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A Comprehensive Review Study on Muscular Dystrophy and its Associated Impact on Health and Individuals

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Abstract

Muscle dystrophy is a genetic muscle disease which leads to progressive loss of muscle mass and a weakened musculoskeletal system. There are more than 30 types of muscular dystrophy which vary in severity, symptoms, and causes but the major ones are nine types. Duchenne MD is the most common type of muscular dystrophy, and it takes place in most of the cases around 50% of them. Usually, boys are more affected by Duchenne MD because of mutations in X chromosome (X-linked recessive). However, females who carry mutated gene will have few symptoms. If one of the genes responsible for producing and protecting the protein is impacted, Muscle Dystrophy can be affected. The family history of muscular dystrophy and young aged boys are at higher risk of developing the disease (Duchenne MD). However, it exists in all ages, races and both sexes. The general clinical feature of MD is a continuous weakness, diminishing of muscle size, mass, bulk, changes in overall posture and reduction of weight. In advanced cases of muscular dystrophy, patients may not be able to run, kneel, bend, jump or even carry heavy objects. The pathophysiology, it is a defect in a gene positioned on the short arm of chromosome X near the p21 locus which is responsible for the manufacture of dystrophin. There's no cure for any of the types of Muscular Dystrophy (MD) but the symptoms can be managed by medications, therapies and surgical interventions. The life expectancy of patients varies depending on the progression and type of the disease. This is a comprehensive review study of different aspects of muscular dystrophy and its impact on physical, familial, cultural and socioeconomic life of an individual.

Keywords:
Muscular dystrophy; Duchenne muscular dystrophy; Becker muscular dystrophy

Abbreviations: MD: Muscular Dystrophy; LGMD: Limb-gridle Muscular Dystrophy; FSHD: Facioscapulo-Humeral Muscular Dystrophy; DMD: Duchenne Muscular Dystrophy; DGC: Dystrophin-associated Glycoprotein Complex; CMD: Congenital Muscular Dystrophy; EDMD: Emery-Dreifuss Muscular Dystrophy

Introduction

We all wake up every day, go to work and do whatever we want to do. We do all of these by using our muscles. As in maintaining our position and for moving from one place to another, Muscle generates the force and locomotion which is required in doing these functions. Furthermore, it helps our internal organs to move and function, as the heart and gastrointestinal track. However, sometimes our muscle genes could be disrupted leading to loss of function. So what is muscle dystrophy (MD)? MD, in general, is a muscle disease which leads to progressive loss of muscle mass and a weakened musculoskeletal system. It has more than 30 genetic disorders that progress over time leading to degeneration and weakness of the muscle. And this decreases the capability of the muscle to do its function. The word "progress over time" means that it gets worse with aging, increasing the level of disability. MD caused by abnormal gene interferes with the normal production of protein. There are many people who lose their ability to walk because of this disease [1]. In this present comprehensive review literature, we will discuss all it, starting from its epidemiology, causes, its pathophysiology, clinical signs, and symptoms. In addition to these, it was also discussed about diagnoses, complications, treatment, and prognosis [2,3].

Incidence and Prevalence of MD Worldwide

The most common inherited muscle disease in childhood is Duchenne muscular dystrophy with an incidence 1 of 3500 boys (Figure 1). There is another type of muscles disease called Becker muscular dystrophy and it is less common than Duchenne muscular dystrophy. The incidence of Becker muscular dystrophy 1 of 18,518 males' birth (Figure 2). The diagnosis of both types of muscles disease is based on the clinical picture of progressive muscular weakness in affected boys and calf hypertrophy, in the presence of positive family history. This study based on the natural history of diseases. This study shows the prevalence of Duchenne muscular dystrophy [4,5].

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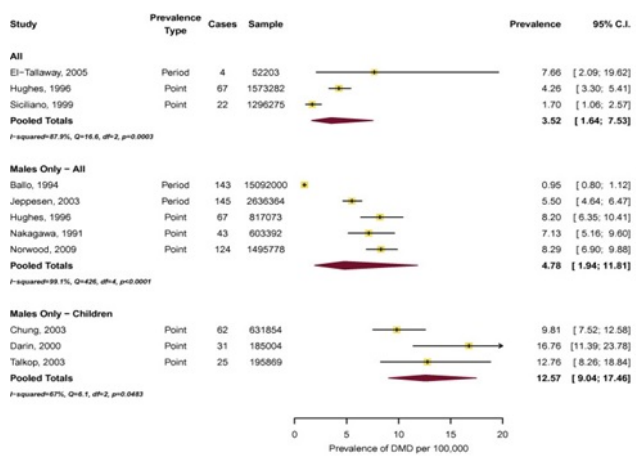

Figure 1: Prevalence in Duchenne MD.

Here is another study shows the prevalence of Becker muscular dystrophy. This study is part of the National Population Health Study of Neurological Conditions [6].

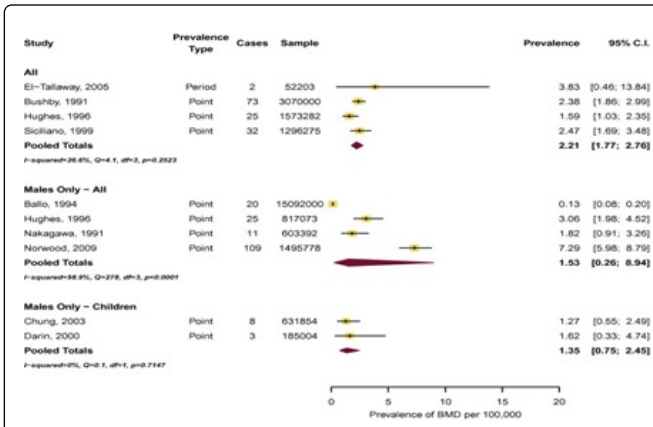

Figure 2: Prevalence of Becker MD.

Different Types of MD

There are more than 30 types of MD which vary in severity, symptoms, and causes. There are nine common and major type of MD classify according to the distribution of muscle weakness, the age of onset, progression, symptoms, severity, and family history [7].

Duchenne MD

Duchenne MD (Figure 3a) is the most common of the MD and it forms 50% of cases. It is affecting boy more because of mutations in X chromosome (X-linked recessive). However, females who carry the mutated gene will show some symptoms. Duchenne MD due to an absence of dystrophin (a protein that connects the cytoskeleton of muscle fiber to the surrounding extracellular matrix through the cell membrane [8]. Duchenne MD is usually appearing during the early years when the child starts walking, the affected child will show weakness and muscle wasting in the upper legs and pelvis then spreading into the upper arm. However, wasting muscle may appear normal as a result of the accumulation of fat and connective tissue this called pseudohypertrophy. Also, the affected child shows loos of some refluxes, waddling gait, frequents fall, difficult breath and swallow, scoliosis, and cardiomyopathy. They usually lose the ability to walk by early adolescence and die in the early twenties because of heart muscle weakness and respiratory complication [9].

Becker MD

Becker MD (Figure 3b) is less severing than previous and causes by the insufficient function of the dystrophin. It starts around age 11 and occurs late around 25, affected people usually able to walk and live until middle age or late. The progressive rate is symmetric and is noticed in the upper arms and shoulders, upper legs, and pelvis. Symptoms of this condition include frequent falls, muscle cramping, walking on one's toes, and cardiac complication but not like Duchenne MD [10].

Congenital MD

Congenital MD is autosomal recessive MD which starts at birth or first months and affected male and female. They have a problem with motor function and muscle control, the muscle degeneration is mild to severe. Also, they can't sit or stand without support and sometimes they can't learn how to walk. In addition, they may have chronic shorting of the tendon and muscle called contractures which lead to hard movement of joint, also they have scoliosis, the problem in swallowing and respiratory. Congenital MD may affect CNS and lead to vision and speech problem, seizure, and brain structural changing. They usually die in infancy. Finally, it has 3 subtypes: [11]

- Merosin-negative disorders, where the protein merosin is missing
- Merosin-positive disorders, merosin is present but other proteins are missing
- Neural migration disorders, the neurons aren't in the proper location

Distal MD

Distal MD (Figure 3c) is a disease that affects distal muscle (hands, forearms, feet, and legs) in rare condition affects other muscle like heart, it is starting between age 40 to 60 and affect both sexes. Distal DM usually less severe and affect less muscle than other type and progressing slowly. An affected person have difficulties in walking, standing, and extend fingers. In this case, a Dysferlin protein which responsible for skeletal muscle repair and its gene located on chromosome 2p 12-14 is lacking.

Emery-dreifuss MD

Emery-dreifuss MD has two forms: one is X-linked recessive and another one id autosomal dominant. Male more affected than female. It usually is at age 10 but the symptoms start at mild twenties. The disease causes a slow wasting of muscle and symmetric weakness, but it is progressive. Also, it can cause contractures in the spine, knees, ankles, elbows, and back of the neck. The elbows become locked in a flexed position due to Contractures. In addition, when disease progress the spine become rigid. Affected individuals will have heart problem around 30 age and they need pacemakers. Females who carry this disorder often have a cardiac complication but without weakness of muscle.

Facioscapulohumeral MD

Facioscapulohumeral MD (Figure 3d) is affecting muscles of face, shoulder, and humerus. It is an autosomal dominant disorder, and it is the third most common of MD. The onset of the disease in teenage but may occur early or late. FSHD causes asymmetric weakness and this is a hallmark. First muscles being affected are these around eyes and moths. Then, followed by weakness of muscles of shoulder, chest, and upper arm. An affected person usually shoulder blades appear winged, lordosis, also they have fascial changing like a crooked smile, a pouting look, sometimes can't pucker their lips, difficulty swallowing, chewing, or speaking. In this case, cardiac muscle not usually affected.

Limb-girdle MD

Limb-girdle MD (Figure 3e) refers to more than 20 conditions that causes symmetric weakness of proximal muscle. Autosomal dominant limb-girdle was known as type 1, while autosomal recessive known as type 2. Some autosomal recessive because of deficiency of one of the four dystrophin-glycoprotein complex proteins. The recessive LGMD begin in childhood and teenage, while dominant LGMD being adulthood. LGMD affects both sexes. Weakness starts around hip then go to shoulder, leg, and neck. The affected patient will have a rigid spine because of contractures in the back muscles, also proximal reflux impaired. People who have LGMD may become severely disabled within 20 years after onset.

Myotonic dystrophy

Myotonic dystrophy (Figure 3f) is affecting both sexes between ages 20-30. It causes an inability to relax muscle followed by sudden contraction. Weakness begins in the muscles of face and neck and produces long, thin face and neck, then affect forearm. Myotonic dystrophy affects many body systems include CNS, heart, adrenal gland and thyroid, eye, GI tract.

Oculopharyngeal MD

Oculopharyngeal MD is affecting both sexes begin in the forties or fifties. The weakness of facial and pharyngeal muscles. Affected people show difficult swallowing, tongue atrophy, changing the voice, double vision, ptosis (drooping of the upper eyelid), the cardiac problem [12].

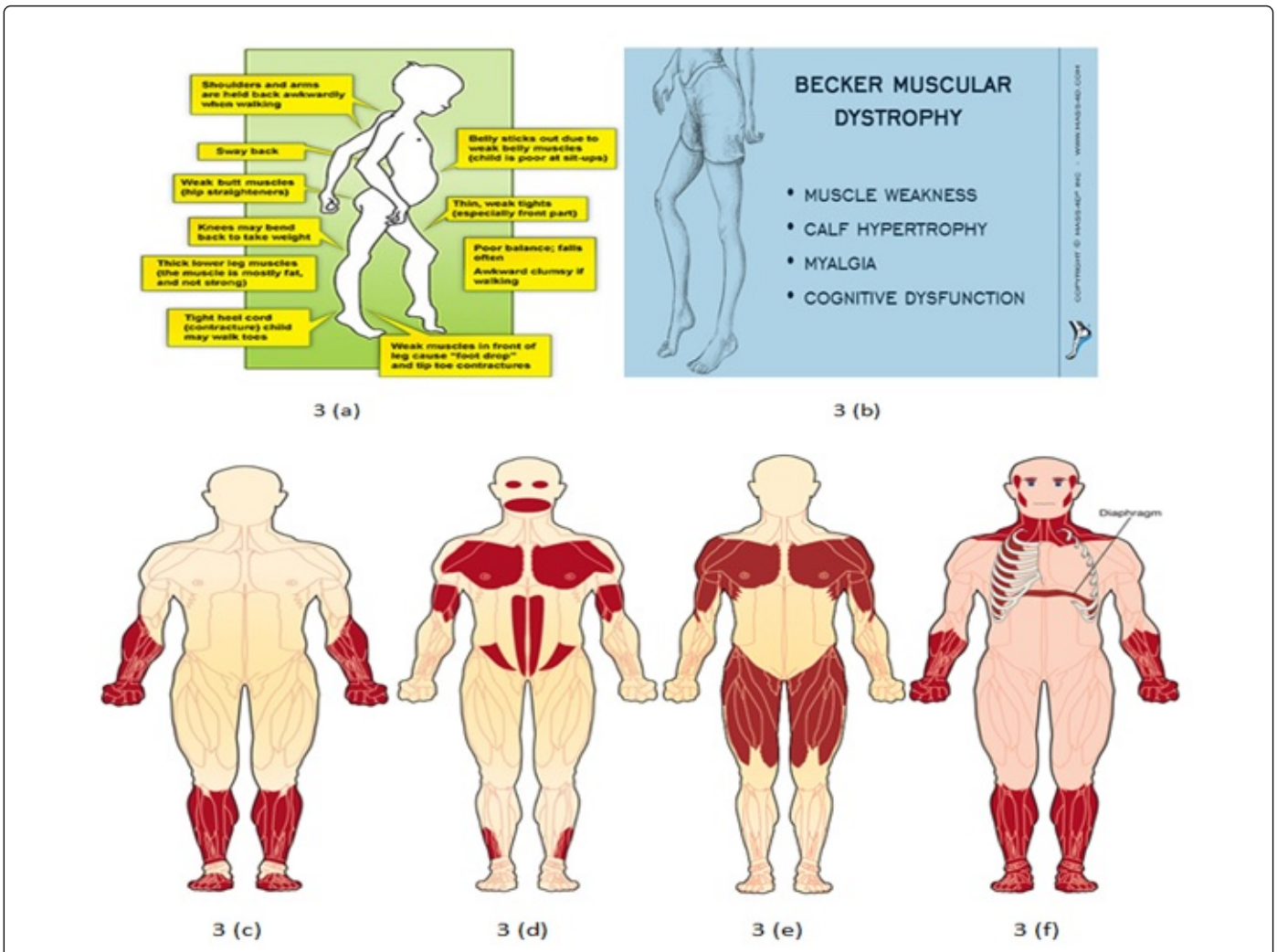

Figure 3: (a) Duchenne muscular dystrophy (b) Becker muscular dystrophy (c) Distal Muscular Dystrophy (d) Facioscapulohumeral Muscular Dystrophy (e) Limb-girdle Muscular Dystrophy (f) Myotonic Dystrophy.

Complication of MD

MD has a lot of complication these are contractures which mean shortness of tendon and muscle lead to loss of joint movement. Also, it affected heart muscle and diaphragm that give rise to heart and respiratory problem respectively. Furthermore, it affects back muscle which makes them unable to support the spine and may lead to scoliosis, also walking is difficult among these people. Finally, it affects other muscle around the face and throat that lead to difficult swallowing [13].

Genetic Predisposition and Variation in MD

There are a number of genes in our body responsible for making proteins that protect our muscles from taking damage. When one of these genes is defective muscular dystrophy occurs. MD has many forms, each form is caused by a genetic mutation to that form of the disease. A number of these mutations are inherited. But some occur in the developing of the embryo [14].

Facioscapulohumeral MD (FSHD)

DUX4 encodes for a transcription factor when it overexpressed he can cause abnormalities that lead to muscular dystrophy in mice and zebrafish. Also, it is been noticed that it is elevated in Facioscapulohumeral patients.

Duchenne MD

It is a devastating neuromuscular disorder which is inherited. The responsible is gene is dystrophin and its products. 30% of boys with Duchenne MD (DMD) did not have a family history of DMD, because the gene involved may be subject to abnormal change in the sequence (spontaneous mutation).

Becker muscular dystrophy

It results from mutations in the dystrophin that leads to the production of a mutated form but partially functional protein.

Myotonic dystrophy (DM)

Myotonic dystrophy it is caused by mutations on 19q13 (DM1) or 3q21 (DM2/PROMM). Myotonic dystrophy is the most common in adults. Also known as Steinert's disease, the patient won't be able to relax the muscle at will following contractions.

Congenital MD (CMD)

About 40% of congenital MD have a defect in (MDC1A) of the laminin α2 chain of merosin (laminin-2) because of mutations in LAMA2 gene. Some CMD syndromes are mapped to chromosome 1q42. In seven families with CMD mutations in the FKRP gene have been identified.

Limb-girdle MD (LGMD)

Mutations in calpain 3 which is the proteolytic enzyme can cause LGMD type 2A. Patients will have difficulty in lifting the front part of the foot.

Distal MD (DMD)

Distal muscle dystrophy is because of a dysferlin mutation.

Emery-Dreifuss MD (EDMD)

Emery-Dreifuss MD is known by early contractures of Achilles tendons and elbows, slowly progressive muscle weakness and muscle wasting. It is caused by mutations in the EMD and LMNA genes.

Oculopharyngeal MD

They are two types autosomal dominant and autosomal recessive. Both types are because of mutations in the PABPN1 gene [15].

Risk Factors of MD

Muscular dystrophy exists in all ages, races and both sexes. However, Duchenne usually occurs in young boys. If the patient has a family history of muscular dystrophy, he is at higher risk of developing the disease or passing it on to their offspring [16].

Clinical Signs and Symptoms of MD

The general clinical feature of patients with MD is that of continuous weakness, diminishing and degeneration of the muscles' size, mass, bulk, and change in overall posture and reduction of weight, it could progress rapidly or slowly depending on the type, cause and the location of the dystrophy. Patient at first may have difficulties standing after sitting or lying down without using hands or being assisted by others or walk with a waddle (waddling gait). Repeated falls are common and unpredictable. Furthermore, using the upper extremities might be hard for raising hands over the level of the head. Doing regular activities such as combing hair or reaching shelves seems very hard [17-19]. In advanced cases with MD, patients may not be able to use the ladders or stairs. They may lack the ability to run, kneel, bend or jump or carrying heavy objects, Moreover, dysphagia (difficulty swallowing) or difficulty in chewing. Double vision, ptosis (dropped eyelids) and dysarthria (unclear speech), Facial weakness or drop sometimes associated with changes in facial appearance [20].

In limited cases, patients have a history with hypothyroidism or they underwent thyroidectomy. History of increasing creatine levels also observed. In the examination, patients with MD will show soft feeling during palpation, it doesn't have to be visible or clear wasting due to normal nutrition in most cases and muscles are replaced by connective tissue and fat. Usually, the severity is more in the lower extremities comparing to the upper extremities. Patients begin to be unable to left or resist the objects' weight then they may not be able to move the limb against gravity [21]. Some clinical features occur in for some specific types of MD. The patient may walk on his/her tiptoes, they have cramping muscles and difficulty moving the hands especially extending the fingers. Also, they may have foot deformities, intellectual disabilities, and rigid spine. Insufficient breathing due to lack of synchronization, cardiomyopathy [22].

Pathophysiology of MD

MD is instigated by a defective gene positioned on the short arm of chromosome X near the p21 locus which is responsible for the manufacture of dystrophin [17-19]. The Dystrophin protein resides in the muscle fiber membrane which acts as a spring or shock absorber

due to its helical structure. As the protein binds actin in the cytoskeleton and dystroglycans of the muscle cell plasma membrane which used to refer as the extracellular sarcolemma [21,22]. The mutation leads to a lack of the dystrophin protein as well as the reduction or absence of the dystrophin-associated glycoprotein complex (DGC) proteins, which is responsible for the development of muscular dystrophy with various phenotypes in terms of the muscle, age, and the presence of cardiomyopathy. The membrane becomes permeable and fragile due to the absence of dystrophin. Due to that reason the intracellular calcium concentration increase and triggers a distinctive process of necrosis and fibrosis in the various types of the muscle [23]. It induces the activation of some signaling pathways like calpain, a calcium-dependent proteinase, which degrades proteins and contributes to the demise of the cell mediated by the mitochondria [24]. Furthermore, Microscopic lesions form in the sarcolemma with the mechanical action of the muscles [25,26]. With the absence of these proteins, the castamere can't fulfill its role. In addition, the creatine kinase amount elevates forming cracks in the membrane and intensifying its permeability as well as the calcium concentration [27,28]. The skeletal muscle has 3 isoforms of NO synthase which are: the neuronal isoform (nNOS) which is the most abundant, the endothelial isoform (eNOS) and the inducible isoform (iNOS) which are in insignificant quantities. The neuronal isoform activity is reduced due to the absence of dystrophin. As a result, several NO-dependent pathways degranulate counting the regulation of contraction, mitochondrial metabolism, glucose homeostasis, deregulation of metabolic, immune and vascular responses. It might also induce vasoconstriction due to reduced cyclic GMP production in arteriolar smooth muscle cells indorsing exertional ischemia and impaired performance [29]. It's also noted that there is a disproportionate production of free radicals or reactive oxygen species (ROS). The production elevates further during exercise due to the mitochondrial consequences of intracellular calcium elevation. The increase in the reactive oxygen species enriches the activation of the mechanisms of inflammation and promoting cell necrosis through the activation of calpain [30]. The skeletal muscles have a quite low ability to generate local immune responses, as it has a very few masts, dendritic, and pro-inflammatory cells. During the birth of a muscular dystrophy patient part of the immune system is activated specifically the innate system due to the impairment signals to the cell receptors, in addition to the expression of major histocompatibility class 1. The leakage of substances through the tears in the sarcolemma in response to the absence of dystrophin triggers the innate immune system and the process of inflammation. Pro-inflammatory cytokines tempt the expression of class I and II MHC, the recruitment of T and B-cells, and the generation of an adaptive immune response in muscle. In turn, it contributes to the degradation of the muscles and leads to its death [31]. The skeletal muscle is a tissue subjected to mechanical stress constantly where it gets damaged then repaired. However, in muscular dystrophy, the muscle gets exhausted since the disease is permanent. Thus, gives rise to an imbalance between degeneration and regeneration ultimately leading to inflammation, fibrosis of the tissue and loss of the function of the muscle.

Treatment and Management of MD

There's no complete cure for any type of MD but the symptoms can be managed to reduce the problems of the spine and joints to allow mobility for people. The treatment includes medications, occupational and physical therapies, and surgery if needed.

Medications

- Exondys 51 (Eteplirsen) is the first drug to be approved by the FDA. Although it appears safe, the effectiveness of the drug is still not clear. The aim of the drug is to reduce the progression of MD. It helps the body produce dystrophin protein [32,33]
- Glucocorticoids: Prednisone can increase the strength of the muscles, ability and also the respiratory function and slow MD progression. Long-term use of the drug increases the risk of high blood pressure, increase in body weight and weakened bones [33-35]
- Heart medications: If MD progresses to the point that it damages the heart, certain medications can be used like Angiotensin-Converting Enzyme (ACE) inhibitors and beta blockers [34]
- Emflaza (deflazcort): Treats symptoms of DMD in patients older than 5 years old. It's a corticosteroid prodrug and has an anti-inflammatory effect, reducing damage caused by the immune system and reduce swelling [36,37]

Therapy

The quality and length of life in people with MD can be improved by several types of assistive devices and therapies.

- Exercises: Aerobic exercises like swimming and walking help maintain strength, health, and mobility [36]
- Stretching and range of motion exercises: MD can restrict the mobility and flexibility of joints and these exercises can help keeping the joints flexible [36]
- Mobility aids: Wheelchairs, canes, and walkers help maintain movement and independence
- Support: Muscles and tendons can be flexible and stretched by using braces to slow progression of contractures
- Respiratory therapy: Sometimes the respiratory muscles for people with MD can weaken and they need to use sleep apnea device to improve the oxygen delivery during the night. Ventilators can be used in severe muscular dystrophy [32,35]

Surgery

If the MD progresses gradually the patient might need surgery. Operations include insertion of the feeding tube, muscle biopsies, foot surgery and spinal surgery to correct the curvature of the spine caused by scoliosis [32,35].

Prognosis of MD and Conclusion

The life expectancy varies depending on the progression and type of the disease. In some cases, some patients produce severe muscle weakness and lose their ability to walk or any functional disability, but they can reduce the progression of the muscle weakness with great healthcare, medications, and therapies. In other cases, the progression of the disease is mild and result in a normal lifespan [32,38].

Conflict of Interest

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