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Muscular Dystrophy: A Review

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ABSTRACT

Muscular dystrophies are a group of muscle-related genetic disorders caused by mutations in someone's genes. Over time, muscle weak point decreases mobility, making regular responsibilities tough. There are many kinds of muscular dystrophy, each affecting specific muscle organizations, with signs and symptoms appearing at extraordinary a while, and varying in severity. Muscular dystrophy can run in families, or a person can be the first of their circle of relatives to have muscular dystrophy. There can be several one-of-a-kind genetic types within every form of muscular dystrophy, and those with the identical kind of muscular dystrophy may additionally experience one-of-a-kind symptoms. Depending on the kind and severity of someone's MD, the outcomes may be slight, progressing slowly over an average lifestyles span. In different cases, it may be competitive, progressing fast and shortening a person's existence. There is presently no manner to save you or reverse MD. However, different sorts of remedies and drug treatments can improve a person's nice lifestyle and delay the progression of signs.

INTRODUCTION

"Muscular Dystrophy" is a hereditary disorder leading to slow or fast progressive, a muscular disorder caused by inadequacy or absence of glycoproteins in the sarcolemma membrane.[1] Muscular dystrophy is a disease with vivid variations being a non-communicable disease.[2] It is seen in different variations each consisting of the specific pattern seen in inheritance, rate of muscle loss, and onset period [2]. Different representations of disease are often seen due to the effect of specific alterations in the gene. It is observed in the research conducted on muscular dystrophy in the past that semitendinosus, gracilis, sartorius, and semimembranosus muscles get primarily affected [3]. Deformity of equinovarus nature, a tilted pelvis, contractures at multiple sites in the body, lordosis or may be scoliosis, in the case of an eye, it can lead to cataracts or even bilateral ptosis [4-7]. Beginning typically happens in the third to fourth decades.[9] But, it might uncover in the early stages or go through sped-up decay close to the period of onset.[10] Parents of impacted people might introduce worry that their kid isn't strolling just as different kids their age.[11][12] The kid might experience difficulty kicking a ball due to weakness.[13] Pseudo-drop occasions brought about by shortcoming of quadriceps muscle may likewise be present.[5] Both guardians could be healthy.[14] On actual assessment, the impacted individual will have gigantic lower leg muscles, in addition, to bringing down appendage proximal muscle weakness.[15] This condition will make impacted people need to use their arms and hands to help with ascending from a situated position.[16] Other grumblings can include a background marked by deferred ambulation, toe strolling, calf hypertrophy, and proximal hip support muscle instability.[17]

Clinical indications such as an asymptomatic and sudden increase in serum creatine kinase (CK), language delay, dilated cardiomyopathy, intolerance (excretory), quadriceps myopathy, and malignant hyperthermia, [18]. For some types of muscular dystrophy, the diagnosis is supposed to be suspected by genetic family history, elevated liver enzymes, the clinical evidence for the above-mentioned indications are unclear.[19] Enzymes like aspartate aminotransferase and alanine aminotransferase are suspected clinically [19].

The inheritance of muscular dystrophy is X-linked, males are observed to suffer more from the disease majoritarian [20]. The reasonable explanation of it being visible in females is turner syndrome, the skewed X chromosome caused inactivation, uniparental disomy, and mutated gene translocation to an autosome [21]. Most of the symptomatic females are in

infancy suffering from proximal weakness of muscles in primary sites [22] it also risks increased weakness in adults, sopasms, myalgias, and lethargy as first seen clinical manifestations. Conditions such as scoliosis hyperventilation of alveoli can lead to severe problems in mystropic infants or children [23].

1. Muscular Dystrophy:

Muscular dystrophy may be a result of mutations in various genes and may be transferred in an autosomal dominant, X-linked, or autosomal recessive way mostly observed.[24] Changes in the X-related gene DMD, which encodes dystrophin, are the maximum common motive of muscular dystrophy.[20] This is why the phenotype is manifested in hemizygous men due to the fact they have the handiest unmarried replica of the X chromosome.[25] One needs to be aware that mutations in dystrophin also create allelic heterogeneity.[26] Mutations in the DMD gene, for example, may also cause muscular dystrophy of both Duchenne or the much less critical Becker, primarily based on the extent of the lack of protein.[27]

Although the phenotypic traits of a number of these issues are definite, the phenotypic spectrum produced utilizing mutations in numerous genes overlaps, wherein spanning to non-allelic heterogeneity.[28] Identification of non-allelic heterogeneity is essential for particular reasons: (1) the potential to understand disease loci in linkage research is decreased with the aid of introducing topics with associated phenotypes, however, separate genetic disorders[29]; (2) genetic trying out is further complex because several wonderful genes need to be analyzed at the side of the chance of special mutations in all of the candidate genes[29]; and (three) data is involved about how genes or proteins partner, consequently offering novel insights internal mobile molecular physiology.[29]

Photocopies are for that reason produced, which can be incidents wherein nongenetic sicknesses simulate a genetic disease. [30] For instance, features of virus or toxin-brought on neurologic symptoms can reflect those visible in muscular dystrophy. As in non-allelic heterogeneity, photocopies retain to confound linkage research and genetic testing. [30] Patient records and correct differentiation in phenotype can normally render symptoms that differentiate those maladies from comparable genetic illnesses. It is vital to word that muscular dystrophy has variable expressivity and incomplete penetrance and, consequently, can be mixed over a phenotypic spectrum in various affected individuals, further demonstrating the aspect of variable expressivity. [31]

2. Etiology

Muscular dystrophy most often outcomes from defective or absent glycoproteins in the muscle membrane. [32] Each form of muscular dystrophy affects by distinct gene deletions or mutations, inflicting various enzymatic or metabolic defects. [33] The dystrophin gene is the most important within the human genome, with 79 exons. [34] The dystrophin gene is a problem with an excessive rate of spontaneous mutations due to its sizeable size (>2 × 106 bases) [35].

Table No. 1: Types of muscular dystrophy their symptoms, affected muscles, and prognosis

Type	Symptoms	Age of Onset	Affected Muscles	Prognosis
Becker	Weakening muscles affects only males	Between 2 and 16: up to 25	Affects arms, legs, and spine can cause heart problems	Can live into adulthood
Congenital	Weakening muscles, joint stiffness, and shortening of muscles	Presents at birth	Primarily affects many voluntary muscles	Progression varies, can shorten the lifespan
Duchenne	Muscles. Can also cause breathing issues and/or heart issues. Affects only males.	between the ages of 2and 6	Legs and spine.	Usually, live until the teenage years or early 20s.
Emery-Defuses	weakening in upper arms and lower legs	between childhood and teenage years	lower legs, chest, shoulders	Slow progression
Facioscapulo humeral	Difficult walking chewing and speaking	Usually between teenage and	Face shoulder blade and upper	Slow progression

		early adult ages	arms	
Limb-Girdle	Weakening in hips shoulders arms and legs	Teens to early adulthood	Hips shoulder legs and arms	Medium progression typically live to middle childhood
Myotonic	Stiffening and spasms of muscles	Anytime from childhood to adulthood	Overall muscle weakening can also affect the central nervous system	Slow progression decreased life expectancy
Oculopharyngeal	Weakening in eye and face muscles	Appears between 40-60 years	Face muscles and possibly pelvic and shoulder muscles	Slow progression
Distal	Causes weakening in distal muscles	Appears during adulthood	Affects distal muscles such as hands feet and lower legs	Slow progression; less severe than other forms

3. Pathophysiology

Dystrophin is a 427kDa cytoskeletal protein that localizes to the cytoplasmic face of the sarcolemma and is enriched at costameres in muscle fibers [36]. Dystrophin protein has 4 predominant functional domains; an actin-binding amino-terminal domain (ABD1), a crucial rod domain, a cysteine-rich area, and a carboxyl-terminus (Figure 2A). ABD1 includes 2 calponin homology domain names (CH1 and CH2) [37]. This conventional CH-actin binding domain binds immediately to F actin, linking dystrophin to the subsarcolemmal actin network [38]. Dystrophin, and the dystrophin complicated, also function as a broader cytoskeletal integrator, crucial for muscle membrane balance. For instance, ABD1 additionally binds to

costamere-enriched intermediate filament protein cytokeratin 19 (K19), connecting dystrophin to the contractile apparatus in skeletal muscle cells [39, 40]. Dystrophin's primary rod domain consists of 24 spectrin repeats that are ~ one hundred ten AA motifs which include triple α-helices folded into small ~ five nm rods [41, 42]. The rod area additionally harbors a 2nd actin-binding motif (ABD2) that spans a unique collection of spectrin repeats enriched in simple amino acids, suggesting that an electrostatic interaction underlies the interaction with acidic actin filaments [43]. ABD2 falls near the middle of the rod and collaborates with ABD1 to shape a sturdy lateral affiliation with actin filaments [44]. The rod domain additionally mediates dystrophin interaction with microtubules through spectrin-like repeats 20–23 and is needed for the business enterprise of microtubule lattice in skeletal muscle cells [45, 46]. This disordered microtubule network in mdx mouse skeletal muscle cells has been related to extra ROS signaling and increased intracellular calcium, contributing to the pathophysiological phenotype in mdx mice [47].

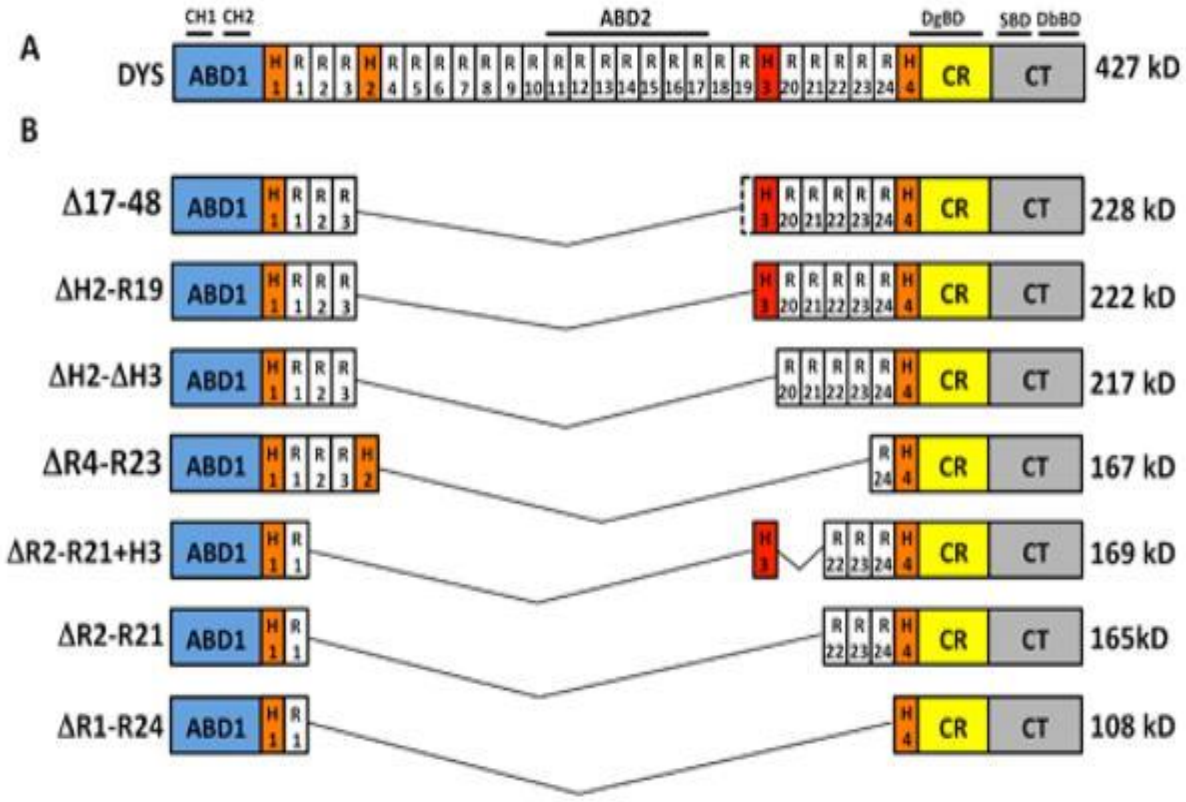

Figure No. 1: Dystrophin Functional Domains [23]

A. Dystrophin protein functional domain

B. Domain structure of internally truncated dystrophin

Dystrophin's rod has additionally been shown to bind membrane phospholipids *in vitro* through the tryptophan residues within the spectrin-like repeats [48]. This interplay is thought to further facilitate the sarcolemma targeting of dystrophin, similarly to dystrophin's association with F-actin. In addition, the rod bureaucracy is a bendy linker among the amino- and carboxyl-termini. The 24 spectrin repeats are interrupted using 4 brief proline-rich spacers, known as "hinges" as they offer elasticity to the protein [49]. Hinge four is at the give up of the rod area and contains a WW domain, a website implicated in protein-protein interactions [50] The WW domain at the side of neighboring EF-hands binds the carboxy-terminus of β-dystroglycan, anchoring the dystrophin at sarcolemma [51]. The EF-hand motifs consist of two α-helices, connected using a brief loop place that has been implicated in calcium-binding [52]. In dystrophin, the two EF-hands are placed in the cysteine-wealthy domain, which resides among the vital rod and C-terminus. The cysteine wealthy area additionally incorporates a zinc finger (ZZ) area that contains conserved cysteine residues and folds to form area shape within the presence of divalent metallic cations including Zn2+ [53]. The ZZ area of dystrophin binds to calmodulin in a calcium-based manner [54]. The cysteine wealthy domain in dystrophin has additionally been shown to bind to ankyrin-B, an adaptor protein that is required for preserving dystrophin at the sarcolemma [55]. In addition, the cysteine-rich area and positive repeats within the rod have been proven to bind to intermediate filament protein synemin, strengthening the link among costameric areas and myofibrils [56]. The carboxy-terminal (CT) domain incorporates polypeptides that fold into α-helical coiled-coils much like the spectrin repeats inside the rod area [57]. Coiled coils are common protein motifs that are worried in protein-protein interaction. The CT area affords binding websites for dystrobrevin and syntrophins, mediating their sarcolemma localization [58].

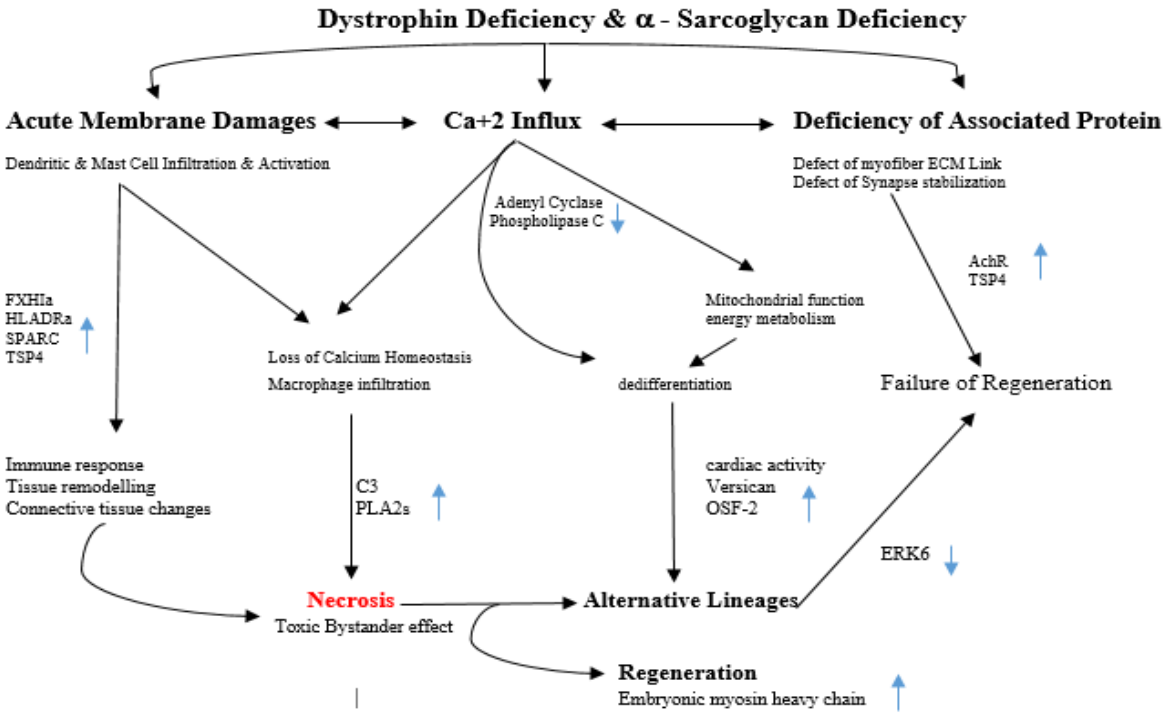

Chart No. 1: Pathophysiology of Muscular Dystrophies

4. Symptoms

The following are signs and symptoms of muscular dystrophy:

● Poor balance: Balance troubles may also cause dizziness and make you feel as although you're spinning or transferring while you're without a doubt standing or sitting still. As a result, you cannot sense properly. This can interfere with your day-by-day life. It also can lead to falls, which can motive broken bones and different injuries [59] [61].

● Scoliosis: Scoliosis is when the vertebrae form a curved line rather than being straight. Sometimes additionally they rotate, like a corkscrew. Small curves commonly do not reason issues. But a curve that receives worse may be awful for a person's fitness. Very large curves can damage the joints and reason arthritis of the backbone [61].

● Progressive inability to walk: Muscle weak point is the primary symptom of muscular dystrophy. Weekend becomes reasons for issue in taking walks or running [61].

● Waddling gait: Waddling gait happens due to weakness on your hip girdle and top thigh muscle tissues. To make up for the weakness, you sway back and forth and your hip drops with every step. It's additionally called myopathic gait [60,61].

● Calf deformation: Bending of leg, or knees in an inward course causing troubles in taking walks. Very much like circumstance known as knocked knees [61].

● Limited range of movement: Muscular Dystrophy influences the voluntary muscles that manipulate movement within the fingers, legs, and trunk. It's due to incorrect genetic information that stops the body from making the proteins needed to construct and preserve healthful muscular tissues. Over time, people with muscular dystrophy lose the ability to do such things as walk, sit upright, breathe without problems, and circulate their hands and arms. Chewing, swallowing, and talking troubles can occur [61].

● Respiratory difficulty: A commonplace function of muscular dystrophy is respiratory failure, i.e., the inability of the respiratory machine to provide the right oxygenation and carbon dioxide removal. In the lung, respiration failure is because of recurrent aspiration and leads to hypoxemia and hypercarbia [61].

● Cardiomyopathy: Cardiomyopathy is a disease of the coronary heart muscle that makes it harder for your heart to pump blood to the relaxation of your frame. Cardiomyopathy can result in heart failure. Both the Duchenne and Becker forms of muscular dystrophy are related to a heart condition referred to as cardiomyopathy. This form of heart ailment weakens the cardiac muscle, stopping the heart from pumping blood efficiently. As the disease progresses, normal heart tissue steadily turns into fattier and greater fibrotic, particularly within the atria (the components of the coronary heart that fill with blood before it pumps). This can motivate issues within the heart's electrical circuitry, ensuing in arrhythmias [59, 61].

● Muscle spasms: Muscle spasms, which are twitches or cramps that can be painful and make fine muscle control more difficult, are common when muscles weaken[59, 61].

● Gowers' sign: The Gowers' sign is a pharmacological intervention that suggests proximal muscular weakness, specifically in the lower leg. Due to a lack of hip and thigh muscle strength, the patient must "walk" up their own body from a squatting position using their hands and arms. Gowers' sign is most commonly seen in Duchenne muscular dystrophy,

where it appears between the ages of 4 and 6, but it can also appear in centronuclear myopathy, myotonic dystrophy, and a variety of other proximal muscle weakness-related conditions such as Becker muscular dystrophy, dermatomyositis, and Pompe disease [60, 61].

5. Treatment [62]

Table No. 2: Types and their treatments

TYPES	TREATMENT
BECKER	1] Becker muscular dystrophy (BMD) has no known cure, this treatment focuses on alleviating symptoms and improving quality of life. Inactivity (such as bed rest) can exacerbate muscle disease, so affected patients are encouraged to stay active [63]. 2] Physical therapy can aid in the stretching of tight muscles and the use of assistive devices; occupational therapy can assist with daily living skills, and speech therapy can aid in the treatment of dysphagia (difficulty swallowing). Scoliosis that progresses and develops contractures may necessitate surgery [63].
CONGENITAL	1. Medications for symptom relief [64]. 2. Muscle weakness requires physical therapy [64]. 3. Respiratory treatment is used to treat breathing problems [64]. 4. Occupational therapy for people who have trouble swallowing [64]. 5. Cognitive therapy is a type of behavioural treatment that is used to help people improve their cognitive abilities [64]. 6. Diet and nutrition advice for people who have trouble chewing or swallowing [64]. 7. Consultations with a social worker to connect you with community resources [64].
DUCHENNE	1] Although the disease's molecular origins have been recognized for several years, there is still no cure. Corticosteroids are the only medication that has been found to decrease the progression of the

	sickness so far. They have altered DMD's natural history. Their particular method of action, however, is still unknown [65]. 2] The major medication treatment for DMD is glucocorticoids, specifically prednisone and deflazacort [65]
EMERY-DREIFUSS	1] EDMD does not have a specific treatment. Individual symptoms are used to determine treatment [66]. 2] Antiarrhythmic medications for AV dysfunction, and anti-thromboembolic therapies to prevent cardiac-related cerebral thromboembolism [66]. 3] Depolarizing muscle relaxants (i.e. succinylcholine) and Volatile anesthetic drugs (i.e. halothane, isoflurane) should be avoided [66]. 4] Muscular dystrophy has no viable treatment at the moment. For the treatment of Duchenne Muscular Dystrophy, however, gene-based therapy is being investigated. This could lead to a therapy option for EDMD in the future [66].
FACIOSCAPULO HUMERAL	1] Facioscapulohumeral muscular dystrophy is currently incurable. Treatments are administered to improve quality of life and to control symptoms [67]. 2] Muscle strength can be maintained through physical treatment. Other therapeutic options include: [67]. A. Occupational therapy can help you enhance your regular activities [67]. B. Oral albuterol can help you gain muscle mass (but not strength) [67]. C. Speech therapy is a type of therapy that involves the use of a winged scapula repaired with surgery [67]. D. If you have ankle weakness, you may need to use walking aids and foot support devices [67]. E. BiPAP is a breathing aid. In patients with a high CO2 level, oxygen alone should be avoided (hypercarbia) [67]. F. Services for counseling (psychiatrist, psychologist, social worker) [67].

LIMB-GIRDLE	1] Physical and occupational therapy programs are frequently included in LGMD treatment plans. Physical therapy stresses mobility and (where possible) strengthening of vast muscular groups, whereas occupational therapy concentrates on specific activities and functions, particularly the use of the hands [68]. 2] The fundamental goals of physical therapy are to improve joint mobility and prevent contractures. Because these issues might emerge when movement is restricted, patients must move as much as possible. When a patient's mobility is restricted, several issues can occur, and it's critical to avoid them for the patient's comfort and function [68]. 3] The goal of occupational therapy is to improve talents in areas such as employment, recreation, and everyday living. Arm supports, for example, can make chores like using the computer or arranging your hairless taxing [68].
MYOTONIC	1] Myotonic dystrophy currently has no cure or specific treatment. The goal of treatment is to alleviate the disease's symptoms. Physical activity appears to aid in the maintenance of muscle strength and endurance, as well as the management of musculoskeletal discomfort. As muscle weakness worsens, canes, braces, walkers, and scooters can help [69]. 2] There are also drugs available to help with the pain of moronic dystrophy. Pain can be controlled with the help of drugs recommended by a doctor [69]. 3] Current research is focusing on how we might one day be able to remove the clumps of RNA that cause the symptoms of moronic dystrophy utilizing gene-editing technology or other treatments. In humans, however, this therapy is not yet possible [69].
OCULOPHARYNGEAL	A myology of the upper oesophageal sphincter muscles is the most common treatment for dysphagia in OPMD. However, while this will relieve constriction of the upper oesophageal sphincter muscles and enhance temporary swallowing, it will not stop the pharyngeal

	muscles from deteriorating. Aspiration and significant difficulties swallowing will eventually follow from this progressive loss of contractility, increasing the risk of aspiration pneumonia and severe weight loss, which are the most common causes of mortality in OPMD patients [70].
DISTAL	The distal myopathies have no cure. The treatment is tailored to the individual's exact symptoms. Physical and occupational therapy to build muscle strength, as well as the use of various devices such as braces (e.g., ankle-foot orthosis) or wheelchairs to assist with walking, are all possible treatment options (ambulation). Affected individuals and their families may benefit from genetic counseling [71].

6.1. Medications

● Prednisone and deflazacort (Emflaza), for example, are corticosteroids that can improve muscle strength and slow the course of certain kinds of muscular dystrophy. However, long-term usage of these medicines can lead to weight gain and weakening bones, increasing the risk of fracture.[62]

● Eteplirsen (Exondys 51), a newer medicine, was the first to be licensed by the Food and Drug Administration (FDA) for the treatment of some persons with Duchenne muscular dystrophy. In 2016, it was given conditional approval [62].

● The FDA approved golodirsen (Vyondys 53) in 2019 for the treatment of certain Duchenne dystrophy patients who have a specific genetic mutation [62].

● If muscular dystrophy damages the heart, cardiac medicines such as angiotensin-converting enzyme (ACE) inhibitors or beta-blockers may be used [62].

6.2. Therapy:

People with muscular dystrophy can benefit from a variety of therapies and assistive equipment that can improve their quality of life and even lengthen it. Here are several examples:

● Stretching and range-of-motion activities: Muscular dystrophy can impair joint flexibility and movement. Limbs tend to draw inside and stay in that position. Exercises that increase range of motion can help to keep joints as flexible as possible [62].

● Exercise: Walking and swimming are examples of low-impact aerobic exercises that can assist preserve strength, mobility, and overall health. Some strengthening exercises may also be beneficial. However, you should see your doctor beforehand because some forms of exercise may be dangerous [62].

● Braces: Braces can assist keep muscles and tendons stretched and flexible, which can help contractures proceed more slowly. Braces can also help with mobility and function by supporting weak muscles [62].

● Mobility aids: Mobility and independence can be maintained with the use of canes, walkers, and wheelchairs [62].

● Assist with breathing: A sleep apnea gadget could assist enhance oxygen delivery during the night as respiratory muscles weaken. Some persons with severe muscular dystrophy require the use of a machine that pumps air into and out of their lungs (ventilator) [62].

6.3 Surgery:

Surgery may be required to repair contractures or a spinal curvature that could make breathing problematic in the future. A pacemaker or other cardiac device may help to improve heart function. [61, 62]

7. Recent Developments

7.1. Stem cell therapy:

Medical research is looking for alternative treatments for patients with muscular dystrophy. New advances in the management of DMD are using exon bypass therapy, gene therapy, and cell therapy to change the disease process and slow it down. Exon skipping refers to genetic defect skipping that results in an incomplete but potentially better functioning protein sequence. Gene therapy aimed at introducing the missing dystrophin gene using different vectors and adeno-associated virus vectors were used; they do not cause disease in humans

and can persist for many years. However, several practical difficulties to date have prevented gene therapy from becoming a viable and clinically viable option. [72]

The recent study proved that stem cell therapies, in particular, which have the potential to treat muscular dystrophies as it provides cells that can both deliver functional muscle proteins and replenish the stem pool. Stem cell therapy is one of the effective treatments for Transplanted cells that have myogenic potential i.e. the muscle cells can repair and regenerate by dividing into mature myocytes. Pre-clinical evidence ensures that stem cell therapy can restore dystrophin protein which leads to the formation of muscle fibers that are resistant to easy damage and degeneration. [72] Stem cell therapy for the treatment of DMD can proceed in two ways. The first was an autologous stem cell transfer involving cells from a DMD patient that is genetically engineered *in vitro* to restore dystrophin expression and then re-implanted. The second is the transfer of allogeneic stem cells, containing cells from a functional dystrophin individual, that are transplanted into a dystrophin patient.[72] The limb-girdle muscular dystrophy, Becker's muscular dystrophy, Duchenne muscular dystrophy, and Facioscapulohumeral Muscular Dystrophy (FSHD) can be cured with Muscular Dystrophy Stem Cell Treatment Therapy in India.[76]

Ongoing studies suggest that mesenchymal stem cells (MSC) can assist relieve the DMD symptoms through aiding muscle cell regeneration and repairing damaged muscle cells. Since umbilical cord stem cells are at an early improvement stage, they can take the shape of any cell. Therefore, the use of Umbilical Cord Mesenchymal Stem Cells (UCMSCs) *will increase the muscle cells' capability and replenish the stem pool. In a look at carried* out on mice through a team of Harvard Stem Cell Institute researchers, the final results seem promising. The researchers transplanted healthy stem cells into the muscles of mice with muscular dystrophy and observed that those new cells advanced the damaged muscle groups' functions and made the contract. They additionally observed that the healthy stem cells replenished the diseased stem cell pool, which can restore any damage to the muscles at some point of future injuries. [75]

7.2 Recent Drugs

In August 2020, the U.S. Food and Drug Administration approved the Viltepso (viltolarsen) injection for the treatment of Duchenne muscular dystrophy (DMD) in sufferers who have a confirmed mutation of the DMD gene this is amenable to exon 53 skipping. This is the

second FDA-authorized targeted treatment for patients with this kind of mutation. Roughly about 8% of patients with DMD have a mutation that is amenable to exon 53 skipping. Viltepso became evaluated in two clinical research with a complete list of 32 patients, all of whom were male and had genetically confirmed DMD. The boom in dystrophin manufacturing became established in a single of these researches, a study that covered 16 DMD patients, with eight patients receiving Viltepso on the recommended dose. In the study, dystrophin levels increased, on average, from 0.6% of normal at baseline to 5.9% of normal at week 25. [76]

8. Clinical Trials

8.1 Exon skipping technology

Dystrophy Annihilation Research Trust (DART) has efficiently evolved India's 1st customized medicinal drug for Duchenne Muscular Dystrophy (DMD) with the use of Antisense Oligonucleotides (AO) primarily based exon-skipping technology. [76]

Duchenne muscular dystrophy (DMD) is the most common childhood neuromuscular disorder. It is a result of mutations in the DMD gene that disrupt the open reading frame (ORF) stopping the production of functional dystrophin protein. [77] The lack of dystrophin in the long run results in the degeneration of muscle fibers, progressive weak spots, and premature death. Antisense oligonucleotides (AOs) targeted to splicing factors inside DMD pre-mRNA can result in the skipping of targeted exons, restoring the ORF and thus will result in the production of a shorter however functional dystrophin protein. This technique can also additionally result in an effective disease-modifying treatment for DMD and development towards clinical application has been rapid. [77, 78]

The first study regarding this was published in 1998 that proves the use of AOs to modify the DMD gene in mice and the results of the first intramuscular proof of concept clinical trials. Currently, the phase II and III trials are underway, the heterogeneity of DMD mutations, efficient systemic delivery, and targeting of AOs to cardiac muscle remain significant challenges. [2][3]

The trials are currently being conducted in nine hospitals in India. This is India's first personalized genetic intervention to treat the disorder. [79] The 'Gene exon skipping therapy' has been delivered to a 10-year-old who is suffering from Duchenne Muscular Dystrophy

(DMD) for the first time in India. He is one of the first patients in India and 27th in the world to receive this advanced treatment. He was 3.5 years old when he was diagnosed with Duchenne Muscular Dystrophy (DMD). [80]

8.2 Vyondys 53

The US FDA had approved a Genetic Engineered medicine called Vyondys 53 for DMD in November 2019. It is based on the gene codon correction at the defective DNA level. Now almost 25 children have been administered with it as a part of clinical trials. The results seem to be very promising. [81] Vyondys 53's clinical trial was approved under the FDA's accelerated approval program which provides for the approval of drugs that treat serious or life-threatening diseases and generally offer a meaningful advantage over existing treatments. It provides earlier patient access to a promising new drug while the company continues to conduct clinical trials to confirm that the drug works well. [81, 82]

Vyondys helps to increase the levels of dystrophin in the muscles of most patients. It is believed that this increase may predict clinical benefits in patients. [81]

There were two types of clinical trials that enrolled patients with DMD:

1. Trial 1/NCT02310906

2. Trial 2/NCT0250381

The trials were conducted in Europe and the US. Trial 1 derived data was used to evaluate the benefit and side effects of VYONDYS 53 and data from Trial 2 to evaluate only the side effects. [83] The first part included 12 DMD patients, with eight patients were treated with Vyondys 53 and four were given a placebo. The second part of the study was open-label and included the 12 patients enrolled in part one of the studies, and 13 additional patients who had not previously been treated. The study showed that on average, dystrophin levels increased from 0.10% of normal at baseline to 1.02% of normal after 48 weeks of treatment with the drug or longer. The most common side effects observed by participants during the treatment of Vyondys 53 in clinical trials were headache, fever (pyrexia), cough, vomiting, abdominal pain, cold symptoms (nasopharyngitis), and nausea. Hypersensitivity reactions, including rash, fever, itching, hives, skin irritation (dermatitis), and skin peeling (exfoliation), have occurred in patients. [83]

9. CONCLUSION

Muscular Dystrophy is a set of over 30 genetic sicknesses affecting the muscles. DMD is the most common, which causes rapid muscle damage and progressive weak spots from early childhood. Although there may be presently no cure for MD, medicines and numerous cures can slow the sickness and enhance a person's quality of life. DMD is a result of mutations in the DMD gene. When a gene exon is missing (for example, exon 51 or 53), cells do now no longer have the right commands to make dystrophin, which results in a sort of muscle damage that causes DMD. Dystrophin enables strengthening and defending muscles. If needed, your medical doctor can take a look at you for the DMD gene mutation. Treatment of DMD has been palliative for decades. With discoveries related to stem cells and their properties, as well as therapeutic applicability and factors for their release, new approaches to the treatment of the most common progressive pediatric myopathies and another disease appeared.

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