A comprehensive review study on muscular dystrophy and its associated impact on health and individuals

Abstract

Muscle dystrophy is a genetic muscle disease which leads to progressive loss of muscle mass and 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. Family history of muscle dystrophy and young aged boys are at higher risk of developing disease (Duchenne MD). However, it exists in all ages, races and both sexes. The general clinical feature of MD is 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, backer 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 lose of function. So what is muscle dystrophy? Muscle dystrophy in general is a muscle disease which lead to progressive loss of muscle mass and 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. Muscle dystrophy 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 about 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 muscular dystrophy worldwide

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

Different types of muscular dystrophy

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

Duchenne MD is the most common of the muscular dystrophy and it is form 50% of cases. It is affecting boy more because of mutations in X chromosome (X-linked recessive). However, females who carry mutated gene will show some symptoms. Duchenne MD due to an absence of dystrophin (protein that connects the cytoskeleton of muscle fiber to the surrounding extracellular matrix through the
cell membrane. Duchenne MD is usually appearing during early years when child start walking, affected child will show weakness and muscle wasting in the upper legs and pelvis then spreading into upper arm. However, wasting muscle may appear normal as a result of accumulation of fat and connective tissue this called pseudohypertrophy. Also, affected child shows loos of some reflexes, 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.

Table 1: Prevalence in Duchenne MD

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence Type</th>
<th>Cases</th>
<th>Sample</th>
<th>Prevalence</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>El-Tallaway, 2005</td>
<td>Period</td>
<td>4</td>
<td>52203</td>
<td>7.66</td>
<td>[2.09; 19.62]</td>
</tr>
<tr>
<td>Hughes, 1996</td>
<td>Point</td>
<td>67</td>
<td>1573282</td>
<td>4.26</td>
<td>[3.30; 5.41]</td>
</tr>
<tr>
<td>Sicilano, 1999</td>
<td>Point</td>
<td>22</td>
<td>1298275</td>
<td>1.70</td>
<td>[1.06; 2.57]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>3.52</strong></td>
<td><strong>[1.64; 7.53]</strong></td>
</tr>
</tbody>
</table>

**Males Only — All**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Sample</th>
<th>Prevalence</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ballo, 1994</td>
<td>143</td>
<td>1509200</td>
<td>0.95</td>
<td>[0.80; 1.12]</td>
</tr>
<tr>
<td>Jeppesen, 2003</td>
<td>145</td>
<td>2633684</td>
<td>5.50</td>
<td>[4.64; 6.47]</td>
</tr>
<tr>
<td>Hughes, 1996</td>
<td>67</td>
<td>817073</td>
<td>8.20</td>
<td>[6.35; 10.41]</td>
</tr>
<tr>
<td>Nakagawa, 1991</td>
<td>43</td>
<td>603392</td>
<td>7.13</td>
<td>[5.16; 9.60]</td>
</tr>
<tr>
<td>Norwood, 2009</td>
<td>124</td>
<td>1495778</td>
<td>8.29</td>
<td>[6.90; 9.88]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td></td>
<td></td>
<td><strong>4.78</strong></td>
<td><strong>[1.94; 11.81]</strong></td>
</tr>
</tbody>
</table>

**Males Only — Children**

<table>
<thead>
<tr>
<th>Study</th>
<th>Cases</th>
<th>Sample</th>
<th>Prevalence</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung, 2003</td>
<td>62</td>
<td>631854</td>
<td>9.81</td>
<td>[7.52; 12.58]</td>
</tr>
<tr>
<td>Darin, 2001</td>
<td>31</td>
<td>185004</td>
<td>16.76</td>
<td>[11.39; 23.78]</td>
</tr>
<tr>
<td>Taklop, 2003</td>
<td>28</td>
<td>158589</td>
<td>12.76</td>
<td>[8.26; 18.84]</td>
</tr>
<tr>
<td><strong>Pooled Totals</strong></td>
<td></td>
<td></td>
<td><strong>12.57</strong></td>
<td><strong>[9.64; 17.46]</strong></td>
</tr>
</tbody>
</table>

**Becker MD** is less severing than previous and causes by insufficient function of the dystrophin. It starts around age 11 and also occur 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.

**Congenital MD** is autosomal recessive muscular dystrophies which start at birth or first months and affected male and female. They have 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, 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:

- a) Merosin-negative disorders, where the protein merosin is missing.
- b) Merosin-positive disorders, merosin is present but other proteins are missing.
- c) Neural migration disorders, the neurons aren’t in proper location.

**Distal MD** is a disease that affect 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 sever and affect less muscle than other type and progressive slowly. 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** has two form: one is X-linked recessive and other one id autosomal dominant. Male more affected than female. It usually being at age 10 but the symptoms start at mild twenties. The disease causes 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 elbow 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 carries this disorder often have cardiac complication, but without weakness of muscle.

**Facioscapulohumeral MD** is affecting muscles of face, shoulder, and humerus. It is an autosomal dominant disorder, and it is third most common of MD. Onset of the disease in teenage but may occur early or late. FSHD causes asymmetric weakness and this its hallmark. First muscle being affected are these around eyes and moths. Then, followed by weakness of muscles of shoulder, chest, and upper arm. Affected person usually shoulder blades appear winged, lordosis, also they have fascial changing like 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** refers to more than 20 condition that cause symmetric weakness of proximal muscle. Autosomal dominant limb-girdle 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 start around hip then go to shoulder, leg, and neck. Affected patient will have rigid spine because of contractures in the back muscles, also proximal reflux impaired. People who have LGMD may become severely disable within 20 years after onset.

**Myotonic dystrophy** is affecting both sexes between ages 20-30. It causes an inability to relax muscle followed by sudden contraction. Weakness begin in the muscles in the face and neck and produce 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** is affecting both sexes begin in forties or fifties. Weakness of facial and pharyngeal muscles. Affected people show difficult swallowing, tongue atrophy, changing voice, double vision, ptosis (drooping of the upper eyelid), cardiac problem (Table 2) (Figure 1–6).

**Complication of muscular dystrophy**

Muscular dystrophy has a lot of complication these are contractures which mean shortness of tendon and muscle lead to lose 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 make them unable to support spine and may lead to scoliosis, also walking is difficult among these people. Finally, it affects other muscle around face and throat that lead to difficult swallowing.

---

**Figure 1** Duchenne Muscular Dystrophy.

**Figure 2** Becker Muscular Dystrophy.

**Figure 3** Distal Muscular Dystrophy.
A comprehensive review study on muscular dystrophy and its associated impact on health and individuals

Copyright: ©2018 Alaniz et al.


Genetic predisposition & variation in muscular dystrophy:

There are 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. Muscular dystrophy has many forms, each form is caused by genetic mutation to that form of the disease. Number of these mutations are inherited. But some occur in the developing of the embryo.

Facioscapulohumeral (FSHD): DUX4 encodes for a transcription factor, when it over expressed he can cause abnormalities that leads to muscular dystrophy in mice and zebra fish. Also, it is been noticed that it is elevated in Facioscapulohumeral patients.

Duchenne type muscular dystrophy: It is a devastating neuromuscular disorder which is inherited. The responsible is gene is dystrophin and its products. 30 percent of boys with Duchenne muscular dystrophy (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 production of a mutated form but partially functional protein.

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

Limb-girdle muscular dystrophy: Mutations in calpain 3 which is the proteolytic enzyme can cause limb-girdle muscular dystrophy type 2A. Patients will have difficulty in lifting the front part of the foot.

Distal muscle dystrophy: Distal muscle dystrophy is because of a dysferlin mutation.

Emery-Dreifuss muscular dystrophy (EDMD) 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 muscular dystrophy: They are two types autosomal dominant and autosomal recessive. Both types are because of mutations in the PABPN1 gene.13

Risk Factors of muscular dystrophy

Muscular dystrophy exists in 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 muscular dystrophy

The general clinical feature of patients with muscular dystrophy 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 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 muscular dystrophy, 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 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. In examination, patients with muscular dystrophy 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 for specific types of Muscular dystrophy. Patient may walk on his/her tiptoes, they have cramping muscles and difficulty moving the hands specially 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 muscular dystrophy

Muscular dystrophy is instigated by a defective gene positioned on the short arm of chromosome X near the p21 locus which is
A comprehensive review study on muscular dystrophy and its associated impact on health and individuals

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

Medications:

a. Exondys 51 (Eteplirsen): Is the first drug to be approved by the FDA. Although it appears safe, but 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.

b. Glucocorticoids: For example, 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 also weakened bones.

c. 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.

d. Emflaza (deflazacort): 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 also reduce swelling.

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

a. Exercises: Aerobic exercises like swimming and walking help maintain strength, health and mobility.

b. Stretching and range of motion exercises: MD can restrict the mobility and flexibility of joints and these exercises can help keeping the joints flexible.

c. Mobility aids: Wheelchairs, canes and walkers help maintain movement and independence.

d. Support: Muscles and tendons can be flexible and stretched by using braces to slow progression of contractures.

e. 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.

Surgery: If the muscular dystrophy progresses the patient might need a surgery. Particular operations include insertion of feeding tube, muscle biopsies, foot surgery and spinal surgery to correct the curvature of the spine caused by scoliosis.

Prognosis & 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.

Conflicts of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.
Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References
3. https://www.mayoclinic.org/
36. FDA approves drug to treat Duchenne muscular dystrophy. 2018.