



Review Article

Role of Physical Therapy Intervention and Gene Therapy on Muscular Dystrophies, Current Status and Future Perspectives: A Narrative Review

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ABSTRACT

Muscular dystrophies form a collection of genetic disorders marked by progressive muscle weakness and degeneration. The identification of the majority of responsible genes has enabled precise diagnosis and subtype-specific anticipatory care. Over the years, various therapies, encompassing genetic, cellular, and pharmacological approaches, have emerged for muscular dystrophies. This narrative review thoroughly explores the ongoing developments in muscular dystrophy therapeutics, including antisense therapy, CRISPR, gene replacement, cell therapy, based gene therapy Adeno-associated viral vector (AAV), and disease-modifying small molecule compounds. The review is particularly significant as it reflects advancements in supportive medicine that have altered the standard of care, leading to an overall improvement in the quality of life, clinical course and survival for affected individuals. In this study, our focus is on the clinical manifestations, molecular pathogenesis, diagnostic strategies, and therapeutic advancements related to this group of conditions. The study involved the review of 20 pertinent English-language articles, publications, reports, and online resources.

INTRODUCTION

Muscular dystrophies are inherent muscle disorders caused by mutations in over 40 genes, leading to dystrophic alterations observed in muscle biopsy. With the identification of the majority of genes associated with these conditions, it is now feasible to achieve precise diagnoses and establish subtype-specific anticipatory care. This is particularly crucial because obstacles, such as respiratory and cardiac muscle involvement, exhibit significant variations among individuals. Advancements in functional medicine have altered the standard of care, leading to an overall enhancement in the clinical trajectory, rates of survival, and quality of life for individuals

exaggerated by these conditions [1]. Muscular dystrophy involves genetic mutations that hinder the body's ability to produce the essential protein (dystrophin) required for constructing healthy muscles. Globally, an estimated 3.6 cases of muscular dystrophy occur per 100,000 individuals. The prevalence of the most common types, namely Duchenne's and Becker's muscular dystrophies, is approximated at 4.6 and 1.6 cases per 100,000 persons, respectively. Notably, Americans exhibit the highest prevalence at 5.1 cases per 100,000, while Africans have the lowest prevalence at 1.7 cases per 100,000 people [2]. Muscular dystrophies that onset during infancy and

childhood are marked by a distinct pattern and advancement of motor dysfunction. Progressive muscular dystrophies in childhood have a wide range of causes involving diverse genetic pathways and genes responsible for encoding protein [3]. CMDs (Congenital muscular dystrophies) are hereditary conditions primarily impacting skeletal muscles, characterized by hypotonia and weakness manifesting before achieving independent ambulation. These disorders involve a delay or halt in reaching major motor milestones and exhibit dystrophic muscle pathology. Allelic mutations in various genes can lead to onset either before or after ambulation, serving as a practical distinction between CMDs and limb-girdle muscular dystrophies (LGMD). Muscle biopsy findings can vary in severity, encompassing a range of pathological observations such as differences in muscle fiber size, degeneration and regeneration, and increased fibrosis. Elevated levels of creatine kinases (CK) are typically, though not constantly, observed [4]. To reduce the likelihood of a recurrence, the global prevalence of DMD (Duchenne muscular dystrophy) and BMD (Becker muscular dystrophy) has been significantly heightened. This underscores the need for enhanced emphasis on genetic counselling and prenatal screening, especially for families with a history of these conditions [5]. Muscular dystrophies represent a diverse set of inherited muscle disorders marked by gradual muscle weakening, often accompanied by cardiac and respiratory muscle complications. Traditionally perceived as incurable conditions with serious prognoses, recent progress has unveiled the responsible genes for most muscular dystrophies. Early diagnosis is now attainable through accurate advanced genetic testing and clinical recognition. This article explores current breakthroughs in the expansion of innovative treatments and biomarkers for muscular dystrophies commonly observed in the pediatric population [6].

MANAGEMENT AND REHABILITATION OF MUSCULAR DYSTROPHY

The treatment of muscular dystrophy should be all-encompassing and customized based on the individual characteristics of the patient and current stage of clinical progression [7]. MRI evaluations revealed a potential signal suggesting that givinostat may possess the ability to hinder or decelerate the advancement of Becker muscular dystrophy (BMD). The efficacy and safety of givinostat, an HDAC inhibitor that impedes enzymes called histone deacetylases (HDACs) involved in the regulation of gene expression within cells, impacting muscle regeneration in Duchenne and Becker muscular dystrophies were assessed in adults with muscular dystrophy [8].

Although many treatments for patients with muscular

dystrophy remain unavailable, there is hopeful introduction of gene therapy based on Adeno-associated viral vectors (AAV). These viral vectors have the ability to transduce various tissues and exist as extrachromosomal concatemers. This treatment is emerging as a potential treatment for different kinds of muscular dystrophy, including various limb-girdle muscular dystrophies, myotonic muscular dystrophy 1, facioscapulohumeral muscular dystrophy, and congenital muscular dystrophies. This marks a hopeful era for gene therapy in the context of muscular dystrophy [9]. Individuals with Becker's muscular dystrophy engage in exercise routines on a cycle ergometer or treadmill, incorporating aerobic activities. This practice has demonstrated efficacy in counteracting physical deterioration and preserving functional abilities [10]. Children affected by Duchenne muscular dystrophy experience challenges in postural adjustments. In these cases, aerobic exercise in the form of treadmill training has proven to enhance walking capacity and balance more efficiently compared to the use of a bicycle ergometer in such children [11]. The loss of walking ability in Duchenne muscular dystrophy is frequently associated with diminished physical and mental health. Powered wheelchair standing devices (PWSD) are utilized to alleviate muscle and joint pain, demonstrating an enhancement in mental well-being and joint angles when adolescents with Duchenne muscular dystrophy are in a standing position [12]. For individuals having Duchenne muscular dystrophy, the incorporation of individual virtual reality systems, featuring three-dimensional simulated environments, can serve as a valuable tool in physiotherapy. These systems can be applied in rehabilitation programs aimed at enhancing patient performance during training, particularly focusing on the upper limbs [13]. Individuals with muscular dystrophy (MD) often experience respiratory muscle weakness, leading to respiratory failure and, ultimately, death over time. Various techniques, including glossopharyngeal breathing, manual cough-assisting manoeuvres, air stacking using a resuscitator bag or volume-cycle ventilator, and the use of a mechanical insufflator-exsufflator can be employed to address respiratory challenges in muscular dystrophy [14]. The integration of yoga and physiotherapy intervention during early stages is acknowledged as a therapeutic strategy to improve pulmonary functions in individual having DMD. Studies have emphasized the positive influence of respiratory muscle training and breathing exercises on enhancing pulmonary functions in children diagnosed with DMD [15]. Performing calf massages on ambulant boys with DMD is a safe practice and has been linked to positive outcomes in terms of muscle length and stiffness. Administering calf massages to ambulant boys with is a

secure practice and has been associated with positive outcomes in terms of muscle length and stiffness. The procedure is well-tolerated and has demonstrated an increase in muscle length along with a reduction in stiffness. Utilizing massage appears to be a helpful approach in the management of muscle length in boys diagnosed with Duchenne muscular dystrophy [16]. Individuals having DMD experience compromised therapeutic gait, and various clusters of individuals exhibit distinct gait patterns. Three-dimensional (3D) gait analysis has given rise to gait indexes such as the GDI (Gait Deviation Index) and the GPS (Gait Profile Score), allowing for the calculation of the GVS (gait variable score). It is advisable to commence rehabilitation for individuals with DMD early in the course of the disease, with a particular focus on the joint of hip as a therapeutic target [17]. Regarding DMD, there exist connections between falls and the fear of falling (FOF), physical performance, balance, and ambulation in children. Ambulatory children with superior performance scores exhibit reduced levels of FOF. As the symptoms of the disease advance, there is a tendency for FOF to escalate. Examining the history of falls and FOF from the earliest stages will provide guidance for implementing timely precautions and necessary interventions in treatment programs [18]. The OPTIMISTIC study in Europe has shown a substantial, although varied, impact of Cognitive Behavioral Therapy (CBT) for patients with Myotonic Dystrophy type 1 (DM1) [19]. Individuals having DMD experience a disruption in cardiac autonomic function, characterized by a reduction in parasympathetic activity and a predominance of sympathetic activity. The cardiac autonomic modulation in individuals with MD undergoing therapy with Prednisone/Prednisolone and Deflazacort is a subject of investigation [20]. Due to the side effects linked to the use of corticosteroids, there is a demand for more effective alternatives to the current standard of care. The high cost serves as a hindrance for patients in accessing medications that have yet to demonstrate established efficacy. While additional therapies hold promise for individuals with DMD, most are several years away from obtaining approval for patient use [21]. DMD results from the deficiency or reduced levels of the muscle cytoskeletal protein dystrophin. Ongoing clinical trials are investigating vector-mediated gene therapy that delivers micro- and mini-dystrophin. Advanced therapeutic strategies, such as CRISPR/Cas9-based genome editing and stem cell-based cell therapies, are also in the process of development [22]. In the realm of Muscular dystrophy treatment, particular attention is given to the therapeutic potential of human pluripotent stem cells (hPSCs). These cells exhibit significant potential for muscular dystrophy (MD) treatment as they can be guided

toward a myogenic lineage and subsequently employed for autologous transplantation. Recent advancements have demonstrated notable progress in techniques for isolating and differentiating myogenic cells derived for human pluripotent stem cells (hPSCs), with goal of achieving effective transplantation outcomes [23]. We have recently introduced the term 'Satellite Cellopathies' to characterize inherited neuromuscular conditions marked by dysfunction in satellite cells. These myogenic stem cells play a crucial role in muscle regeneration throughout an individual's lifespan and are observed in both muscular dystrophies and myopathies [24].

CURRENT STATUS AND FUTURE PERSPECTIVE REGARDING TREATMENT OF MUSCULAR DYSTROPHY

Our research examined the significant economic impact of DMD on society, outlining variations across the different stages of the condition. The majority of this financial burden is carried by household, leading to catastrophic expenditures that in turn contribute to reduced adherence to treatment and a decline in the overall quality of care. Additionally, our study revealed a significant compromise in the quality of life (QOL) for individuals affected by DMD. These findings can serve as valuable insights for shaping future healthcare policies and conducting economic evaluations of emerging therapies for DMD [25]. A significant concern lies in the emphasis on skeletal and respiratory muscle results compared to cardiac improvements. While it is supposed that enhancements in skeletal and respiratory function would lead to better patient outcomes, the gradual shift toward cardiac condition as the primary determinant of patient survival underscores the importance of incorporating standardized cardiac parameters, such as LGE (late gadolinium enhancement, a technique used in MRI for cardiac tissue characterization) on cardiac magnetic resonance imaging (MRI) and changes in left ventricular (LV) function, in clinical trials. Moreover, it is noteworthy that efficacy reports on most FDA-approved treatments are predominantly centered around skeletal muscles. Nevertheless, initial findings from continuing trials, demonstrating higher skeletal MD (muscle dystrophin) restoration and enhanced cardiac conditions, suggest a more promising future [26]. Recommendations for muscular exercise include enhancing endurance during walking and incorporating its role in multidisciplinary approaches. Future trials should investigate the specific types of muscle exercises that result in improved muscle strength and identify exercises that contribute to enhanced endurance and aerobic capacity. It is essential to conduct well-designed trials to address these open questions and provide clarity on the optimal approaches for maximizing the benefits of muscular exercise [27].

The Hybrid Assistive Limb (HAL) is a standing device and orthosis utilized for walking. Evaluations have been conducted to assess its impact on quality of life, participation in activities, and patient satisfaction. The findings suggest that HAL is demonstrated to be more effective than conventional methods in patients with muscular dystrophy diseases [28]. Our findings offer positive insights into the effects and acceptability of a home-based training program for individuals with Myotonic Dystrophy type 1 (DM1). These programs have the potential to alleviate the financial burden on the health system. Given that muscle weakness is a significant hallmark of DM1, leading to notable limitations in functional mobility and an increased risk of falls, strength training emerges as a non-pharmacological, accessible, and safe intervention of choice for this population [29]. In the last three years, experimental efforts have been dedicated to the pursuit of cell-based therapies for muscular dystrophies. Various cell types, each possessing distinct characteristics and originating from different tissues, such as progenitor cells and myogenic stem, stromal cells, and pluripotent stem cells, have undergone investigation and recently entered clinical trials with varied outcomes. In this review, we deliver an overview of past endeavors, detail the recent status of cell-based therapies targeting cardiac myopathy and skeleton myopathy in dystrophic patients, highlight existing challenges, summarize recent advancements, and offer commendations for upcoming research and clinical trials [30]. This review offers a comprehensive examination of existing conventional therapies for the patients with Muscular Dystrophy (MD). It explores emerging therapeutic approaches and outlines future perceptions. While these therapies are presently sanctioned for the treatment of specific hematological malignancies, inherited retinal dystrophy, and spinal muscular atrophy, there is potential for their application in correcting the genetic modifications associated with the record of prevalent sarcomere forms of hypertrophic cardiomyopathy [31]. In the present state of Duchenne muscular dystrophy treatment, the potential benefits of exercise training remain uncertain. Additional research is necessary to thoroughly investigate the impact of exercise training on promoting functionality and enhancing health-related worth of life in individuals with DMD [32].

CONCLUSIONS

This study provides valuable insights into the use of standers among individual with Duchenne muscular dystrophy (DMD), offering guidance for decision making on stander utilization before complications arise. The goal is to support optimal health despite reported barriers. The call for researchers and clinicians to thoroughly investigate the role of physical therapy in DMD, drawing from

contemporary evidence. The aim is to deepen understanding, refine therapy recommendations and address the challenges faced by affected families. As providers, the responsibilities are to promote best practices and contribute to shaping future interventions, studying their impact on impairment, activity and participation levels in individual with muscular dystrophy. As providers, the responsibility is to promote best practices and contribute to shaping future.

RECOMMENDATIONS

Muscular dystrophies, particularly impactful in children, necessitate tailored treatment approaches based on specific type and individual needs. Medications like corticosteroids maybe prescribed to manage symptoms and slow disease progression. Adaptive equipment such as braces or wheelchairs can aid mobility, while respiratory function should be monitored, potentially requiring devices like cough assist machines. A balanced diet is recommended for overall health and emotional support is crucial for both the child and their family. Assistive technologies and accommodations can enhance participation in various activities. Genetic counseling is advisable to address family planning, inheritance patterns and potential risks in future pregnancies.

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Conflicts of Interest

The authors declare no conflict of interest.

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