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REVIEW ARTICLE

Distrofia muscular de Duchenne e suas intervenções terapêuticas: uma revisão integrativa da literatura

Duchenne muscular dystrophy and its therapeutic interventions: an integrative literature review

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ABSTRACT

Introduction: Duchenne Muscular Dystrophy (DMD) is associated with a mutation in the gene encoding dystrophin, present on the X chromosome. Clinical manifestations are associated with muscle degeneration, leading to muscle weakness, mobility problems and respiratory failure. Rapid and accurate diagnosis is important to minimize symptoms and improve survival, especially in childhood. Among the indicated therapies are corticosteroid drugs, gene therapy and physiotherapy. **Objective:** To provide a comprehensive overview of the therapeutic methods most used to treat the symptoms of its carriers. **Methods:** Integrative review in PubMed, SciELO and Google Scholar databases using as descriptors "Duchenne Muscular Dystrophy", "Muscular Dystrophies", "Therapeutic", in Portuguese and English, with publication between 1998 and 2020. **Results:** Physical activity, in general, was the most cited therapeutic intervention, together with corticosteroid treatment, the latter with benefits in the neurological development of patients, along with promising gene therapies that enable a more assertive treatment. It is important to highlight the importance of introducing other individualized treatments, such as non-invasive mechanical ventilation, which has proven beneficial for patients with DMD with respiratory failure. This therapeutic combination associated with early diagnosis enables better disease progression and symptom management, although there is no cure. These, however, are hopeful options for the future, but still need studies and popularization in the present. **Conclusion:** Moderate physical activity is the most recommended treatment, although there is disagreement among professionals. In addition to improving mobility, exercise is essential to minimize the effects of respiratory failure and cardiac degeneration - symptoms of DMD that pose the greatest risk to patients. It is important to treat patients in a multidisciplinary way, articulating resources in order to mitigate the consequences of dystrophy and ensure a comprehensive treatment of symptoms.

Keywords: Duchenne muscular dystrophy; Muscular dysthropy; Therapeutics.

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RESUMO

Introdução: A Distrofia Muscular de Duchenne (DMD) está associada a uma mutação no gene codificante da distrofina, presente no cromossomo X. As manifestações clínicas estão associadas à degeneração da musculatura, levando à fraqueza muscular, problemas de mobilidade e insuficiência respiratória. O diagnóstico rápido e preciso é importante para minimizar os sintomas e melhorar a sobrevida. **Objetivo:** Fornecer uma visão abrangente dos métodos terapêuticos mais utilizados para tratar os sintomas de seus portadores. **Método:** Revisão integrativa nas bases de dados PubMed, SciELO e Google Acadêmico usando como descritores "*Duchenne Muscular Dystrophy*", "*Muscular Dystrophies*", "*Therapeutic*", em português e inglês, com publicação entre 1998 e 2020. **Resultados:** A atividade física foi a intervenção terapêutica mais citada, em conjunto com o tratamento com corticoides, este com benefícios no desenvolvimento neurológico dos pacientes, juntamente com as promissoras terapias gênicas que possibilitam um tratamento mais assertivo. É importante ressaltar a importância da introdução de outros tratamentos individualizados. Essa combinação terapêutica associada com o diagnóstico precoce possibilita uma melhor evolução da doença e manejo dos sintomas, apesar de não existir cura. Essas, contudo, mostram-se opções esperançosas para o futuro, mas ainda carecem de estudos e popularização no presente. **Conclusão:** A atividade física moderada é o tratamento mais recomendado, ainda que haja discordâncias entre os profissionais. Além de melhorar a mobilidade, é fundamental para minimizar os efeitos da insuficiência respiratória e da degeneração cardíaca — sintomas da DMD que representam maior risco aos pacientes. É importante tratar os pacientes de forma multidisciplinar, articulando recursos a fim de amenizar as consequências da distrofia e garantir um tratamento integral dos sintomas.

Palavras-chave: Distrofia muscular de Duchenne; Distrofias musculares; Terapêutica.

Introduction

Duchenne Muscular Dystrophy (DMD) was first described in 1961, in France, by the physician Guillaine Benjamin Amand Duchenne. This disease is considered the most common among degenerative myopathies, with an estimated incidence of 1 case per 3500 males[1].

DMD is genetically linked to the short arm of the X chromosome, specifically at the Xp21 locus, and is generated by a mutation in the gene encoding the protein dystrophin. The disease occurs mainly in males, while females are only the carriers in most cases and may develop the disease in some situations such as in Turner Syndrome or when receiving two affected genes[2]. The mutations described are mostly (65%) the result of deletions, 30% occur due to point mutation, and only 5% are duplications[2]. Studies show that one-third of cases are due to new mutations, while two-thirds are inherited from the asymptomatic mother since men generally do not live long enough or are unable to have children[2].

Mutations can lead to abnormal production of dystrophin or even its absence. This protein makes up the sarcolemma, the membrane that surrounds the muscle fiber, anchoring it to the cytoskeleton of the cell. In individuals with affected sarcolemma, there is instability of the cell membrane and the basal lamina of the muscle cells, leading to the disruption of these structures when there is exacerbated muscle activity. This rupture causes a massive entry of calcium into the muscle cells, ultimately promoting the activation of proteases and muscle necrosis. Due to cell death, there is a release of enzymes present in the

muscle cells into the blood, especially creatine kinase (CK)[3]. At disease onset, the muscle fibers regenerate, but, as time goes by, necrosis overrides regeneration and the muscle is replaced by fibroadipose tissue[3].

The clinical symptoms of DMD are present from birth but become evident after the age of three. The most frequently noted changes are muscle weakness, especially in the lower limbs, balance problems, delayed psychomotor development, and orthopedic deformities. The degeneration of the respiratory musculature is the main cause of the complications that can lead to death during the second or third decades of the patient's life. Associated with respiratory problems, cardiac involvement is the second leading cause of death in people with DMD[3].

The diagnosis of DMD is made by symptom analysis, accompanied by family history, genetic research, serum CK levels, and muscle biopsy or electron microscopy. There is a consensus among DMD researchers, who report the frequent delay in recognition and diagnosis in almost all patients. According to them, this delay hampers family genetic counseling and the efficiency of early treatments[1]. In all cases, it is necessary to recognize which is the best therapeutic intervention to be performed according to each patient, considering the evolution of the disease to mitigate the pathogenic effects and increase the quality of life of the carriers.

Among the treatments used in DMD, the most recurrent in the medical literature is physical therapy, which maintains muscle strength and mobility, in addition to preventing respiratory complications, aiming at promoting the patients' independence for daily activities. On the other hand, research warns that physical exercises that require a lot of strength can be harmful and potentiate the evolution of the disease; therefore, care must be taken not to fatigue the weakened muscles during physical therapy sessions[3].

Another possible treatment option commonly adopted is the use of hydrotherapy in children with DMD. It is reported that heated water can facilitate movements by the force of thrust and the heat can relieve muscle pain[4]. In addition to the above, the pool is a useful environment for activities for children of different age groups, and case reports have confirmed significant changes in inspiratory and expiratory pressures[4].

Among therapeutic strategies, glucocorticoid corticosteroids have emerged as promising medications to attenuate symptom progression and optimize patient functionality. In addition, other immunosuppressants, such as deflazacort, are being investigated and used in the long term. Parallel to medications, genetic research has provided new information on mutations and their connections to clinical manifestations. Despite advances, the challenges of finding more effective therapies require continued research to improve understanding of the disease and the quality of life of affected patients[5-8].

Objectives

This integrative review aims to compile data on different types of treatment that can be offered to patients affected by DMD and the relationship with the improvement observed in patients. It highlights the importance of knowing alternative therapeutic forms considering the varied spectrum of severity presented by the patients and, more importantly, the need for more scientific research aimed at contributing to the improvement in the quality of life of these individuals and their families.

Methods

An integrative review was conducted based on the guiding questions: "What are the therapeutic interventions used in the treatment of DMD?" and "What are the impacts of the diagnosis and treatments on the quality of life of the patient and family?"

Case reports and qualitative and quantitative studies addressing forms of DMD treatment, with a publication date between 1998 and 2020, were included. In addition, review articles and articles with abstracts that did not apply to the topic or did not answer the guiding question were excluded.

PubMed, SciELO, and Google Scholar were used to select articles from the electronic databases. The following descriptors in Portuguese were used: "Duchenne Muscular Dystrophy", "treatments", and "therapeutic interventions". The main Boolean operator used for the searches was "and", followed by "or".

The investigation, carried out in March 2022, was initiated with the selection of articles from the reading of titles and abstracts, seeking the exclusion of those that did not meet the objective of this scientific research. First, 240 references on the subject were located in the database search. After reading the titles and abstracts, following the inclusion criteria of these original articles, given publication and exclusion, 17 original articles were chosen and read in their entirety, being approved to proceed with the work. The languages of the articles searched and included in the review were English and Portuguese.

Results

The study "Analysis of two cases of DMD in the rural area of Manhuaçu" conducted by Lopes et al. (2018)[2], aimed to study the case of two siblings, not twins, with DMD. The investigation intended to analyze the characteristics of the disease of each patient, considering the genetic, physiological, and immunological aspects of the disease, and comparing the case with articles that address the topic. The main results obtained were that the diagnosis of DMD is usually late since doctors often do not know how to identify the disease. This difficulty in identification may occur due to the waiting time for the test results, the doctor's lack of information about the characteristics of the family's clinical condition, and the children's non-attendance at the consultations. The diagnosis of the siblings was made taking into account the clinical signs of muscle weakness, and late onset of gait in one of the siblings, the 9-year-old,

while the younger brother, 7 years old, started walking at the appropriate period but had the habit of walking on the other brother's tiptoes; besides this, frequent falls and difficulty in performing skills such as jumping, running and playing were taken into consideration.

Furthermore, they had significant laboratory findings, changes in the levels of the enzyme creatine phosphokinase (CPK) being the most specific laboratory technique to analyze this type of muscle injury. In the case studied, the two brothers were diagnosed late, since the average in Brazil is 7.5 years old; in addition, in the older brother the dystrophy was confused with hip problems. Because it is a genetic disease, there is no effective treatment and, as a therapy to control the symptoms, corticoids and physical therapy are used to relieve symptoms, strengthen muscles, and slow the progress of the clinical condition. This alternative treatment was chosen by the patients' families to delay the disease and manage the symptoms.

The second study analyzed, called "Physiological and metabolic changes in individuals with DMD during physiotherapy treatment: a case study"[3], aimed to evaluate the physiological and metabolic changes in individuals with DMD during a physiotherapy program, relating them to the subjective perception of effort (PSE), and was conducted by Gevaerd et al. (2013)[3]. The study was developed with the analysis of data of only one patient, a 17-year-old male individual diagnosed with DMD. He presented the first symptoms, such as constant falls, feeling weak, and difficulty walking, at the age of 4. At the age of 5, he was diagnosed with DMD, and at the age of 10, the child was no longer able to walk without assistance and started using a wheelchair. For the study, the data of resting PSE, HR, RR, BP, [AL], and [GLI] were measured. This measurement is divided into three parts: from 0 to 15 minutes, 15 to 30 minutes, and 30 to 45 minutes. Each phase had different procedures and objectives, aiming at the different weaknesses presented by the volunteer. At the end of the study, 6 physiotherapy sessions were performed, with intervals of 1 or 2 days between each session. In each session 4 data collections of HR, RR, BP, SBP, [AL], and [GLI] were performed, one at rest and the others at the end of each phase of the physiotherapy session. After analyzing the data collected, it was observed that the PSE increases as a consequence of the physiotherapy sessions. It was also possible to notice a linear relationship between the metabolic variables and PSE, and that the physiological variables do not present a proportional relationship with PSE.

Another study analyzed by Caromano et al. (1998)[4] intended to analyze the physiological responses in 20 male children between 8 and 15 years old with DMD, in 40-minute hydrotherapy sessions with active deambulation exercises and breathing exercises. The data analysis was done through the difference of means between the measurement periods for each of the five variables studied for the group of children. Regarding heart rate, a reduction of 7.3 bpm was observed between the initial immersion period and the pre-immersion period. Between the final immersion period and the beginning of immersion there was a mean increase of 7 bpm; a mean decrease of 0.3 bpm was also observed between the pre-immersion period and the end of immersion. The oral temperature showed an increase of 0.1 °C between the final immersion period and the initial immersion period. Regarding oxygen saturation, a decrease in the values obtained after immersion was observed, where there was a decrease of 2.7% between the initial period of immersion and the pre-immersion period; furthermore, there was an increase of 0.9% between the initial and final periods of immersion. Regarding the maximal inspiratory pressure, there was a decrease of 8 cm between the initial immersion period and the pre-immersion period. On the other hand, the maximum expiratory pressure between the pre-immersion and initial immersion periods was observed to increase by 7.4 cm of water.

The study "Evaluation of heart rate and blood pressure in soil and immersion in patients with DMD", done by Franzini et al. (2012)[9], aimed to evaluate the difference between heart rate (HR) and blood pressure (BP) in soil and immersion in patients with DMD. With this in mind, the HR and BP of 32 individuals with this disease were measured and analyzed on land and after immersion in 3 stages, which were immersion up to the seventh cervical vertebra, in the xiphoid process; and dorsal floating, being divided into 2 groups exposed to different immersion times. Among the main results of this study, a significant reduction of HR during and after immersion of the patients and an important increase of systolic and diastolic BP after immersion can be pointed out in both groups. As for the HR, it was observed that it decreased from 105 bpm to 99 bpm in group A, and from 102.5 bpm to 97.5 bpm in group B. Regarding BP, there was an increase both in diastolic and systolic levels in both groups. After immersion, BP went up from 106.8 x 66.5 mmHg to 115.3 x 76 mmHg in the mean of the measurements of individuals in group A, and from 107.5 x 68.4 mmHg to 113.3 x 77.17 mmHg in the mean of the measurements of individuals in group B. Regarding the BP, we noticed an increase in both diastolic and systolic BP in both groups. After immersion, it rose from 106.8 x 66.5 mmHg to 115.3 x 76 mmHg in the mean of the measurements of individuals in group A, and from 107.5 x 68.4 mmHg to 113.3 x 77.17 mmHg in the mean of the measurements of individuals in group B. These detected changes were related to a set of cardiovascular responses triggered by the immersion of patients, promoting an increase in venous return, cardiac filling, and contraction volume in patients with DMD. Thus, the study concludes that there is the need to evaluate HR and BP to determine the immersion time in the conduct of hydrotherapy in patients with this disease.

The study by Pereira et al. (2020)[10], entitled "Can simple and inexpensive motor function evaluations help in the diagnostic suspicion of Duchenne muscular dystrophy?"[10], in turn, aimed to determine the sensitivity of simple and inexpensive methods in screening children for early diagnosis of DMD, such as time to stand up, time to walk 10 meters,

and time to run 10 meters. In this work 472 children - 344 of them healthy and 128 known to have the disease - were analyzed according to the parameters in question to measure the difference between the measurements obtained by these groups and thus evaluate the efficiency of these tests.

Among the main results of this study was a progressive and significant worsening in the three motor tests, occurring on average from 7 years of age. In the "time to get up from the ground" and "time to walk 10 meters" tests, the worsening was more pronounced between 6 and 9 years of age, with stable parameters until 5 years of age; while after 9 years, most patients could not perform these activities. As for the "time to run 10 meters", an earlier worsening of this parameter was observed, being significant from 4 years of age and progressing rapidly until 7 years of age, with patients unable to continue after this age. From the analysis of these data, the authors were able to define cut-off points for screening, which were for the Time to Stand Up, 2 seconds; for the Time to Walk, 10 meters, 5 seconds; and for the Time to Run, 10 meters, 4 seconds.

Still on the evaluation of the functional capacity of patients with DMD, the study "Evaluation of patients with Duchenne muscular dystrophy in a gait computerized laboratory through the gait alteration index", by Melanda et al. (2011)[11], aimed to evaluate the application and correlation of the gait alteration index (GDI), functional mobility scale (FMS), and the Sutherland index (SI) in patients with DMD, to more fully trace the profile of manifestations of this disease and thus favor and potentiate its therapeutic approach.

This study included 11 male DMD patients aged 6 to 11 years, who underwent the aforementioned tests to evaluate, at the end of the analysis, the main DMD alterations. The main results presented were the mean GDI at 82.5 (±13.5), with values ≥100 expected for normal, FAQ, FMS (50/500m), and strong with IS (p>0.83 and p≤0.05). Hence, the author concludes that the use of these parameters for the evaluation of the most significant DMD alterations and their impact on the patient's quality of life is very effective and can be used for the determination and study of new therapeutic approaches.

Allied with the evaluation of the functionality of patients with DMD, we found the study "Quantification of muscle strength and motor ability in patients with Duchenne Muscular Dystrophy on steroid therapy" by Parreira et al. (2007)[12]. This study involved ninety patients with DMD, aged 5 to 12 years, who were submitted to corticotherapy using deflazacort or prednisolone, for a variable period of one to seven years, evaluating the natural evolution of the disease and what the impact of corticoid therapy would be. At the end of the study, it was noted that the MRC index, used to assess muscle strength, was lower, on average, in patients whose age at evaluation was nine years or more. With this, it was concluded that the age/MRC ratio decreases by an average of 0.80 points with each year of increased age (3.65 points in natural history). Added to the MCR index, the age/Hammersmith score ratio, used in the evaluation of the neurological part of childhood, decreased by 0.76 points with each year of increased age (2.23 points in natural history), thus pointing to a reduction of progressive neurological development in these patients.

In the study "Genetic diagnosis as a tool for personalized treatment of Duchenne muscular dystrophy", by Bello e Pegoraro (2016)[13], the authors analyzed whether genetic counseling is a better alternative in the management of patients with DMD, providing more assertive and individualized treatments.

To verify this statement, the study took into consideration positive and negative MLPA patients, delimiting the best treatment for each group. In the case of MLPA-positive patients showing a skipping of exons 44, 45, 51, or 53, they are more likely to be treated with antisense oligonucleotides or, in the case of exon 51, with clinical trials of the drug eterplisen in the USA. Patients with negative MLPA but with nonsense mutations, on the other hand, are more amenable to treatment with stop codon trans-reading compounds such as ataluren. There are also promising new clinical studies using CRISPR-Cas9 for DMD-specific mutations.

In the article by Santos et al. (2006)[14] with the title "Clinical and functional profile of patients with Duchenne Muscular Dystrophy assisted in the Brazilian Association of Muscular Dystrophy (ABDIM)", an analysis and characterization of the clinical and functional profile presented by patients with DMD who had a follow-up in the Brazilian Association of Muscular Dystrophy (ABDIM) was performed.

For this analysis, 58 medical records of individuals between 9 and 25 years of age were evaluated to collect numerous data such as age, which is more frequent in the adolescent age group, while the most frequent clinical complications were: hypoventilation, retractions and muscle shortening, especially of the lower limbs, and osteoarticular deformities such as rectification of the thoracic and lumbar regions of the spine. Moreover, regarding the level of independence concerning functionality, dependence was perceived for hygiene, clothing, and locomotion activities. Finally, the clinical and functional profile of these patients was classified as heterogeneous; hence, the progression of the disease varies from individual to individual within the population studied, even when considering the age range.

The comparison of the quality of life of patients diagnosed with DMD from two perspectives, under that of the patients themselves and their caregivers, performed using the AUQEI scale (Autoquestionnaire Qualité de Vie Enfant Imagé), was analyzed in the article "Quality of life: comparative analysis between children with Duchenne muscular dystrophy and their caregivers", by Gonçalves et al. (1999)[15]. This assessment boils down to a questionnaire on the child's quality of life scale, assessing the subjective feeling of well-being, and was applied to 36 individuals, 18 patients diagnosed with DMD (age range between 6 and 12 years), and 18 caregivers. The analysis of categorical variables was performed using Fisher's Exact Test and numerical variables by the Student Test. Finally, no analytical differences

between the responses of the 2 interviewed groups could be observed, and both judged that the patients do have a good quality of life.

Another option for therapeutic intervention in patients with DMD with respiratory insufficiency is non-invasive mechanical ventilation, but many young patients do not adapt to this type of interface. The analysis "Mouth ventilation in Duchenne muscular dystrophy: a rescue strategy for non-adherent patients" performed by Fiorentino et al. (2017)[16] discusses this theme. Two patients refused to use non-invasive ventilation, due to physical discomfort and the social inconvenience of the method, which mainly impairs communication and can cause claustrophobia.

The acceptance of both patients to mouth ventilation was beyond expectations, and its use decreased sleep apnea in patient 1 and improved the nocturnal breathing pattern in patient 2 who has sleep hypoventilation syndrome. Buccal ventilation was shown to require fewer backups and equipment adjustments, reduced air blowing in patients, and prevented alarms from going off on the devices, which increases and facilitates the patients' adaptation to the device.

Corticosteroids are widely used in the treatment of DMD. In the study "Developing standardized corticosteroid treatment for Duchenne muscular dystrophy" described by Guglieri et al. (2017)[17] corticosteroid interventions in children with DMD were evaluated, taking into consideration the most common steroid prescriptions, the complications of these treatments and the prevention of side effects. The study followed 300 children in 5 different countries for 3 years, who were randomly assigned to one out of three different corticotherapy regimens: daily prednisolone, daily deflazacort, or intermittent doses of prednisolone (10 days yes/10 days no).

Intermittent day treatments have been shown to be less effective than daily treatment and, despite clear and consistent evidence of the benefits of corticosteroids in DMD, prescribing remains highly variable between countries. There are some nations such as France and China where corticosteroids are prescribed infrequently, while in the rest of the world this is more frequent. The study showed that patient survival has been prolonged from the late teens to the late 20s possibly due to the health care of the carrier, including the use of corticosteroids. Factors responsible for the non-acceptance of corticosteroid use include concerns about side effects and the lack of familiarity with preventing them. Finally, the authors expose the need for the approval of standardization in the treatment of DMD to guarantee the use of corticosteroids, improving the health care of patients with this disease.

Discussion

Regarding the intervention cases and their results, it can be inferred that, although DMD is incurable, there must be a multidisciplinary treatment to minimize symptoms and ensure the patient's well-being. This disease presents clinical manifestations from birth, and early diagnosis and treatment are crucial. In general, the literature reviewed exposes physiotherapy, low-impact exercise, hydrotherapy, and respiratory rate (RR) assessments as the main treatments. Corticosteroids are a valid drug treatment option. Finally, genetic counseling in DMD brings a new era of molecular treatment, which promises many advances in clinical interventions in cases of dystrophy in the coming decades.

The beginning of the fight against the evolution of DMD is in the disease diagnosis, essential for targeted treatments. Pereira et al. (2020)[10] conducted a clinical trial in which 472 children - 344 healthy and 128 with DMD - were submitted to 3 simple and inexpensive motor tests: time to stand up, time to walk 10 meters, and time to run 10 meters. These tests aimed to verify the difference in results between the groups and, based on this, establish parameters for screening individuals with dystrophy, allowing an earlier follow-up and treatment[10].

In this study, we observed results with significant differences between the groups starting at age 7 in the times of standing up and walking. This age is the period in which there is an intense and progressive worsening of the clinical picture of DMD. From this, the authors were able to define values within the motor tests that strongly indicate the manifestation of the disease related to the times of standing up, walking, and running, which enables the introduction of these tests in pediatric tests. These parameters favor an early diagnosis through their use as triage in the pediatric physical examination, allowing treatment to be started before more severe complications of DMD arise, thus having great potential for improving the quality of life of these patients[10].

Lopes et al. (2018)[2] described a case report of two siblings, aged 7 and 9 years, diagnosed with DMD. The researchers constructed a heredogram from the family history and used the children's tests to compare the cases with papers on the subject. They concluded that the progression of the disease and its complications, although similar in some symptoms, vary considerably depending on the carrier. Furthermore, the need for a correct and careful diagnosis was exposed, a fact evidenced by the report of a proposal of orthopedic surgery on the patients, since the medical team initially mistakenly believed that the brothers' presentation was due to a bone problem[2].

In the field of DMD diagnostic possibilities, genetic counseling, the first step to employing a personalized molecular treatment, is an important tool to establish the exact causes of the dystrophy, determining the mutation exons of each patient. However, the genetic variability of DMD is very wide, generating different manifestations and progressions according to the organism and the genome of each of its carriers[13]. This fact makes the use of a generalized therapeutic resource difficult, but the advance of molecular treatments favors individual and personalized intervention in dystrophy therapies. Nowadays, for Bello e Pegoraro (2016)[13], the ideal diagnostic method is genetic treatment, developed from molecular diagnostic methods for the adoption of treatments directed to the characteristics of each patient[13].

Based on this, it will be possible to choose drugs, interventions, and therapies that are more assertive according to the particularities of the DMD manifestation in each person. Thus, gene therapy is promising, although most of the interventions studied are still in the testing phase. Therefore, this type of diagnosis and treatment is still very expensive and inaccessible to the majority of the population, which hinders its widespread use.

Facing the general reality of the population, the most accepted treatment when it comes to muscular dystrophies is physical therapy. Gevaerd et al. (2013)[3] expose a study developed with a 17-year-old patient with DMD3 in which respiratory rate (RR), heart rate (HR), blood pressure (BP), lactate and glucose concentrations in the blood and the subjective perception of the patient were evaluated. In this work, physical therapy was performed in three stages: passive mobilization to stretch the muscles, respiratory conditioning, and the individual's active movements of moderate strength. At the end of the session, data collection was repeated and the following changes were observed: the PSE and lactate concentration increased linearly during physiotherapy; glucose concentration and RR did not change; HR varied randomly, and BP was reduced[3].

Among the results of this study, it was observed that physical therapy, besides working on maintaining mobility and muscle strength, plays a crucial role in the prevention of respiratory complications in patients[3]. Due to the weakening of the diaphragm with the progression of the disease, there is greater difficulty in ventilation in patients with DMD, resulting in respiratory failure, which is more common in these patients[3]. Still according to Gevaerd et al. (2013)[3], the use of the Borg CR10 Scale for PSE in the physical therapy of patients with DMD can be extremely important to grade the patient's tiredness, since fatigue is the limiting factor of the treatment[3]. However, these data are based on only one case study and further studies are necessary.

In another study focusing on the vital signs of patients with DMD, Franzini et al. (2012)[9] evaluated HR and BP at rest and during immersion, in addition to delimiting the importance of exercise time and intensity, since drastic variations in the levels of vital signs are very dangerous especially in frail patients, such as those with DMD, who usually present serious myocardial and diaphragmatic involvement. Therefore, a significant decrease in HR was noted in those who remained immersed, in addition to important increases in the BP of patients who were submitted to dorsal floating[9].

Most authors warn about activities that require maximum muscle strength against the action of gravity since these can increase muscle degeneration and cause a more rapid evolution of DMD in children with DMD. Despite this warning, some authors, among them Franzini et al. (2012)[9], also state that physical activity is necessary, since inactivity is completely inadvisable because its effects can potentiate the progression of the disease. Thus, regular low-impact physical activity is the most appropriate and consensual prescription for DMD carriers.

Caromano et al. (1998)[4] collected data during hydrotherapy sessions with 20 male children with DMD using the HR, oxygen saturation, maximum inspiratory pressure, and maximum expiratory pressure of the patients as variables. In this study, significant changes were observed in maximal inspiratory and expiratory pressures, with a decrease of 8 cm of water and an increase of 7.4 cm of water, respectively, after immersion. Added to this, little significant change was observed in heart rate and oxygen saturation, proving that hydrotherapy helps in the respiratory process and does not overload children with DMD[4].

Therefore, Franzini et al. (2012)[9] and Caromano et al. (1998)[4] agree that hydrotherapy is a very efficient activity for people with DMD, although they present different methods and evaluations. Since it is a low-impact activity with reasonable stimulus to the body, hydrotherapy is related to lower risks of muscle overload and, consequently, avoids negative developments in the patients' conditions[3].

Like Franzini et al. (2012)[9], Gevaerd et al. (2013)[3] advocate for the controlled practice of physical activities that are appropriate to the needs of the patient, aiming to develop balance and increase the contraction strength of the respiratory muscles. However, other scholars believe that there are difficulties in achieving these objectives due to the limitations of the patient with DMD, mainly due to muscle weakness. In addition, the methods used in rehabilitation are quite restricted because of the care needed not to fatigue the patient, since muscle exhaustion can worsen their condition[3].

Regarding drug interventions in DMD, the study by Parreira et al. (2007)[12] discusses the use of corticotherapy in the treatment of patients. The work compares the muscle strength and motor skills of patients submitted to treatment with prednisone, prednisolone, and deflazacort, corticosteroids used to reduce the rates of muscle loss, scoliosis progression, and wheelchair confinement[12]. In an evaluation with the MRC index, which measures muscle strength, it was observed that patients older than 9 years showed a worse response to drug treatment, which corroborates the idea that interventions must be done as early as possible. In addition, it was possible to infer that in children treated with corticoids the evolution of the disease occurred more slowly. Therefore, according to the authors, this treatment can increase muscle strength, prolong ambulation, reduce the progression of orthopedic problems and heart disease, and increase lung capacity[12].

However, it is important to intervene from the first signs and symptoms to develop effective therapies and significantly improve the quality of life of patients[12].

Although these studies show that the use of corticosteroids can reduce the expected loss of muscle strength in DMD patients over time, it does not change the history of the disease. Currently, there is research on treatments that effectively change this aspect[11].

According to Melanda et al. (2011)[11], computerized gait monitoring may help these new treatments, since it allows the global assessment of ambulation after an intervention, which cannot be detected directly at the intervention site. Furthermore, the gait alteration index (GDI) was

demonstrated to be capable of measuring the gait and producing a single numerical index which works as a grade for the individual's ambulation through nine variables collected in three-dimensional machines[11]. Correlated to the GDI, the functional assessment questionnaire (FAQ) allows the professional evaluator to understand the daily life of the patient, while the functional mobility scale (FMS) provides the classification of the walking ability and perception of changes over time for distances of 5, 50, and 500 meters. This multifactorial evaluation allows a more complete profiling of the manifestations of the disease, facilitating the approach to the patient with adequate therapies[11].

Guglieri et al. (2017)[17] are developing a clinical trial in 5 countries with children aged 4-7 years with DMD. This trial evaluates corticosteroid treatment and seeks to establish the standardized management of patients with dystrophy. For 3 years, a group of 300 children from all over the world will be randomly treated with daily prednisolone, daily deflazacort, or intermittent prednisolone protocols (10 days on, 10 days off)[14]. In this way, researchers will be able to evaluate the efficacy of treatments, common side effects, and their prevention, based on pre-established evaluation criteria. This promising study is a great hope for the development of knowledge on corticosteroid treatment in DMD, which still lacks evidence but has been shown to be effective in preventing the progression of the disease[14].

Given these possibilities, it is important to observe the general profile of the DMD patient, despite the many different manifestations of the dystrophy. Santos et al. (2006)[14] presented research carried out in the medical records of 58 male patients undergoing physiotherapy, intending to trace the clinical and functional profile of DMD patients. The data collected referred to age, clinical complications, daily activities, use of orthoses, age at gait loss, trunk control, Gowers sign, and the presence of shortening, retraction, and spinal changes.

Regarding age groups, the majority were adolescents between 9 and 25 years[14]. As to the most frequent clinical complications, retractions, hypoventilation, and altered spine curvatures were observed. Regarding the degree of independence concerning functionality, the question of feeding with and without support was exposed, and it was inferred that, within feeding, 64.6% were independent with support and 35.4% without support[14]. Gowers' sign was numerically relevant between 6 and 8 years of age, and gait loss ranged from 6 to 17 years. In addition to these data, it was observed that from 13 years of age on, the patients started having cardiomyopathies and, among the muscles affected, the diaphragm was the last one to be affected, which is an advantage, since this is the main muscle responsible for breathing[14]. Bone loss was found in 31% of the studied population which can be aggravated by the use of corticosteroids.

On the other hand, Parreira et al. (2007)[12] present corticosteroid therapy as a possible reducer of orthopedic problems, which leads to the need to study this divergence in future research. Santos et al. (2006)[14] point out that the clinical and functional profile of patients with DMD is diversified, that is, the evolution of the disease is different for each patient.

In DMD progression, the most uncomfortable and dangerous symptom is respiratory failure, which intensifies with tissue damage to the diaphragm. In the face of this symptom, ventilatory intervention is often necessary to ensure adequate oxygenation of the patient's body, avoiding drastic outcomes such as cardiac arrest[17].

In this sense, Fiorentino et al. (2017)[16] discuss using oral ventilation devices to replace traditional non-invasive ventilation (NIV). The researchers state that NIV is the object of resistance among patients who need ventilatory support, given the compilation of inconveniences that the device presents. It is composed of a large mask that covers the entire face, connected to the device that performs the patient's ventilation. This mask, besides not adapting well to all types of faces, can cause contact injuries and makes communication difficult for the patient, who cannot, for example, call his family. All these factors discourage treatment, which leads to worsening of the symptoms and poor patient outcomes.

Thus, buccal ventilation (MBV) proved to be an excellent alternative to traditional NIV[17]. Treatment compliance was greatly increased and patient outcomes were improved thanks to this. Both patients in the study reported improvements concerning the discomforts of NIV, such as air leakage, which ended with BV; undue triggering of alarms, which occurred frequently since the masks did not adapt,; and less need for backups[17]. Personally, the sleep apnea picture of patient 1 was reduced, while for patient 2, an improvement in the nocturnal breathing pattern and a reduction in respiratory effort were conferred, improving his hypoventilation sleep syndrome. Thus, the importance of developing strategies to adapt treatments for DMD patients, who have such delicate prognoses and need discipline and constancy in the proposed therapies, is evident. In addition, the improvements are remarkable when the interventions are followed to the letter[17].

Finally, to verify the well-being of patients with DMD, Gonçalves et al. (1999)[15] carried out a study to correlate the quality of life of patients from their own perspectives and those of their caregivers. For this, an assessment was performed using the AUQEI scale (Autoquestionnaire Qualité de Vie Enfant Imagé), developed in France by Manificant and Dazord, in 1997, validated and adapted in Brazil by Assumpção Jr. et al., in 2000[15]. This assessment consists of 26 questions that evaluate family and social relationships, activities, health, and bodily functions, assessing the child's subjective sense of well-being. Each question has a maximum score of 3, which corresponds to very happy, and 0 being very unhappy. Thus, the maximum score on the scale is 78 points.

The researchers invited 36 male volunteers, half of them diagnosed with DMD, aged between 6 and 12 years (mean age: 8±2.05 years and mean time of onset of symptoms of approximately 4 years); and the other half being composed of the mothers of these patients.[15] As a conclusion of the

studies by Gonçalves et al. (1999)[15], the scores of the scales between the patients and their mothers did not show statistically significant differences, which indicates that the quality of life of the family as a whole is related. Moreover, the scores of mothers and patients of different ages and stages of the disease showed that the quality of life is directly related to the stages of the disease, being higher in the early stages. Therefore, it is very important to develop early and effective treatments to intervene as soon as possible and avoid dystrophy progression, leaving patients with minor sequelae and preserving their mobility and health.

From the literature review, it was noted that the field of conventional therapies has much to investigate about DMD and the needs of those who suffer from the disease. More tests are needed to evaluate the progression of the disease, in addition to planning to improve the quality of life according to the evolution of each patient.

It is important to emphasize that DMD treatment must be multidisciplinary, that is, different types of therapy are indicated simultaneously for the patients. In addition, there must be communication between different areas of the health sciences to adapt the treatment to each carrier and improve the quality of life of these patients. Furthermore, despite the disagreements in methods, all the articles used as references converge in the adherence to treatments with physical activity to slow down symptoms such as respiratory failure and increase the life expectancy of each patient.

Conclusion

Throughout this review, the difficulties of health professionals in finding effective and indicated methods for the treatment of the symptoms of dystrophy were demonstrated, added to the obstacles encountered by those suffering from DMD in living with the disease, since it has no cure and presents extremely disabling symptoms. Despite this, physical therapy is the most used and indicated alternative, even though there are disagreements about its effects.

In the articles covered here, the recognition of the need for exercise in these patients is unanimous. However, authors disagree about the intensity of the activities, which can worsen the symptoms when performed vigorously, since high-intensity physical activity leads to muscle fiber injury. Thus, it is important to have a professional physiotherapist adapt the sessions to each patient and their needs and limitations, according to the degree of involvement of the DMD.

In addition to exercise, interventions with corticosteroid drugs are also addressed in the articles in an attempt to slow the progression of the disease in the patient's body. There is controversy over adherence to this treatment due to the side effects of prolonged use of this type of medication, which can lead to serious harm to the patient.

Finally, gene therapy, a potential solution for the treatment of dystrophy, proves to be an expensive method that is not accessible to the population. However, clearly, the therapy has positive and desirable effects on the patients, who have a much slower progression of the disease. Thus, the accessibility of this type of therapy to the population is an urgent and necessary agenda.

Therefore, the real and applicable effectiveness of physical therapy in DMD sufferers is noted, improving the symptoms and slowing the progression of dystrophy. It is important to emphasize the need for a broad genetic treatment for patients that, if made available to all and associated with physical therapy, would add to the quality of life and the prospect of improvement of patients.

Author's Contribution

Author contributions are structured according to the taxonomy (CRediT) described below:

Conceptualization, Investigation, Methodology, Visualization & Writing – review & editing: Carvalho, L.R; Gama, H.V.P; Brito, L.A; Avelar, M.S.S; Augusto, L.B.X; Mariante, L.T; Viggiani, L.F. *Project administration, Supervision & Writing – original draft:* Carvalho, L.R; Brito, L. A; Gama, H.V.P; Avelar, M.S.S; Augusto, L.B.X; Mariante, L.T; Viggiani, L.F. *Validation & Software:* Carvalho, L.R; Brito, L.A; Gama, H.V.P; Avelar, M.S.S; Augusto, L.B.X; Mariante, L.T; Viggiani, L.F. *Resources & Funding acquisition:* Carvalho, L.R; Brito, L.A; Gama, H.V.P; Avelar, M.S.S; Augusto, L.B.X; Mariante, L.T; Viggiani, L.F. *Data curation & Formal Analysis:* Carvalho, L.R; Brito, L.A; Gama, H.V.P; Avelar, M.S.S; Augusto, L.B.X; Mariante, L.T; Viggiani, L.F. *All authors contributed to manuscript revision and read and approved the submitted version.*

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