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Review Article

Physical Medicine and Rehabilitation Section

Exploring the Dynamic Concept of Mechanobiology in Regenerative Rehabilitation: A Narrative Review

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ABSTRACT

Physical therapists, equipped with unique diagnostic and treatment capabilities, play a pivotal role in advancing regenerative medicine. The present review explores the integration of mechanotherapy and mechanical techniques in physiotherapy, shedding light on the burgeoning field of mechanobiology and its implications for rehabilitative therapies. A comprehensive literature search was conducted using various databases, including Google Scholar, PubMed, Scopus, Web of Science, and CINAHL. Initially, a total of 217 articles, including research papers, reviews, and systematic reviews, were identified. After thorough evaluation, 26 articles were deemed relevant to the present study. The authors analysed these selected articles to explore the utilisation of mechanotherapy, mechanotransduction, and the integration of mechanobiological principles into physiotherapy practice. Physiotherapists employ mechanotherapy and mechanical techniques, such as manual mobilisation and exercise interventions, to treat diseases and injuries and restore function. Mechanobiology studies the essential functions that these physical variables perform through mechanotransduction, while Mechanotherapies emphasise natural mechano-adaptation to promote healing. They are active mechano-interventions that transform possible damaging mechanical effects into therapeutic benefits. Therefore, interventions should be planned accordingly. The growing field of mechanobiology and regenerative medicine is opening new avenues for rehabilitative therapies. Applying mechanobiology principles to various body systems linked to physical therapy interventions provides scope for future research.

Keywords: Cardiorespiratory diseases, Mechanotherapy, Musculoskeletal diseases, Physical therapists, Regeneration

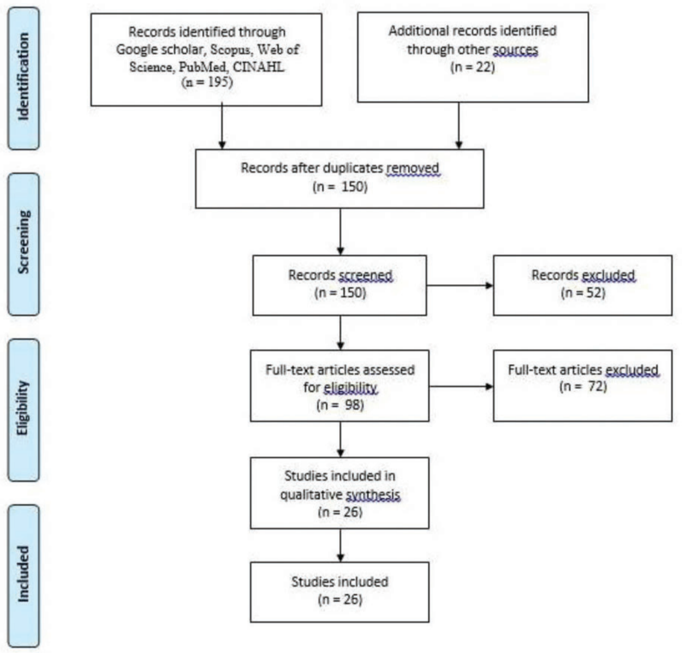
INTRODUCTION

Physiotherapy is effective in reducing disability and costs associated with various musculoskeletal, cardiovascular, respiratory, and neurological conditions. Physical therapy has proven its effectiveness in improving functional abilities, and current clinical practice guidelines advocate for non pharmacological interventions as the primary approach for initial management [1]. The aim of regenerative medicine is to restore tissue and organ function that has been lost due to age, trauma, or illness. It involves the regeneration of impaired tissues and organs within the body by either replacing damaged tissue or facilitating the recovery of previously irreparable tissues or organs. The principles of regenerative medicine hold the promise of enhancing organ function and enabling the regeneration of deteriorated tissues and organs [2]. Similarly, rehabilitation aims to promote tissue repair and enhance physical function. Therapeutic physical stimulation is often necessary for surrogate cells, tissues, or organs transplanted through regenerative medicine approaches to integrate and recover effectively. Rehabilitation therapists, basic scientists, physicians, and surgeons collaborate closely to develop specialised rehabilitation therapies aimed at improving tissue restoration. This approach is known as regenerative rehabilitation. Considering that regenerative medicine aims to restore or recover physiological function, individuals undergoing regenerative therapies will require rehabilitation to optimise their reconstructed anatomy and newly acquired abilities.

Physiotherapists possess specialised qualifications to diagnose and manage a range of conditions, making them valuable participants in the field of regenerative medicine. However, the role of physiotherapists goes beyond simply restoring cellular-level functioning after tissue recovery. In fact, physiotherapists have the potential to be trailblasers in the realm of regenerative rehabilitation [3]. Physiotherapists utilise mechanotherapy and mechanical techniques, such as manual mobilisation and exercise interventions, to treat diseases and injuries and restore function. While the implications of directed movements, as used in physiotherapy, are better understood at the organ and body level, numerous recent research studies have shown that directed movement also significantly impacts cellular activity and tissue adaptability [3,4]. Rehabilitation and regenerative medicine treatments have demonstrated improved outcomes for tissue regeneration [5]. By considering technologies and biological elements aimed at maximising healing potential, regenerative rehabilitation provides protocols for determining when to initiate treatment, the types of stimuli provided, and a graded exercise program. Commonly used physical therapy interventions have the potential to yield positive outcomes following the implementation of regenerative therapies [5]. There is a need for research aimed at identifying the most effective rehabilitation protocols that can optimise tissue healing and promote regeneration. Hence, the present review illuminates the emerging field of mechanobiology and its significance for rehabilitative therapies. Specifically, it explores the utilisation of mechanotherapy, mechanotransduction, and the integration of mechanobiological principles into physiotherapy practice.

Methodology

From 2012 to 2023, an electronic search was conducted in Google Scholar, PubMed, Scopus, Web of Science, and Cumulated Index to Nursing and Allied Health Literature (CINAHL). The search keywords used were mechanobiology, mechanotransduction, physical therapy, physiotherapy, and regenerative rehabilitation. Initially, a total of 217 articles, including research papers, reviews, and systematic reviews, were identified. After thorough evaluation, 26 articles were deemed relevant to the present study. The authors analysed these selected articles to explore the utilisation of mechanotherapy, mechanotransduction, and the integration of mechanobiological principles into physiotherapy practice. Only English language papers were included in the study for analysis and review. Articles with ethical concerns, conflicts of interest, duplicate publications, non peer-reviewed sources, and those that were not accessible were systematically excluded from the review. The following chart provides a step-wise selection of articles [Table/Fig-1].



[Table/Fig-1]: Flowchart showing selection method.

Understanding Mechanobiology and Mechanotherapy

Mechanical forces continually exerted on our bodies have a direct effect on cellular processes. Two examples include the impact of gravity on bone mineralisation and the effect of shear force on the development of atherosclerotic plaque in the vascular system [6]. Cells in bacteria, plants, and animals possess mechanosensors that can detect bending forces and changes in osmotic pressure [7]. Cells can respond to various forces, such as shear, tension, and compression, due to their sensitivity. In response to these forces, cells engage in activities such as proliferation, migration, tissue repair, metabolic changes, and even the differentiation and maturation of stem cells [8]. Mechanobiology studies the essential functions that these physical variables carry out through the mechanotransduction process. It also involves the mechanosensing mechanism, which uses mechanically altering protein structure to regulate cellular operations [9]. Three consecutive processes describe cellular mechanical phenomena: mechanosensing, which refers to a localised molecular response to alterations in force or geometry; mechanotransduction, which involves converting force- or geometry-induced changes into biochemical signals; and mechanoresponses, which entail cellular-level functional modifications through coordinated signal responses by mobile systems in the short-term. Mechanotransduction activates numerous signalling pathways, including but not limited to calcium levels, tyrosine phosphorylation, trimeric G proteins, inositol lipid metabolism, and small G proteins [10]. Mechanobiology studies can also be applied in drug development and translational medicine research [9].

According to the Oxford Dictionary, when mechanotherapy was initially described in the nineteenth century, its definition was "the employment of mechanical means for the healing of disease." Later, the term was expanded to include "the use of mechanotransduction to stimulate tissue repair and remodelling." Mechanotherapies emphasise natural mechano-adaptation to promote healing and are active mechano-interventions that aim to transform potential damaging mechanical effects into therapeutic benefits [6]. Traditional physical therapy focuses on rehabilitating the patient, but recent advances in mechanobiology have revealed the impact of physical variables or forces at the cellular and tissue level, indicating a need to modify the traditional therapy paradigm [6].

Abnormal tissue responds to mechanical stress, and this response can contribute to the causative factors and clinical symptoms of various diseases, including osteoporosis, asthma, heart failure, diabetes, and stroke. The development of tissues and the regulation of cellular biochemistry critically depend on mechanical forces. Hence, cells with mechanotransduction properties can be targeted for intervention [11].

Mechanobiology in Musculoskeletal Rehabilitation

Regenerative rehabilitation combines the principles of exercise with regenerative therapies to facilitate the repair and regeneration of nerves, bones, ligaments, muscles, tendons, cartilage, and other musculoskeletal tissues [5]. Mechanical stimulation and functional loading are important stimuli in orthopaedics. Significant advancements have been made in areas such as bone healing, cartilage repair, muscle regeneration, and nerve regeneration, both in preclinical and clinical settings. Mechanical forces play a beneficial role in musculoskeletal tissues during development and their physiological functions, making it unsurprising that such stress has a significant impact on regeneration and healing. The concept of enhancing muscle tissue healing by combining characteristics of rehabilitation therapy with regenerative medicine is supported by extensive preclinical experimental research. Clinical applications, such as continuous passive motion following external fixation for bone healing and joint surgery, pave the way for realising the full potential of regenerative rehabilitation concepts in orthopaedics [12]. Eccentric exercise effectively demonstrates the potential effects of mechanotransduction on muscle regeneration or repair [5]. A sufficient number of satellite cells is essential for muscle regeneration, and eccentric exercise promotes their activation and proliferation, triggering various cellular responses that can enhance the healing process in muscles. Mechanical forces are incorporated into almost all interventions used in physical therapy. These therapies provide mechanical stimulation to cells and tissues, including muscle stretching, prescribed exercises, soft tissue mobilisation, joint mobilisation, and even neuromuscular electrical stimulation [5]. Immobilisation following an injury typically has negative consequences for musculoskeletal tissues [5]. A common technique is the soft tissue expansion technique, which gradually mechanically stretches the skin to induce endogenous skin growth [6].

Scars often impair skin function and can cause severe deformities, long-term functional loss, psychosocial issues, and growth retardation. There are limited effective nonsurgical therapeutic options available for scar management, such as physical therapy, shock wave therapy, and scar taping [13]. Mechanical forces play a crucial role in extracellular matrix remodelling, scarring, and wound healing. The skin and subcutis, which are involved in wound healing and scarring, contain various cells that constantly perceive different mechanical forces and respond by changing their shape, migrating, proliferating, differentiating, and taking other biological actions to adapt to their new environment. Scar therapists can regulate the response of physical interventions in scar therapy to achieve a promising effect on extracellular matrix remodelling by studying the mechanical stimuli to which connective tissue cells optimally respond and the mechanisms these cells utilise to transform mechanical signals into cellular-level responses. Most scar treatment approaches involve the application of mechanical stress, including silicones, pressure garments, mobilisations, manual massage therapy, adhesive tape, and shock wave therapy [14]. However, the optimal frequency, intensity, and duration of the force applied to produce a beneficial result are still unknown. Specific non invasive physical scar therapies may be employed based on the properties of the scar [14].

Mechanobiology in Cardiorespiratory Rehabilitation

The vascular system's remarkable ability to adapt to changing environmental factors facilitates its vital function of transporting oxygen, nutrients, and waste from the tissues to the bloodstream [15]. Angiogenesis is triggered by increased local metabolic activity or normal tissue growth, which increases blood supply to meet the demand in that area. Blood circulation in the body is primarily a mechanical process. Therefore, the cells in the vascular wall perceive and respond to various mechanical stimuli to maintain vascular integrity and facilitate necessary adaptations [15].

In atrial electrophysiology models, when incorporating mechano-electro feedback models, passive stresses arising from ventricular contraction must be considered [16]. Prolonged stretching primarily induces stretch-induced capacitance changes. Consistent with experimental research, chronic stretching leads to a decrease in conduction velocity and an increase in the duration of the action potential. Therefore, mechano-electro feedback may impact the development and maintenance of atrial arrhythmias [16].

The signalling cascade is activated when laminar shear stress increases during exercise training, stimulating mechanical receptors. Exercise training has beneficial effects on several molecular pathways, resulting in decreased progression and reversal of coronary atherosclerosis, and inducing additional beneficial effects in various systems in the human body [17]. Integrative quantitative models should be a long-term objective for researchers in the fields of cell signalling, vascular biomechanics, mechanobiology, immunobiology, and matrix biology. These models should be rich enough to identify therapeutic targets for inhibiting disease processes without significantly affecting homeostatic processes. Understanding the dynamic physical and regulatory interactions that regulate adaptation, vascular homeostasis, and disease requires a comprehensive approach [15].

Asthma and ventilator-associated lung damage, both caused by high tensile loads, are linked to Nuclear Factor kappa B (NFkB) dysregulation and the resulting deleterious structural and physiological alterations. The aetiology of chronic fibrotic lung disorders, such as idiopathic pulmonary fibrosis, has recently been linked to alterations in the matrix in response to mechanical stimuli [8]. Cilia play a crucial role in cellular homeostasis due to their ability to integrate chemical inputs as well as flow and compression forces. Changes in the extracellular environment influence the signals received by cilia, changing cell growth characteristics [18].

Coughing and mucociliary action are responsible for clearing the airways. Mucociliary clearance depends on the normal active beating of cilia. Failure of this mechanism may result in postoperative sputum retention or acute-on-chronic bronchitis with respiratory failure. In certain disease states, medications such as beta 2-agonists, theophylline, corticosteroids, and mucolytics may enhance clearance. Chest physiotherapy uses physical methods such as gravity-assisted postural drainage and forced expiratory techniques, which may be beneficial [19].

Mechanobiology in Vestibular Rehabilitation

Important stimuli in neurology include electrical signals, mechanical stimulation, and functional loads [12]. Mechanotransduction enables individuals to hear register gravity and movement, perceive touch, and detect changes in cell volume and structure. Inner ear hair cells are specialised mechanoreceptor cells that perceive head movement and sound. Mechanotransduction plays a vital role in various sensory processes, enabling individuals to perceive sound, gravity, movement, touch, and changes in cell volume and structure. Inner ear hair cells, specialised mechanoreceptors, are responsible for detecting head movement and sound. These hair cells exhibit exceptional sensitivity to even the slightest physical displacements, responding within fractions of a millisecond. Recent advancements in identifying the molecular components of hair cell mechanotransduction have provided a new framework for interpreting biophysical data [20]. Both vestibular and auditory hair cells adapt to mechanical stimuli on different timescales. While vestibular hair cell adaptation may be slower compared to cochlear hair cells, the adaptation requirements for these two types of cells are likely to differ. The standard definition of adaptation, which involves restoring sensitivity by reducing the response to a sustained stimulus, is particularly relevant for vestibular hair cells [20]. Medication, physical therapy, surgery, counseling, and reassurance are among the treatment options for dizziness [21]. Vestibular rehabilitation is an exercise-based intervention that aims to minimise the underlying and resultant issues associated with vestibular dysfunction. These exercises usually involve step-wise activities that include head, eye, and body movements to stimulate the vestibular system. Habituation exercises, also known as compensatory exercises, use repetitive motions or provocative stimuli. The movements that cause the patient's symptoms are identified, and the patient performs these exercises until the stimuli no longer elicit unfavourable reactions. Adaptation exercises, involving repetitive head and eye movements, help the central nervous system adjust to changes in vestibular system input while the eyes are fixated on a stationary object and the head is turned to the left and right. Substitution exercises aid in enhancing postural control by organising the use of the remaining sensory inputs [22].

Mechanobiology in Cancer Rehabilitation

Various physical factors present in the tumour microenvironment and related extracellular matrix, including stiffness, intercellular spacing, topology, and matrix orientation, have different impacts on cell behaviour and migration [23]. External physical stimuli acting on the cell surface are detected and transduced across the membrane, where they are transformed into biochemical signals that influence molecular pathways [23]. The resulting biological changes can affect cell shape, motility, and cell forces on the extracellular matrix. Physical factors that modify how actin is organised in the cytoplasm and nucleus can lead to variations in gene expression patterns [24]. Understanding the actin cytoskeleton and associated mechanosensing nuclear components is necessary to unravel the mechanobiological mechanisms in cancer. Cytoskeletal and nucleoskeletal components have a reciprocally important connection with certain biological pathway proteins, making them promising therapeutic targets [23,24]. As solid tumours grow and progress, different mechanical characteristics of cancer cells become apparent [25]. In cancer rehabilitation, it is crucial to consider various aspects of physical therapy beyond the scope of vascular and respiratory conditions. For patients grappling with bone tumours who show a strong adherence to chemotherapy, initiating intensive physical therapy concurrently with treatment emerges as a viable option. This highlights the importance of integrating rehabilitation therapies within chemotherapy wards, prioritising them based on patient satisfaction and well-being. This comprehensive approach not only addresses the specific needs of patients with bone tumours but also underscores the broader role of physical therapy in cancer rehabilitation [26].

CONCLUSION(S)

Rehabilitation, operating at the cellular level, demands a meticulously designed intervention approach. The field of mechanobiology and regenerative medicine is ushering in new prospects for rehabilitative therapies. Practitioners in the rehabilitation field can embrace and contribute to this evolving scientific understanding by exploring the biological and genetic impacts that hold potential for refining existing intervention techniques. The incorporation of mechanobiology into other spheres linked with rehabilitation presents an enticing avenue for future research.

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