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Review

Myths and truths on biophysics-based approach in rehabilitation of musculoskeletal disorders

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***Abstract*:** Musculoskeletal disorders (MSD) are a crucial issue in current literature due to their impact on physical function, social, and economic costs. Rehabilitation plays a pivotal role in the therapeutic management of these disabling conditions with growing evidence underlining positive effects in improving functional outcomes. However, to date, several questions are still open about the mechanisms underpinning functional improvements while recent research is now focusing on a deeper understanding of the biophysical processes underpinning the macroscopical effects of these treatments. Thus, this narrative review aims at providing a comprehensive overview about the state of the art of biophysical dimensions of currently available treatments for MSD. PubMed, Scopus, CENTRAL, PEDro, and Web of Science were searched between March 2022 and October 2022 for *in vitro* and *in vivo* studies, clinical trials, systematic reviews, and meta-analysis addressing the issue of biophysics-based approach in rehabilitation of MSD. Our findings showed that a biophysical approach might be integrated into regenerative rehabilitation, aiming at enhancing regenerative processes by mechanical and biophysical stimuli. In addition, a biophysical-based approach has been proposed to improve knowledge about several instrumental physical therapies, including shock wave therapies, low-level laser therapy, ultrasound, short-wave diathermy, electrical stimulation, pulsed electromagnetic field, and vibration therapy. In accordance, emerging research is now focusing on the biophysical properties of several medical procedures to improve pain management in patients with MSD. Taken together, our results showed promising results of the integration of a biophysical-based approach in rehabilitation, albeit several limitations currently limit its implementation in routine clinical setting. Unfortunately, the state of the art is still inconclusive, and the low quality of clinical studies based on the biophysical approach did not provide clear treatment protocols. Further studies are needed to promote a precise rehabilitation approach targeting biological modification and enhancing the functional improvement of patients with MSDs.

Keywords: biophysics, musculoskeletal disorders, pain, regenerative medicine, rehabilitation

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Introduction

Musculoskeletal disorders (MSD) are highly heterogeneous conditions affecting muscles, tendons, bones, cartilage, ligaments, joints, and nerves, characterized by musculoskeletal pain and decrease in physical function.[1,2] To date, MSDs are very common across the population and represent a significant burden in terms of global health, social, and economic cost.[1,2] In particular, low back pain represents the ninth cause of increased global disability-adjusted life-years in all ages, while osteoarthritis is the 18th cause between 50 and 74 years of age. During the last decades, these pathologies have been following a growing trend for disability burden, as underlined by the Global Burden of Disease Study in 2019.[3]

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In this context, Physical and Rehabilitation Medicine (PRM) is a branch of medicine that aims at improving functional ability and quality of life of patients with physical impairments or disabilities.[4] Although the macroscopical effects of rehabilitation intervention are fully supported by evidence, to date, several questions are still open about the mechanisms underpinning functional improvements.[5–7] In this scenario, biophysics, as the science studying biological systems and biological processes through physics laws,[8] could have a crucial role in understanding how to exploit several physical properties to achieve pain control and healing.[9] On the other hand, a deeper understanding of the biophysical processes, the molecular processes affecting biological factors, and underpinning macroscopical effects of the routinely used rehabilitation intervention might guide clinicians in tailoring effective therapeutic treatments based on biological modifications, enhancing a personalized approach in PRM.[10–12]

Although conclusive data for their mechanism of action are still lacking, treatments based on biophysical properties are routinely administered in PRM. However, to our knowledge, no previous study highlighted the importance of a broad biophysical-based approach in the rehabilitation of MSD and temporomandibular disorders (TMD).

Thus, the aim of this narrative review was to provide a comprehensive overview about the state of the art of biophysical dimensions of currently available treatments for MSD, to promote evidence-based implementation and develop personalized strategies for the multidisciplinary management of these patients.

Methods

This narrative review was carried out in accordance with the Scale for the quality Assessment of Narrative Review Articles (SANRA) quality criteria.[13] It has been performed after a scientific literature research on five different databases (PubMed/Medline, Scopus, Cochrane Central Register of Controlled Trials, Physiotherapy Evidence Database, and Web of Science). These databases were searched for the following keywords: 'Biophysics', 'Biophysics-based approach', 'Biophysical Therapy', 'Biophysical treatment', 'Rehabilitation', 'Regenerative Rehabilitation', 'Regenerative medicine', 'Musculoskeletal disorders', 'Musculoskeletal pain', 'Joint pain', 'Instrumental therapy', 'Physical therapy', 'Medical procedures', 'Injections', 'Neuromodulation'. The literature research has been performed independently by two different reviewers between March 2022 and October 2022. All the studies were screened by two independent reviewers screened the studies for eligibility. A third reviewer was asked if consensus between the two reviewers was not reached through discussion.

We considered both *in vitro* and *in vivo* studies, clinical trials, systematic reviews, and meta-analysis assessing a biophysical approach in MSDs. We excluded all the studies in languages other than English, studies without full text available, conference abstracts, masters, or doctorate theses. A qualitative synthesis of all data extracted has been performed by two reviewers. In case of disagreement, a third reviewer was asked if consensus was not reached by collegial discussion.

History of biophysical approach in medicine

Biophysics is the application of physics aiming at understanding the mechanisms of how biological systems and biological processes work.[8]

Some early biophysical considerations can be traced back to ancient Greek culture, with the earliest theories of life processes and their dynamics. Subsequently, in Renaissance times, mechanical principles were applied for the understanding of movements across the animal kingdom, from walking, to swimming, to flying, for example in the works of Leonardo da Vinci (1452–1519) and Alfonso Borelli (1608–1679).[14] Later, electrical and thermodynamic knowledge was applied in biological studies, in the work of Luigi Galvani (1737–1798). Other scientists, whose works contributed to the development of first physiology and then biophysics between the 18th and 19th centuries, were A. L. Lavoisier, P. S. Laplace, Thomas Young, and Hermann von Helmholtz.[14] In this scenario, the term biophysics was coined by the English mathematician and biostatistician Karl Pearson in 1892, when he used it in his book 'The Grammar of Science' to address the needing for 'a branch of science [. . .] dealing with the application of the law of [. . .] Physics to the development of organic forms'.[15]

A further important step toward the development of biophysics identity as an independent science was the discovery of X-rays and their application to medicine, which required close collaborations of physicists, biologists, and medical scientists.[14] With the background of World War II, an increase in sophisticated scientific tools led, then, to a growth in biophysical research and knowledge.[16] In this context, the 1943 lecture called 'What is Life?' by Erwin Schrödinger paved the road for thermodynamics studies in living systems.[14]

Finally, the Biophysical Society was born in the 1950s, contributing to the rise in scientific activities and knowledge, leading to modern biophysics that encompasses studies on data analysis and structure of DNA, computer modeling, molecules in motion around the cell, neuroscience, bioengineering, nanotechnologies, biomaterials, diagnostic medical imaging, medical applications (such as dialysis, radiation therapy, cardiac defibrillators, pacemakers, and artificial heart valves), and ecosystems.[16]

Biophysics in regenerative rehabilitation

In the recent years, there has been a growing interest in regenerative medicine aiming at enhancing tissue repairing or replacement, through the stimulation of the activity of endogenous stem cell function and/or through the transplant of exogenous stem cells.[17] Understanding biochemical and biophysical factors represents a crucial step toward the success of regenerative medicine approach.[18] On the other hand, PRM focuses on mechanical and biophysical stimuli to restore body function.[17,18] Given the multilevel overlapping of regenerative medicine and rehabilitation, the combination of these two synergetic disciplines created the regenerative rehabilitation approach, defined as 'application of rehabilitation protocols and principles together with regenerative medicine therapeutics toward the goal of optimizing functional recovery through tissue regeneration, remodeling, or repair'.[18] Interestingly, it has been proposed that regenerative rehabilitation might have a role in enhancing tissue and functional restoration, after a damage caused by several causes, including aging, trauma, sickness, or congenital processes.[19]

In this scenario, growing efforts have been made for understanding the biophysical mechanisms promoting regeneration in rehabilitation. More specifically, mechano-transduction plays a key role in influencing gene expression. Cells, in fact, are surrounded by extracellular matrix that conveys biophysical signals in the form of pressures, tensile and compressive forces, shear stresses, and electrical stimuli. They are transmitted from cell's membrane to the nucleus, by means of cytoskeleton, regulating gene expression.[19] For example, at cartilage level, chondrocytes gene expression is stimulated by shear loading in the absence of exogenous growth factor; mesenchymal stem cells are also stimulated to secrete transforming growth factor-β, which plays a pivotal role in chondrocytes homeostasis.[19,20] Taken together, physical exercise has a chondroprotective role. This knowledge could translate clinically to the application of rehabilitation protocols to stimulate native mesenchymal stem cells in the presence of cartilage damage.[20] On the other hand, bone-level responses and adaptations to load application are well established, as stated by Wolff's law,[20] although, to date, molecular pathways remain unclear.[19] The concept of mechanical environment for bone healing has led to the idea of 'Reverse Dynamization', still representing a controversial topic in current literature. This is based on the knowledge that bone heals through an endochondral phase that benefits from load; hence, hypothetically, initial bone healing would benefit from axial loading, while in later phases, when bone formation replaces cartilage, excessive movements prevent angiogenesis, and increased stiffness would be more beneficial.[19] Thus, loads applied during the rehabilitation period might be adapted to the timing of bone healing to optimize biophysical interactions with bone healing and maximize functional recovery.[20] Interestingly, skeletal muscle system is a target for a biophysical approach also at muscular level, where physical exercise has been proven to help the proliferation of transplanted stem cells for repairing muscle injuries.[20]

In addition, regenerative medicine has recently been considered a therapeutic option to achieve functional recovery in neurological lesions.[21] However, to date, preclinical research has been inconclusive in the implementation of regenerative rehabilitation, highlighting the need for a deeper understanding of single therapeutic mechanisms before analyzing their combinations.[21]

Altogether, the data underlined that several promising results were reported in scientific literature about the effects of regenerative rehabilitation.[22] However, it should be noted that most of the knowledge derives from *in vitro* and animal studies, while there is still a large gap of knowledge in translational research integrating preclinical discoveries in clinical settings. Therefore, further studies need to enhance biophysical integration in clinical settings to optimize multidisciplinary management of MSDs tailored to the biological process characterizing the different diseases.[19,22]

Physical agent modalities for musculoskeletal and TMD

Physical agent modalities are adjuvant therapies fully integrated in the comprehensive rehabilitation management of MSDs aiming at improving functional recovery and relieve pain.[23] Several instrumental therapies are currently available in the current literature, including therapies based on heat, light, sound waves, and electricity, with both preclinical and clinical studies supporting the promising effects of these therapies.

To date, shock wave therapies have been recently implemented in the rehabilitation management of MSDs to enhance repair and formation of new bone, tendon, and other soft tissues.[24] This instrumental physical therapy modality might interfere with the transmission of the painful impulse, and it can break down the inflammatory patterns linked to calcifications.[24] Focal shock waves are single pulsation acoustic waves generated in a microsecond by an external source and concentrated on a specific body site, without loss of energy. The radial shock waves are pneumatic waves, distributed radially to the body through an applicator[24–26]; moreover, they could also be successfully used as an adjunctive therapy not only for musculoskeletal diseases[27] but also for myogenous TMD.[28]

Low-level laser therapy is administered through a single wavelength, between 390 and 1600 nm (involving visible red and near-infrared portions of the electromagnetic spectrum), directed toward the painful area enough to produce stimulation, but not heating of the target system.[29] To date, however, the studies that have evaluated its effectiveness in low back pain have had inconsistent results.[30] Two recent systematic reviews with meta-analysis performed by our group evaluated the role of physical agent modalities in the management of both myogenous[31] and arthrogenous[32] TMD patients, reporting the significant efficacy of laser therapy in terms of pain relief.

Ultrasound is widely used in the treatment of many musculoskeletal pain syndromes, usually in combination with other physical therapies, with the rationale that deep tissue warming can bring about various local benefits. Therapeutic ultrasound works by delivering sound waves to the target tissue, causing thermal and mechanical effects, and generally, there are two common frequencies: 3 and 1 MHz. Three megahertz is being transmitted rapidly out of the probe, and it is penetrating the tissue interface very fast with a short wavelength. In general, the depth would be less than or equal to 2 cm or less. If the goal of the treatment is to go deeper, then a 1 MHz setting should be used. That slower frequency allows more of the ultrasound wave to be absorbed by the deeper tissues.[33] As a result, local cellular metabolism, circulation, extensibility of connective tissue, and tissue regeneration are thought to be stimulated. However, a recent Cochrane review found uncertain evidence regarding the effect of therapeutic ultrasound on pain in individuals with chronic nonspecific low back pain.[33] More studies on MSD are warranted.

The short-wave diathermy is classified as an endogenous thermotherapy, and it works by exploiting electrical currents, generated by capacitive or resistive mono-polar radiofrequency at 448 kHz. The proposed mechanism of action is an increase in blood flow caused by the thermal effect, which results in a healing process that decreases pain and improves function in MSD.[34] Although the literature is scarce in clinical studies about the efficacy of this treatment, some promising results are present,[35] which indicates that this technique should be further evaluated.

There is evidence that the electrical stimulation of peripheral nerves is able to modulate pain by altering its nerve conduction. Transcutaneous electrical nerve stimulation (TENS), which generates continuous electrical impulses through surface electrodes, could have an effect by activating opioid receptors and by controlling central pain pathways.[36] On the other hand, a recent Cochrane review on the effect of TENS in chronic pain underlined the low quality of evidence present in the literature, thus, without obtaining a conclusive position.[37]

Approaches based on magnetic fields thought to be involved in this action are the electronic interactions which cause vasodilatation, analgesic, anti-inflammatory, anti-edematous and spasmolytic activity, and eventually healing acceleration.[38] Frequencies that are commonly used in the clinical practice fall between 1 and 100 Hz, with a magnetic flux density up to 100 mT.[38]

In particular, pulsed electromagnetic field (PEMF) therapy is a magnetotherapy that uses pulsed magnetic field and has been shown to prevent cartilage degeneration and maintain subchondral trabecular bone microarchitecture. Interestingly, a recent meta-analysis of randomized clinical trials on patients with osteoarthritis concluded that PEMF therapy had significant beneficial effect on pain, stiffness, and physical function.[39,40] Lastly, *in vivo* studies on endogenous electric fields of skin wound highlighted their role as potential target for promoting wound healing.[41]

Vibrational therapy is a technique used in rehabilitation that aims at improving proprioception and muscle strength, with results depending on the frequency of stimulation, varying from 50 to 300 Hz.[42–44] There could be whole body vibration therapy, in which exercise is performed on a vibrating platform, or focal vibration therapy, focused on a muscle or a group of muscles.[42,43] A systematic review published in 2009 underlined that knowledge on whole body vibration is still weak and more high-quality studies are needed to comprehensively evaluate this therapy.[45] On the other hand, a recent systematic review showed that focal vibration could be an effective means of motor conditioning in healthy individuals.[44] Although some beneficial effects were reported after focal vibration therapy alone or in combination with other physical therapies,[42,43] there is still a gap of knowledge on applications in pathological conditions.

Biophysics and medical procedures in musculoskeletal disorders

To date, emerging research is now focusing on the biophysical proprieties of several medical procedures to improve the management of musculoskeletal pain in the field of PRM. Medical procedures might have the advantage of precisely targeting a specific tissue inducing specific biological modification with both a pharmacological and non-pharmacological approaches.

In this scenario, joint injection of hyaluronic acid (HA) is a very common clinical practice currently accepted by several international guidelines for the therapeutic management of osteoarthritis.[46,47] The intraarticular injection of HA precisely targets the biophysical alteration characterizing joint degenerative diseases, increasing the viscoelastic properties of synovial fluids and its protective action on joint tissues. Moreover, the transmission of mechanical forces is involved in mechanical damage characterizing osteoarthritis, affecting both cartilage degeneration and chronic inflammation in the joint.[48] The biophysical properties of HA, including its adhesivity, mechanical characteristics, and degradability, might severely affect both microscopical and macroscopical effects in clinical settings.[49] In particular, HA can modulate cell function by specific receptors present on cell surfaces (e.g. CD44 and receptor for HA-mediated motility) that might respond to different molecular weights and HA concentration, resulting in modulation of cells adhesion, migration, and proliferation.[49] On the other hand, improvement in the understanding of the biophysical effects of HA supplementation might have a role in the development of more precise identification of the optimal therapeutic administration of this interesting molecule improving not only the pain relief and physical function already supported in current literature, but also promoting potential interactions with the molecular pathways underpinning osteoarthritis.

In this scenario, growing literature is now focusing on platelet-rich plasma (PRP), a platelet concentrated from the centrifugation of autologous blood, which results in a concentrate of platelets devoid of other cellular components.[20,50] The therapeutic effects have been related to greater platelets concentrations that might activate endogenous repair process, interact with inflammation pathways through regulation of expression of crucial inflammatory interleukins such as interleukin (IL) 6 and IL-8, and enhance reparative processes through several growth factors activating mesenchymal stem cells.[20,50,51] Biophysical approaches in this field might improve knowledge about the biological effects of this promising technique, paving the way to a more precise PRP preparation, clarifying the optimal biological characteristics, dosage, and administration modalities.[52] A similar paracrine effect might be exerted by adipose stem cells (ASC), as adipose tissue is known to produce several cytokines regulating the inflammatory process.[53]

Adipose tissue is composed of preadipocytes, pericytes, fibroblasts, smooth muscle cells, endothelial cells, hematopoietic cells, mature immune cells, and ASC, fibroblast-like cells from the stromal vascular fraction. This population, isolated and locally injected, might secrete numerous trophic and growth factors enhancing the regeneration of both bone (*via* BMP-2 production) and cartilage (involving direct engraftment and trophic factors), although biological mechanisms are not completely understood.[54,55]

On the other hand, inflammatory processes might be effectively targeted by other medical procedures, including ozone therapy which has been progressively gaining interest in recent years. In more detail, oxygen–ozone (O_2O_3) therapy has been recently applied in patients with MSDs with promising antinociceptive and anti-inflammatory effects.[43,56–58] Albeit the mechanisms at the basis of its clinical efficacy have not been fully understood, several authors proposed that its oxidizing action might promote the transcription of proteins involved in the antioxidant response, with intriguing implications in the endogenous response to oxidative stress characterizing several chronic diseases.[57,59,60] Furthermore, low doses of O_2O_3 stimulate a direct anti-inflammatory effect by regulating the synthesis of inflammatory prostaglandins, and bradykinin and increasing their secretions by macrophages and leukocytes. In the context of musculoskeletal pain, O_2O_3 might not only promote an indirect anti-inflammatory effect, but also directly stimulates the production of endogenous serotonin and opioids that have a crucial impact on pain relief through antinociceptive transmission.[60] In addition, O_2O_3 seems to stimulate vasodilation and fibroblastic activity, improving the deposition of collagen and the initiation of a tissue repair process.[61] In addition, recent evidence suggested that O_2O_3 might break glycosaminoglycan chains in the nucleus pulposus of herniated disks, promoting a decrease in size of the herniated portion and inducing pain relief; thus, O_2O_3 therapy might be considered an effective complementary therapy in several MSDs.[60] However, a biophysical approach might further characterize the O_2O_3 therapy's biological action on patients with MSDs and clarify its role in a comprehensive rehabilitation approach for these disabling conditions.

Another medical procedure recently introduced in PRM management of MSDs is selective radiofrequency denervation, characterized by the destruction of nerves through the heat generated by a radiofrequency current.[62] In this minimally invasive approach, biophysical administration of a potential difference between a plate and a needle–cannula determines a thermal ablation of the neighboring tissues.[63] Therefore, precise needle–cannula positioning in the proximity of the target nerve is mandatory and several imaging techniques have been proposed to guide the procedure.[64] In the last century, radiofrequency has been used in the clinical management of different types of pain, from facial pain to spinal, pelvic, and appendicular pain.[65,66] Interestingly, a neuromodulation approach of pulsed radiofrequency has been proposed to target motor sensory nerves that cannot be damaged by thermal ablation given the functional consequences in motor function.[67] However, the biophysical basis of the macroscopical effects of pulsed radiofrequency has not been fully understood, despite recent research proposing that this minimally invasive therapy might impact in several pathways including nociceptive signals through the direct modulation of ion channels and the modulation of the release of neurotransmitters, including aspartate, citrulline, metenkephalin, and glutamate.[68,69] On the other hand, also postsynaptic receptors and synaptic function might be targeted by pulsed radiofrequency, resulting in neuromodulation of the afferent signals providing information to the brain cortex.[68,69]

Similarly, percutaneous electrical nerve stimulation (PENS) is a treatment technique that conducts electrical stimulation ranging from low (2–5 Hz) to high (80–100 Hz) frequency through fine needles. Pulse duration can also be modulated, ranging from 250 to 500 μs and targeting several tissues including dermal, muscle, or periosteal tissues.[70] The neuromodulation mechanisms underpinning the therapeutic effects of this medical procedure might include the electrical stimulation of large peripheral afferent nerve fibers that interfere with pain signaling from small pain fibers to the spinal cord, according to the gate control theory. Moreover, there could be activation of inhibiting descending pain pathways.[71] Nevertheless, a recent meta-analysis found low-quality evidence supporting the positive impact of PENS in musculoskeletal conditions, and the effect on pain intensity was limited to short term when compared to sham.[71]

Taken together, this evidence suggested that several medical procedures have been integrated into the rehabilitation management of patients with musculoskeletal diseases and TMD. In this context, a biophysical approach might have a role in optimizing the tailored management of MSDs and provide more high-quality evidence to better characterize the clinical effects in chronic pain that frequently characterize MSDs.

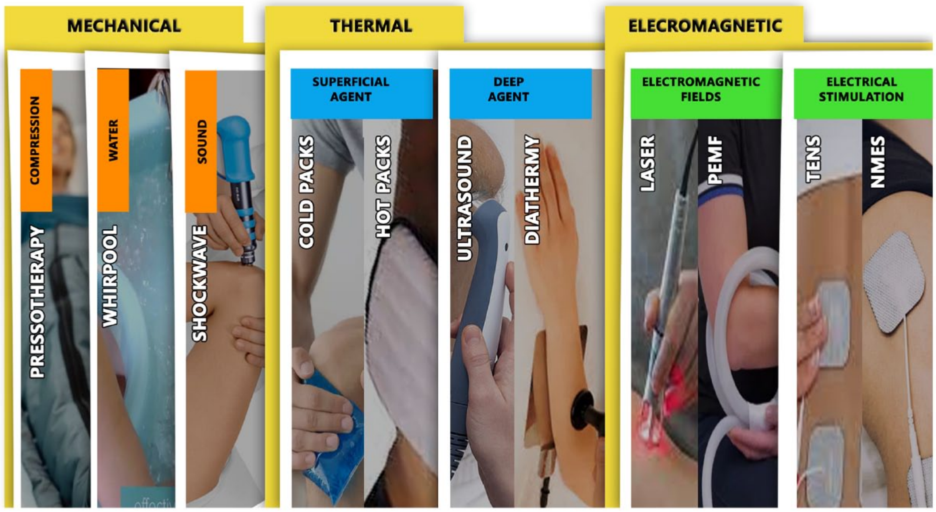

Figure 1. Biophysics-based rehabilitative approaches for musculoskeletal disorders.

Future prospective

The biophysical-based approach in the PRM field represents a suitable option to improve translational knowledge about the macroscopical effects of rehabilitation in patients with MSDs (see Figure 1 for further details).

In this context, a deeper understanding of the multiple pathways at the basis of biophysical processes might guide the prescription of a specific rehabilitation aiming at enhancing healing process and stimulating tissue anabolic activity.[72] However, it should be noted that despite promising results that have been reported, the current research community is far from providing specific indications about a precise personalization of rehabilitation based on biophysical stimuli on biological system.[73,74] On the other hand, it is widely accepted that precise biophysical stimulation should not be suggested in all patients, but adapted to the type of injury, risk factors, and/or clinical conditions in accordance with a patient-centered approach, while careful considerations of the potential synergisms between different biophysical stimuli might further enhance a specific tissue response, including osteogenic, chondrogenic, anabolic, and anti-inflammatory processes.[72,73]

In this context, there is a solid rationale for implementing prehabilitation to counteract biophysical changes in tissue proprieties related to specific conditions, such as immobilization, surgery, or cancer treatments.[75]

On the other hand, it should be noted that several limitations affect the utilization of this approach. The state of the art is still inconclusive, and the low quality of clinical studies based on the biophysical approach included in this review did not provide clear treatment protocols.

Moreover, the main limitation of this review is the lack of a deeper presentation of the several topics related to biophysics approach in rehabilitation. However, it should be noted that the aim was to provide a broad overview about the currently available literature on this topic, aiming at emphasizing the need for further studies that might have a role in promoting a more precise rehabilitation approach targeting biological modification and enhancing functional improvement of patients with MSDs.

Altogether, several controversies still exist about the optimal approach providing specific biophysical modifications in human tissues, leading to conflicting results.

Conclusions

Taken together, several barriers still affect the integration of biophysical-based treatments in the rehabilitation management of MSD. Despite remarkable efforts that have increased current understanding about the molecular mechanisms underpinning the macroscopical effects of rehabilitative interventions, the implementation of a biophysical approach is still a challenge in the rehabilitation field. On the other hand, the current evidence reported promising features of biophysical-based treatments, that might have potential implications in a focused therapeutic intervention aiming at optimizing functional recovery of patients with MSDs and targeting specific pathways underpinning the diseases.

Future studies are needed to improve knowledge in this emerging field providing additional evidence supporting a more tailored approach to MSDS triggering specific biological modifications and focusing resources on more precise therapeutic treatments.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Alessandro de Sire: Conceptualization; Methodology; Supervision; Writing – original draft.

Lorenzo Lippi: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Nicola Marotta: Data curation; Investigation; Writing – original draft.

Martina Ferrillo: Data curation; Formal analysis; Investigation; Visualization; Writing – review & editing.

Arianna Folli: Data curation; Visualization; Writing – review & editing.

Alessio Turco: Data curation; Visualization; Writing – review & editing.

Antonio Ammendolia: Investigation; Project administration; Writing – review & editing.

Marco Invernizzi: Investigation; Methodology; Supervision; Writing – review & editing.

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