotAnalyst yielded 496 sources. After applying the exclusion criteria and screening the papers by title and abstract, the final selection for this narrative review comprised 273 sources: 151 *in vitro* studies and 122 original articles and clinical trials. Considering the heterogeneity of the aspects covered in the selected articles, we focused on those most prominently highlighting the actual or potential clinical application of biostimulation-based physical therapies. We further focused on articles emphasizing future perspectives and development areas of biophysical stimulation in the context of musculoskeletal regenerative medicine.

Discussion

Preclinical and clinical evidence for biophysical stimulation in musculoskeletal regenerative medicine

Several *in vitro* studies highlight the plasticity of mesenchymal stem cells, which can be modulated through signaling pathways, transcription factors, or microenvironmental cues. Under *in vitro* conditions, it has been shown that committed cells can be induced to adopt alternative fates [4]. However, the path from bench to bedside comprises several stages, starting with a deeper understanding of both the biology underlying mesenchymal cell plasticity—which could provide a roadmap for promoting regeneration—and the mechanisms of the crosstalk between microenvironments and regenerative pathways [5]. In recent years, bone, cartilage, and soft tissue microenvironment regulation has been suggested to be crucial for efficient stem cell-mediated tissue regeneration [5,6]. This “pro-regenerative” regulation of local microenvironments in regenerative medicine, including advanced therapeutic strategies such as cell-based therapies, gene editing, bioengineered scaffolds, and biomaterial innovations, also seems to be influenced by appropriate use of external biophysical stimulation [7]. Clinical biophysics is the discipline that studies the relationship between non-ionizing physical energy and the human body [8]. From a biological point of view, biophysical stimulation acts mainly at the level of the cell membrane, where physical stimuli are converted into biological signals and transmitted to intracellular signaling pathways [9]. Non-invasive biophysical stimulation devices of several kinds have received US FDA approval for orthopedic applications and are classified into: electromagnetic energy applied via coils (pulsed electromagnetic fields, PEMFs), electrical energy applied directly to tissue via adhesive electrodes (capacitively coupled electric fields, CCEFs), ultrasound energy (low-intensity pulsed ultrasound system, LIPUS), extracorporeal shock wave therapy (ESWT), and low-level laser therapy (LLLT) [2, 10]. PEMFs were the first form of biophysical therapeutic stimulation studied and, to date, have been extensively investigated in preclinical *in vitro* and *in vivo* studies and level I clinical studies. The biological and clinical response is related to physical wave features—i.e. pulse shape, frequency and amplitude—and is dose-dependent. In this regard, all forms of biophysical stimulation share the presence of a “window effect”—on osteogenesis for example— related in particular to four parameters: intensity, frequency, waveform, and duration of the biophysical stimulus. These represent the basic parameters that the clinician must consider when implementing therapy of this kind. Preclinical studies have assessed the anabolic effects of PEMFs on articular cartilage, subchondral bone, and synovia: PEMF therapy has been found to be capable of enhancing cell proliferation in chondrocytes and synoviocytes in articular cartilage explants and animal models, promoting extracellular matrix production and down-regulating chondrocyte apoptosis and inflammatory intra-articular cytokines [9,10]. In stem cells, PEMFs have been shown to help regulate cell fate through calcium-mediated pathways, enhancing chondrogenesis [11]. Moreover, PEMFs potentiate the chondrogenesis of bone marrow mesenchymal stem cells and stimulate effective cartilage repair by regulating the Wnt/β-catenin signaling pathway [7,12]. Another form of biophysical stimulation that has been the focus of several studies in the last 20 years is ESWT, with growing evidence supporting its application in many musculoskeletal conditions [9]. ESWT is characterized by specific acoustic shock waves that carry energy capable of producing intracellular and extracellular responses in biological systems; in particular, from a regenerative perspective, many studies have shown that shock wave therapy can promote cell proliferation and tissue regeneration in numerous musculoskeletal injuries [13]. More recently, other physical therapies have emerged as useful tools to promote tissue regeneration; for example, LIPUS and CCEFs, which, *in vitro*, have shown the ability to enhance chondrogenic differentiation and matrix production, acting via partially understood mechanisms, including inhibition of the TNF signaling pathway [7,14]. With regard to electrical and biophysical stimulation in musculoskeletal regenerative processes, another increasingly prominent strategy in recent years is the use of piezoelectric scaffolds. These are materials that convert physical (mechanical) forces such as focused ultrasound into localized electrical cues to activate mechanosensitive and voltage-gated channels that trigger early regenerative signaling pathways. These phenomena have been well described *in vitro*, promoting further studies on the subject [15]. Another research field offering increasing preclinical evidence on musculoskeletal and joint regeneration has investigated the effects of different physical stimuli on the transition zones between different tissues, which are characterized by changing physical, mechanical, and biochemical properties. Although understanding of these aspects remains partial, studies suggest that adequate biophysical stimulation of these zones may play a crucial role in promoting biological regeneration [16].

From bench to bedside: a "wobbly" bridge between biological and clinical evidence

Beyond these new strategies for joint regeneration, attempts to regenerate cartilage *in vivo*, especially large cartilage defects, are generally unsatisfactory, mainly because the restored cartilage does not have the same resistance to biomechanical loading as genuine articular cartilage [17]. Similarly, the scientific literature review highlights a relative lack of studies documenting musculoskeletal tissue regeneration *in vivo* following the administration of forms of physical therapy that have shown anabolic and tissue regeneration activity *in vitro* [2,18]. This discrepancy is mainly attributed to incomplete knowledge of the optimal parameters for *in vivo* tissue stimulation and the appropriate dosage of biophysical stimulation for the treatment of different pathological conditions. Clinical biophysics research may, in the near future, focus on this aspect as an interesting field of study; several studies have already shown that the therapeutic specificity of biophysical stimulation is intrinsically related to the specificity of the administered signal [2,8]. In addition, the different forms of biophysical stimulation share common biochemical pathways, particularly in reparative osteogenesis, albeit via different and potentially synergistic mechanisms of action; however, understanding of the precise interaction between different stimuli and how to use them properly and synergistically for therapeutic purposes remains inadequate [18,19]. The heterogeneity of the therapeutic protocols across studies is a further major limitation that precludes definitive conclusions concerning the clinical application of biophysical stimulation modalities that have shown significant results in preclinical studies. However, the growing number of clinical trials addressing aspects such as *in vivo* dosage, interaction between physical and non-physical stimuli, and interaction between different physical stimuli applied directly to patients' tissues offers an encouraging outlook for understanding the clinical potential of biophysical stimulation.

Future directions and regenerative rehabilitation

As previously described, one of the main challenges in this field is to obtain a deeper understanding of the interactions andamong physical, mechanical, and biochemical factors in regenerative processes, first *in vitro* but later *in vivo*, including the biological effects of rehabilitative exercise. From this perspective, the expanding field of regenerative rehabilitation—defined as "the application of rehabilitation protocols and principles together with regenerative medicine therapeutics toward the goal of optimizing functional recovery through tissue regeneration, remodeling, or repair" [20]—could represent a significant evolution. Rehabilitation interventions, including biophysical stimulation therapies within a primarily exercise-based individual rehabilitation program, can have pro-regenerative effects mediated through mechanotransduction phenomena. These phenomena can, among numerous other effects, promote chemical and mechanical modulation of local stem cell microenvironments, direct stem cell differentiation, mobilize stem cells into circulation, and promote the secretion of regenerative factors [20]. Therapeutic exercise also acts by modulating the expression of numerous chemokines involved in anabolic and catabolic processes, including those that influence the expression of the so-called gerozymes, a class of enzymes that increase with age and contribute to the functional decline of tissues. In this regard, promising recent data on the pharmacological inhibition of some gerozymes show that administration by injection of an inhibitor of the gerozyme 15-PGDH—a protein that degrades prostaglandin E2—in animal models and in osteoarthritic human tissue explants can rejuvenate muscle and regenerate cartilage [21]. A better understanding of these underlying mechanisms would enable a translational approach to cellular mechanobiology, allowing the design of personalized and precision rehabilitation treatments integrated with regenerative medicine to enhance patient outcomes [22-24]. The opportunity to guide the process of tissue healing and repair, and even true tissue "regeneration," constitutes a significant cornerstone in the treatment of musculoskeletal diseases and in rehabilitation medicine, where functional recovery—the true therapeutic/care target—is closely linked to biological recovery and repair. Furthermore, the inclusion of therapeutic exercise, the main rehabilitation tool, in the treatment plan of patients undergoing stem cell therapy or other regenerative medicine interventions may be relevant for improving function and quality of life in patients accessing regenerative medicine services.

Conclusions

From a translational medicine perspective, the path from research to clinical application of innovations in biophysical stimulation for regenerative therapies is still emerging, but thanks to continuous technological development, this goal is increasingly within reach, offering a challenging prospect for the near future of regenerative medicine. However, our review of the scientific literature suggests a relative disconnect between the results of *in vitro*/preclinical studies and clinical evidence, indicating that further clinical research and high-quality clinical trials are needed. For this reason, the question asked in the title of this paper cannot at present be answered affirmatively. Nevertheless, the use of various types of biophysical stimulation in current clinical practice—for example, ESWT, PEMFs, CCEFs, LIPUS, and LLLT—continues to grow, supported by an increasing body of research. Future research in this field should be oriented toward gaining deeper insight into the interaction between different types of pro-regenerative tissue stimulation as well as a better understanding of the parameters of biophysical stimulation when applied directly to patients in clinical practice.

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