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Review Article

Muscular Dystrophy: A Review

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ABSTRACT

Muscular dystrophy is one of the rare diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. There are many different types of muscular dystrophy based on the age of onset, severity and pattern of inheritance, of which duchenne and becker muscular dystrophies being more prevalent. The absence or abnormality of dystrophin, a protein which forms a complex with extracellular matrix to provide mechanical reinforcement to the structure of the sarcolemma and thereby protecting the membrane from the stress or tearing during contraction is the main cause of muscular dystrophy. Muscular dystrophy can be diagnosed by blood & urine tests, muscle biopsies, DNA (genetic) testing, and diagnostic imaging and neurophysiology studies. Treatment includes various therapies such as respiratory therapy, physical therapy, speech therapy, occupational therapy, corrective surgery, drug therapy, and gene therapy.

Keywords: Muscular dystrophy, ducchenne, becker, dystrophin, muscle biopsies, DNA testing, gene therapy

INTRODUCTION

Muscular dystrophy (MD) refers to a group of more than 30 genetic diseases that cause progressive weakness and degeneration of skeletal muscles used during voluntary movement. The word dystrophy is derived from the Greek *dys*, which means "difficult" or "faulty," and *troph*, or "nourish." These disorders vary in age of onset, severity, and pattern of affected muscles. All forms of MD grow worse as muscles progressively degenerate and weaken. Many individuals eventually lose the ability to walk.[3]

People who have muscular dystrophy may have trouble breathing or swallowing. Their limbs may also draw inward and become fixed in that position — a problem called contracture. Some varieties of the disease can also affect the heart and other organs.

While there is no cure for muscular dystrophy, medications and therapy can slow the course of the disease.[1]

History:

The first historical account of muscular dystrophy appeared in 1830, when Sir Charles Bell wrote an essay about an illness that caused progressive weakness in boys.

In the 1850s, descriptions of boys who grew progressively weaker, lost the ability to walk, and died at an early age became more prominent in medical journals. In the following decade, French neurologist Guillaume Duchenne gave a comprehensive account of 13 boys with the most common and severe form of the disease (which now carries his name—Duchenne muscular dystrophy). It soon became evident that the disease had more than one

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PHARMATUTOR
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form, and that these diseases affected people of either sex and of all ages.[3]

In June 1950, Paul Cohen, a prominent New York business leader living with a form of muscular dystrophy, invited a group of individuals to meet in his Rye, N.Y., office. Each had a personal connection to muscular dystrophy, and the gathering focused on the urgent need to raise funds to advance research seeking treatments and cures for muscular dystrophy. The group so vested in the fight against neuromuscular diseases & formed the organization that became the Muscular Dystrophy Association (MDA).

Prevalence:

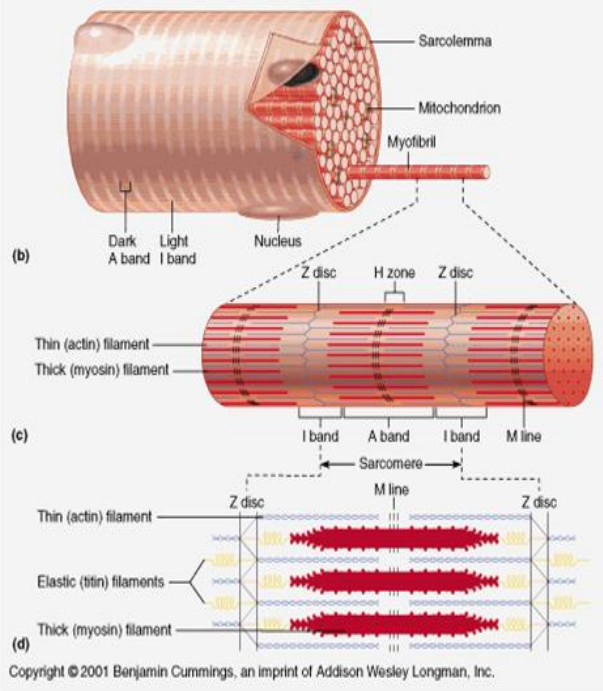
MD occurs worldwide, affecting all races. Its incidence varies, as some forms are more common than others. It is most common form in children, Duchenne muscular dystrophy, affects approximately 1 in every 3,500 to 6,000 male births each year in the United States. Many muscular dystrophies are familial, meaning there is some family history of the disease.[3]

Becker muscular dystrophy (BMD) is a milder form of muscular dystrophy. BMD affects about 1 in 18,500 male births.[2]

Pathophysiology:

Muscles are composed mostly of protein in a highly organized system from large groups to small fibers. Muscle units are separated from other muscle groups by plasma membranes called the sarcolemma and the cytoplasm within is called the sarcoplasm. Within the sarcoplasm are multiple long protein bundles called myofibrils, composed of parallel myofilaments which is where most of the action takes place.

In the myofilaments are contractile proteins called myosin (thick filaments), and actin (thin filaments). When signaled, the actin and myosin interlock and slide over each other to stretch or slide into one another to contraction. They are signaled from the nervous system followed by a series of chemical reactions involving ATP, calcium, sodium and potassium ions.



Aside from the contractile proteins, there are regulatory proteins called tropomyosin and troponin which act like a switch to determine when to contract and when to relax. On the muscle fiber the 'I band' is the space between the myosin (thick) filaments, where lies only the thin filaments. In the middle of each 'I band' is a dark disc called the 'Z disc' made of titan, (elastic filament), which is connected to the sarcolemma by the cytoskeleton. The space between each Z disc, where these filaments interact, is called the sarcomere. As the muscle contracts the 'I band" shrinks and the sarcomere shortens and as the Z disc's come closer together pulling on the sarcolemma shortening the cell. This is how the muscle contracts. One of the most clinically important accessory proteins here is dystrophin which is located just under the sarcolemma in the cytoplasm in the area of the 'I band'. It is produced by specific genes and links the actin

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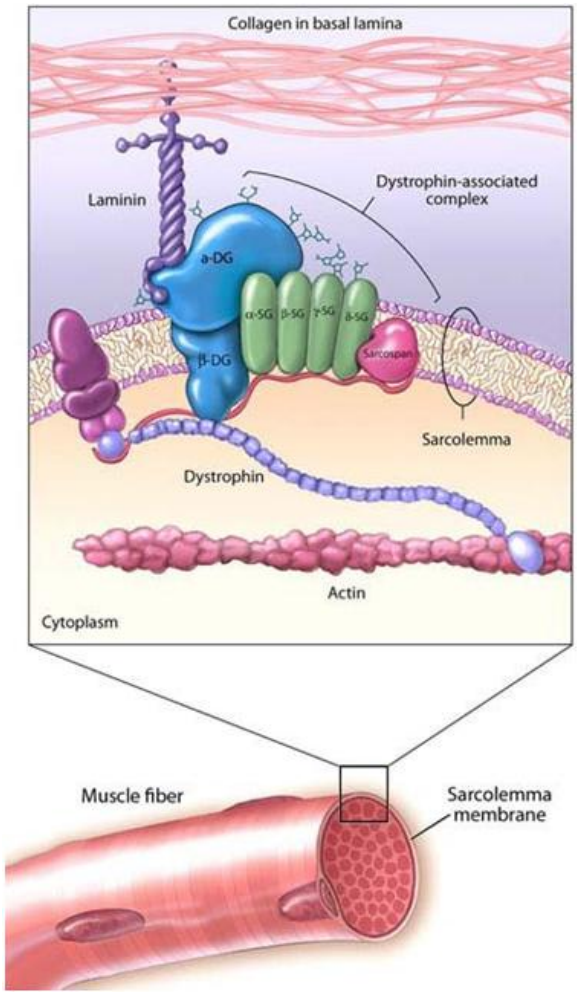
filaments to the protein extracellular matrix in the membrane known as the dystrophin-associated protein complex.



Elements of the dystrophin gene and the protein structure have been identified, yet the exact functional role is still a bit unclear. However as research continues it is thought that its primary function is to provide mechanical reinforcement to the structure of the sarcolemma and thereby protecting the membrane from the stress or tearing during contraction. If dystrophin is defective or absent, the membrane breaks down which then substances and molecules like proteins and enzymes leak out of the fiber into circulation. These enzymes and chemicals that leak out are responsible for certain chemical reactions and necessary for energy production for muscle contraction. At the same time the extracellular substances leak into the fiber through the broken down membrane damaging the fiber and disrupting the process of muscle contraction and may cause irreparable damage.

The absence or abnormality of dystrophin results in a condition known as Muscular Dystrophy.

Muscular Dystrophy is a crippling disease resulting from mutated genes which slowly wastes away muscle tissue. Without dystrophin to help protect the fiber membrane keeping it intact, and assisting to create energy, the muscles begin to degenerate and atrophy, being replaced by fat and fibrous scar tissue creating fascia adhesions throughout the body.[4]

Muscular dystrophies can be inherited in three ways:

I)Autosomal dominant inheritance occurs when a child receives a normal gene from one parent and a defective gene from the other parent. Autosomal means the genetic mutation can occur on any of the 22 non-sex chromosomes in each of the body's cells. Dominant means only one parent needs to pass along the abnormal gene in order to produce the disorder. In families where one parent carries a defective gene, each child has a 50 percent chance of inheriting the gene and therefore the disorder. Males and females are equally at risk and the severity of the disorder can differ from person to person.

II) Autosomal recessive inheritance means that both parents must carry and pass on the faulty gene. The parents each have one defective gene but are not affected by the disorder. Children in these families have a 25 percent chance of inheriting both copies of the defective gene and a 50 percent chance of inheriting one gene and therefore becoming a *carrier*, able to pass along the defect to their children. Children of either

PHARMATUTOR
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ISSN: 2347-7881

sex can be affected by this pattern of inheritance.

III) X-linked (or sex-linked) *recessive* inheritance occurs when a mother carries the affected gene on one of her two X chromosomes and passes it to her son (males always inherit an X chromosome from their mother and a Y chromosome from their father, while daughters inherit an X chromosome from each parent). Sons of carrier mothers have a 50 percent chance of inheriting the disorder. Daughters also have a 50 percent chance of inheriting the defective gene but usually are not affected, since the healthy X chromosome they receive from their father can offset the faulty one received from their mother. Affected fathers cannot pass an X-linked disorder to their sons but their daughters will be carriers of that disorder. Carrier females occasionally can exhibit milder symptoms of MD.[3]

TYPES OF MUSCULAR DYSTROPHY:

There are nine major groups of the muscular dystrophies. The disorders are classified by the extent and distribution of muscle weakness, age of onset, rate of progression, severity of symptoms, and family history (including any pattern of inheritance).

Duchenne muscular dystrophy (DMD) is the most common childhood form of MD, as well as the most common of the muscular dystrophies overall, accounting for approximately 50 percent of all cases.[2] The disease is caused by a defective gene on the 23rd, or X, chromosome that results in the failure of the body to produce a functional muscle protein called dystrophin. Most females who carry the genetic defect are unaffected, but they have a 50 percent probability of passing the disease to each of their sons.[5]

Signs & symptoms:

- waddling gait
- frequent falling
- Difficulty in getting up from a lying or sitting position
- Enlargement of the calf muscles
- Inability to raise the knees
- Disappearance of a normal knee or ankle jerk[5]
- Bone thinning and *scoliosis* (curving of the spine)[3]

Life-threatening pulmonary infections or respiratory failure usually occurs before the age of 20.[5] Some affected children have varying degrees of cognitive and behavioral impairments.[3]

Becker muscular dystrophy (BMD) begins in later childhood or adolescence and progresses more slowly. It is also a sex-linked disorder that is caused by a defective gene on the X chromosome; however, some functional dystrophin is produced. Individuals with this form of muscular dystrophy may function well into adult life, with certain limitations.[5]

Signs & symptoms:

- Walking on one's toes
- Frequent falls
- Difficulty rising from the floor
- Cardiac complications
- Cognitive and behavioral impairments(less common and less severe compared to duchenne MD)

Congenital muscular dystrophy:

- involve mutations in several genes
- autosomal recessive inheritance
-defects in extracellular molecules, i.e components of the extracellular matrix[6]

There are three groups of congenital MD:

- merosin-negative disorders, where the protein *merosin* (found in the connective tissue that surrounds muscle fibers) is missing;
- merosin-positive disorders, in which merosin is present but other needed proteins are missing;

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

and
- neuronal migration disorders, in which very early in the development of the fetal nervous system the migration of nerve cells (neurons) to their proper location is disrupted.

Symptoms include:
Contractures (chronic shortening of muscles or tendons around joints, which prevents the joints from moving freely), scoliosis, respiratory and swallowing difficulties, and foot deformities.
Impairement of intellectual development in some individuals
Weakness in diaphragm muscles may lead to respiratory failure.
Congenital MD may also affect the central nervous system, causing vision and speech problems, seizures, and structural changes in the brain
Limb-girdle dystrophy (dystrophy of the pelvic or shoulder muscles) affects both sexes. . At least 5 forms of autosomal dominant limb-girdle MD (known as type 1) and 17 forms of autosomal recessive limb-girdle MD (known as type 2) have been identified. [2]The first symptoms are manifest in the pelvic region, starting in late childhood. Muscular weakness eventually progresses to the arms and legs, loss of muscle bulk and symmetrical weakening of voluntary muscles, primarily those in the shoulders and around the hips.Symptoms include frequent falling, difficulty in climbing, and a waddling gait.[5]
Facioscapulohumeral MD (FSHD) initially affects muscles of the face (facio), shoulders (scapulo), and upper arms (humera) with progressive weakness. Also known as Landouzy-Dejerine disease, this third most common form of MD is an autosomal dominant disorder. Changes in facial appearance may include the development of a crooked smile, a pouting look, flattened facial features, or a mask-like appearance. [3]
The first symptom may be difficulty in raising the arms. Later symptoms may include weakness of the legs and pelvic girdle, forward sloping of the shoulders, and difficulty in closing the eyes.[5]
Emery-Dreifuss MD (EDMD) primarily affects boys. The disorder has two forms: one is X-linked recessive and the other is autosomal dominant. Although there are 2 modes of inheritance, the symptoms are almost same.[3]
EDMD is a rare, often slowly progressive genetic disorder affecting the muscles of the arms, legs, face, neck, spine and heart. The disorder consists of the clinical triad of weakness and degeneration (atrophy) of certain muscles, joints that are fixed in a flexed or extended position (contractures), and abnormalities affecting the heart (cardiomyopathy) in mainly adults. Major symptoms may include muscle wasting and weakness particularly in arms and lower legs (humeroperoneal regions) and contractures of the elbows, Achilles tendons, and upper back muscles.[7]
Myotonic dystrophy (DM1), also known as Steinert's disease and dystrophia myotonica, is another common form of MD. *Myotonia*, or an inability to relax muscles following a sudden contraction, is found only in this form of MD, but is also found in other non-dystrophic muscle diseases. Myotonic muscular dystrophy may also affect the central nervous system, heart, gastrointestinal tract, eyes, and endocrine glands. Because of the possibility of serious cardiac complications, individuals with this form of muscular dystrophy may require a pacemaker. Myotonic muscular dystrophy type 1 and myotonic muscular dystrophy type 2 are both caused by a genetic mutation, albeit on different chromosomes, that results in defective RNA, the molecule that translates DNA into proteins. Genetic testing can detect these mutations in persons suspected to have the disease.[5]
Distal MD, also called distal myopathy, describes a group of at least six specific muscle

PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

diseases that primarily affect distal muscles (those farthest away from the shoulders and hips) in the forearms, hands, lower legs, and feet. Although distal MD is primarily an autosomal dominant disorder, autosomal recessive forms have been reported in young adults. Distal dystrophies are typically less severe, progress more slowly, and involve fewer muscles than other forms of MD, although they can spread to other muscles, including the proximal ones later in the course of the disease. Distal MD can affect the heart and respiratory muscles, and idividuals may eventually require the use of a ventilator.[3]

Spinal muscular atrophy (SMA) that is caused by a deletion of the SMN gene on chromosome 5 is an inherited progressive neuromuscular disorder characterized by degeneration of groups of nerve cells (lower motor neurons) within the lowest region of the brain (lower brainstem) and certain motor neurons in the spinal cord (anterior horn cells).

Typical symptoms are a slowly progressive muscle weakness and muscle wasting (atrophy). Affected individuals have poor muscle tone, muscle weakness on both sides of the body without, or with minimal, involvement of the face muscles, twitching tongue and a lack of deep tendon reflexes.[7]

Oculopharyngeal MD (OPMD) generally begins in a person's forties or fifties and affects both men and women.

People first report drooping eyelids, followed by weakness in the facial muscles and pharyngeal muscles in the throat, causing difficulty swallowing. The tongue may atrophy and changes to the voice may occur.[3]

TABLE: TYPES OF MUSCULAR DYSTROPHY

S. No.	Type of MD	Inheritance	Major effects/symptoms
1	Duchenne	X linked recessive	Life-threatening pulmonary infections, respiratory failure, bone thinning and *scoliosis*
2	Becker MD	X linked recessive	Frequent falls Cardiac complications Cognitive and behavioral impairments
3	Congenital muscular dystrophy	autosomal recessive	Contractures, respiratory difficulty, CNS problems.
4	Limb-girdle dystrophy	autosomal dominant(type 1) & autosomal recessive(type 2)	weakening of voluntary muscles in the shoulders and around the hips.
5	Facioscapulohumeral MD (FSHD)	Autosomal dominant	difficulty in raising the arms, weakness of the legs and pelvic girdle, forward sloping of the shoulders, and difficulty in closing the eyes
6	Emery-Dreifuss MD	2 forms: one is X-linked recessive and the other is autosomal dominant.	muscle wasting and weakness particularly in arms and lower legs (humeroperoneal regions) and contractures of the elbows, Achilles tendons, and upper back muscles.
7	Myotonic dystrophy (DM1)	Autosomal dominant	*Myotonia*, serious cardiac complications

PHARMATUTOR
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ISSN: 2347-7881

8	Distal MD	Autosomal dominant &autosomal recessive in some cases	affect distal muscles in the forearms, hands, lower legs, and feet.
9	Spinal muscular atrophy (SMA)	-------	muscle weakness and muscle wasting (atrophy)
10	Oculopharyngeal MD (OPMD)	autosomal	Drooping eyelids, weakness in the facial muscles and pharyngeal muscles in the throat, causing difficulty swallowing.

Diagnosis:

Muscular dystrophy (MD) is diagnosed through a physical exam, a family medical history, and tests. These might include:

- Blood & urine tests
- Muscle biopsies
- DNA (genetic) testing
- Diagnostic imaging
- Neurophysiology studies

History: Both the individual's medical history and a complete family history should be thoroughly reviewed to determine if the muscle disease is secondary to a disease affecting other tissues or organs or is an inherited condition.

Blood and urine tests

-Blood tests may reveal elevated levels of the creatine kinase (CK), an enzyme that is found in abnormally high levels when muscle is damaged. The detection of elevated CK levels (usually in the thousands or ten thousands range) can confirm that muscle is damaged or inflamed, but cannot confirm a diagnosis of MD. Testing can also determine if a young woman is a carrier of the disorder.[7]

- Myoglobin is an oxygen-binding protein found in cardiac and skeletal muscle cells. High blood levels of myoglobin are found in people with MD.

- High levels of the enzyme, serum aldolase which is present in most body tissues, are noted in people with MD and some forms of myopathy.

- Serum electrophoresis is a test to determine quantities of various proteins in a person's DNA. A blood sample is placed on specially treated paper and exposed to an electric current. The charge forces the different proteins to form bands that indicate the relative proportion of each protein fragment.

Muscle biopsies are useful to monitor the course of disease and treatment effectiveness. The tissue sample from patient may be gathered either surgically, through a slit made in the skin, or by needle *biopsy*, in which a thin hollow needle is inserted through the skin and into the muscle. The muscle specimen is stained and examined to determine whether the person has muscle disease, nerve disease (*neuropathy*), inflammation, or another myopathy. Muscle biopsies can sometimes also assist in carrier testing.[3]

For Duchenne and Becker muscular dystrophies, muscle biopsy may show whether dystrophin, a muscle protein, is missing or abnormal.[8]

In some cases, a specialized test can be performed on muscle biopsy samples which include various techniques such as immuno-staining, immunofluorescence(fluorescent markers are used to stain the sample) or Western blot (immunoblot) can be used. These tests involve the use of certain antibodies that react to certain proteins such as dystrophin. Tissue samples from muscle biopsies are exposed to these antibodies and the results can determine whether a specific muscle protein is present in the cells and if present, in what quantity and size is present.[7]

PHARMATUTOR
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DNA (genetic) testing

It is used to analyze the condition of the related gene. DNA analysis and enzyme assays can confirm the diagnosis of certain neuromuscular diseases, including MD. Genetic linkage studies can identify whether a specific genetic marker on a chromosome and a disease are inherited together. Advances in genetic testing include whole exome and whole genome sequencing, which will enable people to have all of their genes screened at once for disease-causing mutations, rather than have just one gene or several genes tested at a time. Exome sequencing looks at the part of the individual's genetic material, or genome, that "code for" (or translate) into proteins.[3]

Diagnostic imaging

Magnetic resonance imaging (MRI), is used to examine muscle quality, any atrophy or abnormalities in size, and fatty replacement of muscle tissue, as well as to monitor disease progression. MRI scanning equipment creates a strong magnetic field around the body. Radio waves are then passed through the body to trigger a resonance signal that can be detected at different angles within the body. A computer processes this resonance into either a three-dimensional picture or a two-dimensional "slice" of the tissue being scanned. MRI scans of the brain may be useful in diagnosing certain forms of congenital muscular dystrophy where structural brain abnormalities are typically present.

Other forms of diagnostic imaging for MD include phosphorus magnetic resonance spectroscopy, and ultrasound imaging (also known as sonography).[3]

Neurophysiology studies can identify physical and/or chemical changes in the nervous system.

- Nerve conduction velocity studies measure the speed and strength with which an electrical signal travels along a nerve, so that any presence of nerve damage can be determined.
- Repetitive stimulation studies involve electrically stimulating a motor nerve several times in a row to assess the function of the neuromuscular junction.
- *Electromyography* (EMG) can record muscle fiber and motor unit activity. Results may reveal electrical activity characteristic of MD or other neuromuscular disorders.[3]

TREATMENT OF MUSCULAR DYSTROPHY:

- Treatment approaches include:
- Correct gene defects
- Block deleterious effects of gene defects
- Replace defective genes
- Block muscle degeneration
- Enhance muscle degeneration

DIFFERENT THERAPIES INCLUDE:

- Respiratory therapy
- Physical therapy
- Speech therapy
- Occupational therapy
- Corrective surgery
- Drug therapy
- Gene therapy

Respiratory Therapy

Many people with MD do not realize they have little respiratory strength until they have difficulty coughing or an infection leads to pneumonia. Regular visits to a specialist early in the diagnosis of MD can help guide treatment before a respiratory problem occurs. Eventually, many MD patients require assisted ventilation.[9] Air that includes supplemental oxygen is fed through a flexible mask (or, in some cases, a tube inserted through the esophagus and into the lungs) to help the lungs inflate fully.[3]

Supplemental oxygen therapy may impair central respiratory drive and exacerbate hypercapnia.[10, 11, 12] Thus, supplemental oxygen therapy should be used with caution, as it can

PHARMATUTOR
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improve hypoxemia while masking the underlying cause, such as atelectasis, mucus plugging, or hypoventilation. When patients experience hypoxemia due to hypoventilation, retainedrespiratory secretions, and/or atelectasis, then manually and mechanically assisted cough and noninvasive ventilatory support should be used to maintain SpO2 95% at all times; substitution by oxygen therapy alone is dangerous. [13]

For the prevention of respiratory infections, immunization with 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for patients 2 years of age and older. Annual immunization with trivalent inactivated influenza vaccine (TIV) is indicated for patients 6 months of age and older. PPV23 and TIVare not live vaccines, so either can be administered to patients treated with glucocorticoids.[13]

Physical therapy:

It can help prevent deformities, improve movement, and keep muscles as flexible and strong as possible.

Options include

- Passive stretching,
- Postural correction,
- Regular moderate exercise and
- Repeated low-frequency bursts of electrical stimulation to the thigh muscles may produce a slight increase in strength.[3]

A combination of physical activity and stretching exercises may be recommended.[9]

Speech Therapy

MD patients who experience weakness in the facial and throat muscles may benefit from learning to slow the pace of their speech by pausing more between breaths[14] and by using special communication equipment, such as a computer with voice synthesizer[9]

Occupational Therapy

As physical abilities change, occupational therapy can help patients with MD relearn these movements and abilities. Occupational therapy also teaches patients to use assistive devices such as motorized wheelchairs, wheelchair accessories, and adaptive utensils.[9]

Corrective Surgery

At various times and depending on the form of MD, many patients require surgery to treat the conditions that result from MD.

- Tendon or muscle-release surgery is recommended when a contracture becomes severe enough to lock a joint or greatly impair movement. The procedure, which involves lengthening a tendon or muscle to free movement, is usually performed under general anesthesia.
- Individuals with either Emery-Dreifuss or myotonic dystrophy may require a pacemaker at some point to treat cardiac problems.
- Surgery to reduce the pain and postural imbalance caused by scoliosis may help some individuals. One or more metal rods may need to be attached to the spine to increase strength and improve posture. Another option is spinal fusion, in which bone is inserted between the vertebrae in the spine and allowed to grow, fusing the vertebrae together to increase spinal stability.
- Surgery to remove cataracts (which usually occur in myotonic dystrophy), a clouding of the lens of the eye that blocks light from entering the eye.

Drug Therapy

Certain medications can help slow or control the symptoms of MD. These include the following:

Glucocorticoids, such as prednisone. This is a catabolic steroid that slows the loss of muscle degeneration.[1] Studies show that daily treatment with prednisone can increase muscle strength, ability, and respiratory function and slow the progression of weakness. In some

PHARMATUTOR
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ISSN: 2347-7881

cases walking may be prolonged for up to two years or more. It is the drug most widely used to treat Duchenne. Side effects may include weight gain.[15] Long-term use may result in brittle bones, cataracts, and high blood pressure.[9]Like prednisone, this is a catabolic steroid. As with prednisone, there is evidence that deflazacort significantly improves muscle strength and function. In addition, it appears to have less severe side effects than prednisone.

Anabolic steroids act to build tissues in the body (unlike prednisone and other catabolic steroids that break them down), may help to fight Duchenne by compensating for muscle loss. A pilot study of oxandrolone, a synthetic anabolic steroid, showed some promise in preserving muscle strength.[1]

Anticonvulsants: Typically taken for epilepsy, these drugs may help control seizures and some muscle spasms.[9]

Immunosuppressants may help delay some damage to dying muscle cells. Albuterol is widely used in inhalant form for asthmatics. Preliminary evidence suggests that it may aid Duchenne young men by suppressing the immune cells that rush in to clean up and remove "leaky" muscle cells and debris. As with prednisone, albuterol interferes with the body's normal inflammation response. Though early data indicates few major side effects, all immunosuppresants are potentially harmful in that they may leave the patient unable to fight routine infections. Albuterol also appears to have some anabolic effects in that it promotes the growth of muscle tissue.

Antibiotics are used to treat respiratory infections. Research on mdx mice that simulate human Duchenne has shown that when gentamycin is administered, the premature stop codon is somehow ignored so that the entire gene transcript can be "read" and dystrophin can be produced.[1]

Nutritional supplements: Creatine occurs naturally in muscle. Although it is found in meat and fish, it can also be added to the diet as a powdered nutritional supplement. The idea is that the more creatine muscle has, the more energy it has and thus the stronger its contraction. This is why professional athletes have experimented with extremely high doses.
Recent trials with Duchenne patients show a slight increase in muscle strength with administration of low levels (5 g/day) of creatine monohydrate.

Gene therapy:
The X-linked dystrophin gene is by far the largest of the 30,000 genes that encode proteins in the human genome: its 79 exons cover 2.6 million base pairs (bp). This large size makes the gene prone to rearrangement and recombination events that cause mutations. In most cases, the mutations are deletions of one or more exons (~60%); however, duplications (~6%)1, translocations and point mutations have also been found In general,mutations that disrupt the reading frame of the dystrophin transcript and lead to prematurely aborted dystrophin synthesis cause Duchenne muscular dystrophy (DMD)

Conventional gene-therapy strategies
The size of the dystrophin gene has been an important challenge for gene-therapy researchers. To replace a defective dystrophin gene, an artificial dystrophin cDNA construct must be transferred into the nuclei of muscle cells, where it must be expressed and regulated appropriately. So, to deliver the 14 kb dystrophin cDNA(11.5 kb coding sequence), vectors with a large capacity were needed.The capacity of first generation adenoviral vectors (up to 8 kb) was too small. Later, high capacity (28 kb) 'gutless' vectors, from which all

PHARMATUTOR
PHARMACY INFOPEDIA
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adenoviral genes had been removed, bypassed this restriction and delivered extra benefits in the form of reduced host immune response to the viral vector and improved persistence of transgene expression in muscle[16,17]. In addition to adenoviral vectors, Herpes simplex virus (HSV) and plasmid vectors were also used.

Recent advances in gene therapy are:
- Delivery of functional mini- and micro-dystrophins by recombinant adeno-associated viral (rAAV) vectors;
- Therapeutic antisense-induced exon skipping; and
-Dystrophin replacement by utrophin upregulation.

These three innovative methods have several advantages compared with other approaches which mark them as the most likely strategies to lead to an effective treatment for DMD.[18]

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