IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2023 Vol.:26, Issue:2

A Review on Muscular Dystrophy

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Singh Shivani*, Archana Jorige

Department of Pharmacology, RBVRR Women's College of Pharmacy (Affiliated to Osmania University), Narayanaguda, Hyderabad, Telangana, India.

Submitted: 25 December 2022
Accepted: 31 December 2022
Published: 30 January 2023

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Dystrophinopathy, Genes, Mutations, Biomarkers, Diagnosis.

ABSTRACT

Muscular dystrophies (MDs) are clinically and genetically heterogeneous primary muscle diseases which are characterized by muscle weakness and abnormalities of muscle fibres on histopathological examination. Autosomal recessive inheritance has been seen in most of the congenital and childhood-onset forms of MD, while great majority of later onset, slowly progressive myopathies are caused by dominant mutations. Duchene muscular dystrophy (DMD) is the most common form of childhood onset MD and it is X-linked. MD has shown frequent genetic splitting and lumping, with single genes. In most of the cases precise diagnosis can be soughed and definition of the causative mutation represents the gold standard for diagnosis. Exploration of simple and precise blood biomarkers can make the diagnosis of MD amicable. MDs are classified based on their phenotype, inheritance, genetic defect and protein involved. The muscle involvement pattern and clinical features are the criteria for differential diagnosis of MD. Current novel technologies are most likely to elucidate new causes as well as diagnostic algorithms for MD, with the hope of providing routes for specific therapies. In this review etiopathology, types, diagnosis including few novel biomarkers and treatment strategies of MDs have been discussed.

INTRODUCTION

Muscular dystrophy is a group of inherited diseases that damages and weakens our muscles over time due to lack of a protein called Dystrophin, which is necessary for the normal muscle function. The absence of this protein can cause problems with walking, swallowing, muscle coordination and inability to perform daily activities like brushing teeth and can also affect our lungs and heart. These diseases tend to run in families and can occur at any age, but most diagnoses occur in childhood. Young boys are more prone to have this disease than girls. A child who has a parent with MD may inherit a mutated gene that causes MD. Some people have the mutated gene but don't have MD. These healthy adults can pass the mutated gene to their child, who may develop the MD [1].

Depending on the type and severity of MD, the effects can be mild, progressing slowly over an average life span. In some cases, it can be aggressive, progressing quickly and shortening a person's life. In most of the people's, condition will get worse over time, and people may lose the ability to talk, walk and eventually requires a wheelchair. But that doesn't happen to everyone. some patients can live for many years with mild symptoms.

There are more than 30 kinds of muscular dystrophy, which vary in symptoms and severity, and each is different based on:

- The genes that cause it
- The muscles it affects
- The age when symptoms first appear
- How quickly the disease gets worse [2].

Etiology:

The cause of MD is an abnormality in the genetic code for specific proteins of the muscle. These are classified according to the clinical phenotype, the pathology, and the mode of inheritance. The inheritance pattern involves the sex-linked, autosomal recessive, and autosomal dominant MDs. In each group of heritable MDs, several disorders exist and are characterized by the clinical presentation and pathology.

Heritable MDs include the following:

- Sex-linked MDs - Duchene, Becker, Emery-Dreifuss
- Autosomal dominant MDs - Facioscapulohumeral, distal, oculopharyngeal
- Autosomal recessive MD – Limb-girdle form

Genetic defects & dystrophin

In X-linked forms of MD (Duchene and Becker dystrophies), the defect is located on the short arm of the X chromosome. Hoffman and his co-workers linked the locus of the defect in the Xp21 region, which includes 2 million base pairs approximately.

The gene codes for Dp427, which is an element of the cytoskeleton of the cell membrane. Dystrophin isn't only distributed in the cadaverous muscles but also the smooth muscle, cardiac muscles and the brain. The large size of dystrophin gene explains the ease at which robotic new mutations can occurs, as in Duchenne MD and it also allows miscalculations in protein synthesis to occur at multiple spots.

Defects that intrude with the translation reading frame or with the promoter sequence which initiates synthesis of dystrophin lead to an unstable, ineffective protein, as in Duchenne MD. Any disruption in the translation process further down the sequence leads to production of proteins of lower molecular weight that, although present, are less active and result in the milder variety of Becker MD. Like Duchenne MD, Emery- Dreifuss MD is a sex- linked recessive disorder, but the defect is localized to the long arm of the X chromosome at the q28 locus. Some authors, still, have cited case reports of analogous findings in Emery- Dreifuss that were transmitted in an autosomal dominant pattern. still, this finding is further of an aberration than a normal observation in Emery- Dreifuss MD. In autosomal recessive conditions similar to limb-girdle MD, the inheritable defect is localized to the 13q12 locus. In the autosomal dominant facioscapulohumeral MD, the defect is located at the 4q35 locus. In distal MD, it's at the 2q12- 14 loci [1,5,6].

Symptoms

Progressive muscle weakness is the main sign of the MD. Specific signs and symptoms begins at different age in different muscle groups, based on the type of muscular dystrophy. Most types of MD symptoms start to appears in childhood or in the teen years. In general, children with the condition:

- Fall often, walk on their toes, or waddle
- Have weak muscles and cramps
- Have trouble getting up, climbing stairs, running and jumping
- A curved spine (called scoliosis) and drooping of eyelids
- Heart and vision problems
- Trouble in breathing or swallowing [1,5,6].

Table 1: Types of Muscular Dystrophies. [5,7,11-18,26,28,29]

TYPE OF MD	PROTEIN MISSING /DEFICIENT	AGE OF ONSET AND GENDER	MUSCLES AFFECTED	COMPLICATIONS
Duchenne MD	Dystrophin	Early childhood(5-24years), Boys are more likely to get affected than girls	Muscles of the hips, legs, shoulders, spine and heart	Severe muscle weakness, wasting, scoliosis, contractures, respiratory failure, pneumonia & dilated cardiomyopathy. Death in the early 20s.
Becker MD	Dystrophin	Adolescence or adulthood (11-25 years), mainly affects boys	Similar to DMD	Muscle weakness as in DMD, but with slower progression & much less severe Cardiomyopathy
Tibial MD	Titin	Late adulthood	Anterior compartment of legs	Slowly progressive. Eventually can affect upper extremities & heart.
Emery-dreifuss (EDMD)	Emerin, Lamin	Childhood to early teens, mainly affect males more	Proximal upper and distal lower extremities	Early contractures, cardiomyopathy

		than females.		
Oculopharyngeal (OPMD)	Poly-A-binding protein 2	Age 40-60 years	Eyelids, throat	Ptosis of eyelids, dysphagia, aspiration pneumonia
Facioscapulohumeral (FSHD)	Not identified	Childhood to early adolesc-ence, affects both males & females.	Face, shoulders, proximal upper extremities.	Defects in cardiac conduction, mild loss of hearing, abnormalities in the retina
Limb-girdle **LGMD1A** **LGMD1B** **LGMD1C** **LGMD1D** **LGMD1E** **LGMD1F**	Myotilin Lamin Caveolin-3 Not identified Not identified Not identified	Adolescence to early adulthood, affects both males and females.	Proximal shoulder/ pelvic girdle musculature.	Walking problem (within 20 years of onset)
Myotonic MD	Myotinin protein kinase, ZNF9	From infancy to adulthood, both males and females are affected.	The distal extremity first and then proximal.	Myotonia, cataracts, hypogonadism, cardiac arrhythmias.
Distal MD	Dysferlin	Late adolescence	Posterior compartment of legs.	Affects the anterior compartment & distal arm muscles. Progression is slow & maintains independent ambulation throughout life.

Pathogenesis

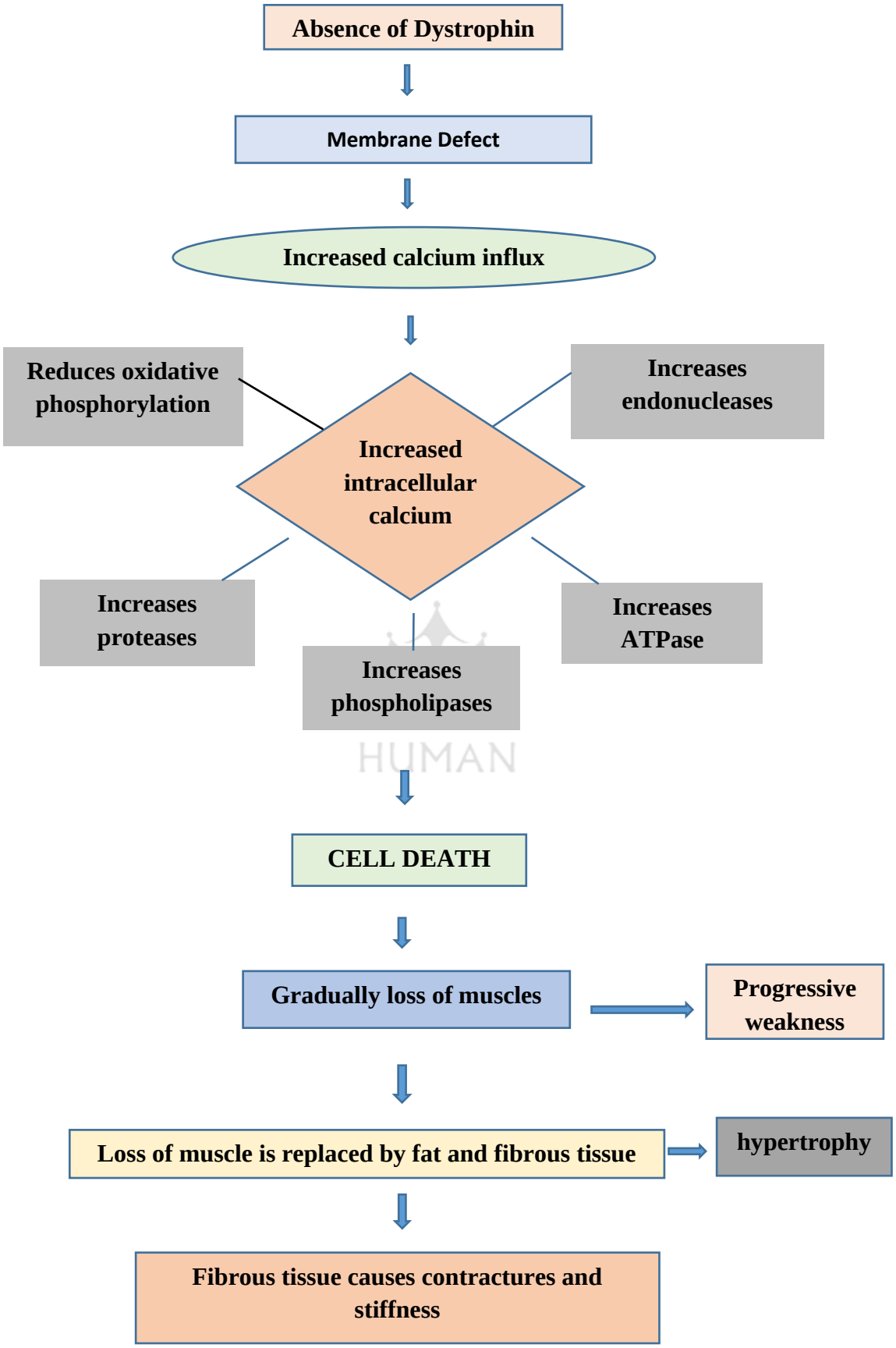

Figure 1: Pathogenesis of Muscular Dystrophy.

Table 2: Biomarkers of Different Types of MD [20-22]

TYPE OF MD	BIOMARKERS
1. Duchene MD	• Myofiber Necrosis ✓ In Blood: Increased CK, Aldolase, Titin, MLC and Filamin-C ✓ In Muscle: Decreased Mir-1 and Mir-29C ✓ In Urine: Titin, Biliverdin, Creatinine and Others • Inflammation ✓ In Blood: Increased TNF, IL-6, Osteopontin ✓ In Muscle: Increased TNF, IL-6, Osteopontin, MPO, and Neutrophil Elastase • Oxidative Stress ✓ In Blood: Increased Albumin Thiol Oxidation ✓ In Muscle: Increased Carbonyls, Chlorotyrosine and Total Thiol Oxidation • Regeneration ✓ In Muscle: Increased Neonatal Myosin's ➢ Fibrosis ✓ In Blood: Increased TGF-**β, IL-13** ✓ **In Muscle: Increased collagen, fibronectin**
2. Becker MD	Increased creatine and myostatin levels
3. FSHD	miR-223-3p and miR-206
4. LGMD2A	miR-143-3p and miR-486-3p
5. DM2	miR-363-3p and miR-25-3p
6. Myotonic D	miR-1, miR-133a, miR-133b, and miR-206
7. OPMD	Muscle Ultrasound
8. MDC1A	miR-1, miR-133a, miR-133b, miR-206

Risk Factors

Muscular dystrophy can occur in sexes, ages and races. However, the most common variety, Duchene, usually occurs in young boys. People with a family history of muscular dystrophy are at higher risk of developing the disease or passing it on to their children [6].

Complications

The complications of progressive muscle weakness include:

- **Trouble walking-** Some people eventually need a wheelchair.
- **Trouble using arms-** Unable to perform daily activities, if the muscles of the arms and shoulders are affected.
- **Shortening of muscles (contractures)-** Contractures can further limit mobility.
- **Breathing problems-** Progressive weakness can affect the muscles that are associated with breathing. People with MD might eventually need a breathing assistance device (ventilator), initially at night but possibly also during the day.
- **Curved spine (scoliosis)-** Weak muscles might be unable to hold the spine straight.
- **Heart problems.** MD can reduce the heart muscle efficiency.
- **Swallowing problems-** If the muscles involved in swallowing are affected, nutritional problems and aspiration pneumonia can develop. Feeding tubes might be required [6].

Diagnosis

Doctor will check different parts of child's body to know if they have muscular dystrophy. They'll start with a general physical exam and also check about family's medical history and the kind of symptoms that are noticing in the children.

Different tests are available to check the conditions that can cause muscle weakness. This includes:

- **Blood test:** To measure the levels of certain enzymes that muscles release when they are damaged.
- **Electromyography or EMG: S**mall needles called electrodes are placed on different parts of child's body & ask them to slowly flex & relax their muscles. The electrodes measure electrical activity.
- **Muscle biopsy:** Using a needle, doctor removes a small piece of your child's muscle tissue. Examining under a microscope to see which proteins might be missing or damaged. This test can show the type of MD that child may have.

- **Electrocardiogram (or) ECG:** It measures electrical signals from the heart and tells how fast your child's heart is beating and if it has a healthy rhythm.

- **Imaging:** This can show the quality and amount of muscle in children's bodies.

They may get:

Magnetic resonance imaging: uses powerful magnets and radio waves to make pictures of their organs.

Ultra Sound: Which uses sound waves to make pictures of the inside of the body [9,23,27].

Treatment

Although there is no cure for any type of MD, treatment for some forms of the disease can help extend the time a person with the disease can remain mobile & help with heart & lung muscle strength. New therapies of trials are ongoing. People with MD should be monitored throughout their lives. The care team should include a neurologist who is expertise in neuromuscular diseases, a physical medicine and rehabilitation specialist, and physical and occupational therapists. Some people might need a pulmonologist, a cardiologist, a sleep specialist, an endocrinologist, an orthopaedic surgeon and other specialists [4,7].

➢ **Pharmacological Treatment:**

Table 3: Medications

MEDICINES	USES
Eteplirsen (Exondys51), Golodirsen (Vyondys53), and Vito Larsen (Viltepso)	For treating DMD. They are injections that help treat patients with a specific mutation of the gene that leads to DMD, specifically by increasing dystrophin production.
Anti-seizure drugs	Can reduce muscle spasms.
Anti-hypertensive drugs	helpful in heart problems.
Immunosuppressants	Slowly damages the muscle cells.
Steroids (prednisone and deflazacort)	Slow down muscle damage and can help to breathe better and can cause serious side effects like weak bones and a higher risk of infections.
Creatine	Normally a chemical is found in the body which can help supply energy to muscles and improve strength for some people.

➢ **Non-Pharmacological Treatment:**

Therapies

Several types of therapy and assistive devices can improve the quality and the length of life in people who have MD. This includes:

- **Physical therapy** -This uses different exercises and stretches to keep muscles strong and flexible.

- **Occupational therapy** -This therapy can help and train patients to carry out everyday tasks more efficiently and can also show them how to use wheelchairs, braces, and other devices that can help them with daily life.

- **Speech therapy -**helps in to teach them easier ways to talk if the throat or face muscles are weak.

- **Respiratory therapy -**can help if your child is having trouble breathing. They'll learn ways to make it easier to breathe or get machines to help.

Surgery

Helps with different complications of muscular dystrophy like heart problems or trouble swallowing [7,9,10,23].

Prevention

Unfortunately, there isn't anything we can do to prevent muscular dystrophy. If anyone have the disease, the following steps can help and can enjoy a better quality of life:

- By eating a healthy diet to prevent malnutrition.
- By drinking lots of water to avoid dehydration and constipation.
- Exercise as much as possible.
- Maintaining a healthy weight to prevent obesity.
- Quit smoking to protect your lungs and heart.
- By getting flu and pneumonia vaccines [19].

CONCLUSION:

Muscular dystrophies are progressive muscle disorders caused by genetic defect. Cardiac and respiratory involvement is commonly observed in MD, which is often the leading cause of death, in particular in Dystrophinopathies. The average life expectancy of MD patients can be prolonged through advances in the diagnosis, treatment and long-term care of patients with DMD. The bioinformatic analysis could be an effective tool for the identification of potential genetic targets. The advent of molecular genetic therapies and personalised medicine has opened up new avenues and raised hopes to cure this debilitating orphan disease. Dystrophin-targeted therapeutic strategies that aim at restoring the expression and/or function of dystrophin, including gene-based, cell-based and protein replacement therapies are few new advents in the management of DMs especially DMD which is the common type of DMs. Nutritional interventions with positive effects on physical activity are also being explored for the possible role in the treatment of DMs.

REFERENCES:

1. Duchenne Muscular Dystrophy (DMD) - Diseases | Muscular Dystrophy Association. [online]. Available at: https://www.mda.org/disease/duchenne-muscular-dystrophy.
2. Understanding Neuromuscular Disease Care. IQVIA Institute. Parsippany, NJ. (2018). - Search. [online]. Available at: https://www.bing.com/search?q=2.%09Understanding+Neuromuscular+Disease+Care.+IQVIA+Institute.+Parsippany%2C+NJ.+%282018%29.&form=ANNTH1&refig=16e71a0f35e64118995e4705cd366ae3.
3. Ryder S, Leadley RM, Armstrong N, Westwood M, De Kock S, Butt T, Jain M, Kleijnen J. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. Orphanet journal of rare diseases. 2017 Dec; 12:1-21.
4. Pathophysiology of Muscular Dystrophy (1).docx - Running head: MUSCULAR DYSTROPHY 1 Pathophysiology Research Paper Name Professor Institution MUSCULAR | Course Hero. [online]. Available at: https://www.coursehero.com/file/97031482/Pathophysiology-of-Muscular-Dystrophy-1docx/.
5. Muscular Dystrophy: Symptoms, Causes, Treatments. [online]. Available at: https://my.clevelandclinic.org/health/diseases/14128-muscular-dystrophy#:~:text=If%20your%20healthcare%20provider%20suspects%20muscular%20dystrophy%2C%20you,tests%20identify%20gene%20mutations%20linked%20to%20muscular%20dystrophy...
6. Muscular dystrophy - Symptoms and causes - Mayo Clinic. [online]. Available at: https://www.mayoclinic.org/diseases-conditions/muscular-dystrophy/symptoms-causes/syc-20375388.
7. Muscular Dystrophy: Symptoms, Diagnosis, and Treatment. [online]. Available at: https://www.webmd.com/children/what-is-muscular-dystrophy#:~:text=Muscular%20dystrophyis%20a%20group%20of%20diseases%20that%20make,some%20people%2C%20the%20disease%20starts%20early%20in%20childhood...
8. Muscular dystrophy - NHS. [online]. Available at: https://www.nhs.uk/conditions/muscular-dystrophy/.
9. Muscular dystrophy - Diagnosis and treatment - Mayo Clinic - Search. [online]. Available at: https://www.bing.com/search?q=Muscular+dystrophy+-+Diagnosis+and+treatment+-+Mayo+Clinic&qs=n&form=QBRE&sp=-1&pq=muscular+dystrophy+-+diagnosis+and+treatment+-+mayo+clinic&sc=5-58&sk=&cvid=E77B2178ED684D168AF33FFF806458B4&ghsh=0&ghacc=0&ghpl=.

10. Muscular dystrophy: Symptoms, treatment, types, and causes. [online]. Available at: https://www.medicalnewstoday.com/articles/187618.
11. What is Muscular Dystrophy? | CDC. [online]. Available at: https://www.cdc.gov/ncbddd/musculardystrophy/facts.html.
12. Zhang, Y., Mann, J., James, K., McDermott, S., Conway, K., Paramsothy, P., Smith, T., Cai, B. and STARnet, M. (2021). Duchenne and Becker Muscular Dystrophies' Prevalence in MD STARnet Surveillance Sites: An Examination of Racial and Ethnic Differences. Neuroepidemiology, [online] 55, (1) , pp.47-55. Available at: https://pubmed.ncbi.nlm.nih.gov/33477152/. [Accessed 1 Jan. 1970].
13. Romitti et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015;135(3):513-521 - PubMed. [online]. Available at: https://pubmed.ncbi.nlm.nih.gov/25934896/.
14. Hilbert, J., Ashizawa, T., Day, J., Luebbe, E., Martens, W., McDermott, M., Tawil, R., Thornton, C. and Moxley 3rd, R. (2013). Diagnostic odyssey of patients with myotonic dystrophy. J Neurol, [online] 260, (10) , pp.2497. Available at: https://pubmed.ncbi.nlm.nih.gov/23807151/. [Accessed 1 Jan. 1970].
15. Turner C, Hilton-Jones D. Myotonic dystrophy: Diagnosis, management and new therapies. Curr Opin Neurol. 2014 Oct; 27:599-606.
16. Wang LH, Tawil R. Facioscapulohumeral dystrophy. Curr Neurol Neurosci Rep. 2016 Jul; 16:66.
17. Wang CH, Bonnemann CG, Rutkowski A, et al. Consensus statement on standard of care for congenital muscular dystrophies. J Child Neurol. 2010 Dec;25:1559-81.
18. Dimachkie, M. and Barohn, R. (2014). Distal myopathies. Neurol Clin, [online] 32, (3), pp.817. Available at: https://pubmed.ncbi.nlm.nih.gov/25037092/. [Accessed 1 Jan. 1970].
19. Prevention of muscular dystrophy | Musculoskeletal Issues articles | Body & Health Conditions center | SteadyHealth.com. [online]. Available at: https://ic.steadyhealth.com/prevention-of-muscular-dystrophy.
20. Koutsoulidou, A., Koutalianos, D., Georgiou, K., Kakouri, A., Oulas, A., Tomazou, M., Kyriakides, T., Roos, A., Papadimas, G., Papadopoulos, C., Kararizou, E., Spyrou, G., Papanicolaou, E., Lochmüller, H. and Phylactou, L. (2022). Serum miRNAs as biomarkers for the rare types of muscular dystrophy. Neuromuscular Disord, [online] 32, (4), pp.332-346. Available at: https://pubmed.ncbi.nlm.nih.gov/35393236/. [Accessed 1 Jan. 1970].
21. Pegoraro, V. and Angelini, C. Circulating miR-206 as a Biomarker for Patients Affected by Severe Limb Girdle Muscle Dystrophies. Genes, [online] 12, (1). Available at: https://www.mdpi.com/2073-4425/12/1/85.
22. Koutsoulidou, A. and Phylactou, L. (2020). Circulating Biomarkers in Muscular Dystrophies: Disease and Therapy Monitoring. Mol Ther Methods Clin Dev, [online] 18, pp.230-239. Available at: https://pubmed.ncbi.nlm.nih.gov/32637452/. [Accessed 1 Jan. 1970].
23. Muscular dystrophy - Diagnosis and treatment - Mayo Clinic. [online]. Available at: https://www.mayoclinic.org/diseases-conditions/muscular-dystrophy/diagnosis-treatment/drc-20375394.
24. Ferri, F. (2019). Ferri's Clinical Advisor 2020. [online] shop.elsevier.com. Available at: https://shop.elsevier.com/books/ferris-clinical-advisor-2020/ferri/978-0-323-67254-2 [Accessed 1 Jan. 1970].
25. AskMayoExpert. Muscular dystrophy. Mayo Clinic; 2018.
26. Darras BT. Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. https://www.uptodate.com/contents/search. Accessed Dec. 21, 2019.
27. Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. The Lancet Neurology. 2018; doi.10.1016/S1474-4422(18)30024-3. Accessed Dec. 21, 2019.
28. Darras BT. Limb-girdle muscular dystrophy. https://www.uptodate.com/contents/search. Accessed Dec. 23, 2019.
29. Duchenne muscular dystrophy (DMD). Muscular Dystrophy Association. https://www.mda.org/disease/duchenne-muscular-dystrophy. Accessed Dec. 21, 2019.