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A review on Duchenne muscular dystrophy associated cardiomyopathy

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Abstract
Duchenne muscular dystrophy (DMD) is a rare genetic disorder primarily affecting males. It is caused by mutations in the DMD gene, which leads to the absence of the protein dystrophin in muscle cells. While DMD primarily manifests as a progressive muscle-wasting condition, it can also have significant cardiac implications, known as DMD-associated cardiomyopathy. DMD-associated cardiomyopathy typically develops as individuals with DMD age, usually appearing in the late teens or early twenties. It results from the gradual replacement of healthy cardiac muscle tissue with fibrous and fatty tissue, impairing the heart's ability to pump blood effectively. This condition can lead to dilated cardiomyopathy, characterized by an enlarged and weakened heart. Common symptoms of DMD-associated cardiomyopathy include shortness of breath, fatigue, palpitations, and edema. If left untreated, it can progress to heart failure, which may necessitate interventions such as medications, pacemakers, or heart transplantation. Regular cardiac monitoring is essential for individuals with DMD to detect cardiomyopathy early. Treatment strategies aim to manage symptoms, improve cardiac function, and prolong life. Medications like ACE inhibitors or beta-blockers can help manage heart function, and some individuals may benefit from cardiac surgery or devices like implantable cardioverter-defibrillators (ICDs). DMD-associated cardiomyopathy is a serious and potentially life-threatening complication of Duchenne muscular dystrophy. Early detection and a multidisciplinary approach involving cardiologists, neurologists, and other specialists are crucial to manage the disease and improving the quality of life for affected individuals.

Keywords: Duchenne muscular dystrophy, cardioverter-defibrillators, ACE inhibitors, Beta-blockers

Introduction
Duchenne muscular dystrophy (DMD) is a X-linked recessive disorder caused by mutation of the dystrophin gene and is a progressive muscle wasting disorder that affects skeletal muscles, myocardium, respiratory, and bulbar muscles [2]. DMD is classified as a dystrophinopathy (A spectrum of muscle diseases caused by alterations in the dystrophin gene) [3]. It is usually recognized at three to six years of age [4]. The life expectancy of DMD patients has gradually increased to 30-35 years of age due to improved treatment and long-term care with the use of assisted non-invasive positive ventilation, glucocorticoid therapy, cardiomyopathy management, and nutritional support [5]. Along with dilated cardiomyopathy (DCM), arrhythmias, and congestive heart failure (HF) also represent the most important life-limiting condition in Duchenne muscular dystrophy (DMD) [6]. In the 21st century, heart failure is a leading cause of death in DMD, with many patients reaching adolescence or adulthood and displaying symptoms of dystrophic heart disease without receiving cardiac therapy [7]. The guidelines released in 2015 recommended that DMD patients start therapy with ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) by 10 years of age or sooner, based on mounting evidence that early stages of cardiac deterioration may have already begun [8]. Dilated cardiomyopathy (DCM) is characterized by left ventricular enlargement and systolic dysfunction. Genetic testing can identify a mutation in 40–50% of DCM patients, affecting >40 genes that encode a heterogeneous group of proteins. Mutations in the *DMD* gene that codes for the cytoskeletal protein dystrophin cause both DCM and skeletal myopathy (Duchenne and Becker muscular dystrophy) independently or in combination [9].

It is measured by echocardiography and cardiac magnetic resonance imaging and causes morbidity and mortality [10]. Since the 1860s DMD had been known as a clinical entity, its cause was not clear until over 100 years later. In 1986, Louis Kunkel identified that the *DMD* gene was responsible for causing DMD. A year later, he demonstrated that mutations resulted in the absence of the 427kDa rod-like protein dystrophin [11]. Dystrophin is a protein that links the cytoskeleton to the extracellular matrix to form the dystrophin glycoprotein complex (DGC). *DMD* is the largest human gene, consisting of 79 exons with at least 8 alternative promoters scattered along the gene [12]. The full-length of dystrophin gene has 3 promoters: the M promoter produces the Dp427m isoform, expressed in skeletal and cardiac muscle; the B promoter produces Dp427c, expressed in the brain; and the P promoter produces Dp427p, expressed in the Purkinje cells in the brain [13]. Mutations in DMD can also cause Becker muscular dystrophy (BMD), milder disease with a later onset and a slower progression than DMD, severe disease [14, 15]. DMDs earliest symptoms are difficulties with climbing stairs, a waddling gait and frequent falls; patients present with these symptoms around 2–3 years of age. Most patients become wheelchair dependent around 10–12 years of age and need assisted ventilation at around 20 years of age. With optimal care, most patients with DMD die between 20 and 40 years of age from cardiac and/or respiratory failure [16]. Routinely cardiovascular evaluation including echocardiography is recommended from 2018, DMD care consideration and sponsored by Centres of disease control and prevention. DMD patients are not candidates for heart transplantation because of the progressive skeletal myopathy, limited functional capacity, and shortage of donor availability [17].

Objective

Dilated cardiomyopathy (DCM) is one of the major complications and leading cause of death in Duchenne muscular dystrophy (DMD). Its onset is variable suggesting modified effects of genetic or environmental factors. Since survival in Duchenne muscular dystrophy (DMD) has greatly increased with long-term ventilation and cough assistance, cardiomyopathy has become an important life-limiting factor [1].

Etiology

DMD is a neuromuscular disease due to a mutation in the dystrophin gene, which is found on chromosome Xp21. Although it is an X-linked recessive disease, about 30% of cases are caused by novel mutations [18, 19]. Dystrophinopathies (Diseases caused by mutations in the dystrophin gene) include Duchenne muscular dystrophy, Becker muscular dystrophy, and an intermediate variant. Due to reduced dystrophin protein production brought on by mutations, the myofiber membrane integrity is lost, leading to recurrent cycles of necrosis and regeneration. Muscle is gradually replaced by fat and fibrous connective tissue, resulting in clinical characteristics. Female carriers do not exhibit any signs of muscle wasting, but symptomatic female carriers have been reported. Up to 20% of female carriers could be affected, or about 2.5%. This might be according to the Lyon hypothesis that the X chromosome with the mutation is expressed while the normal X chromosome is rendered inactive. Female carriers who have Turner's syndrome (45 X) or a mosaic Turner karyotype, balanced X autosome translocations with breaks in the dystrophin gene and preferential inactivation of the normal X, or females with a normal karyotype but non-random X chromosome inactivation with reduced expression of the normal dystrophin allele may develop symptoms. One of the biggest genes in the human genome is the dystrophin gene, which has 2.5 Mb of DNA and 79 exons of coding sequence, producing the 427 kDa protein dystrophin. Most mutations are deletions and duplications, which make approximately 70% to 80% of all mutations.20% to 30% of patients, have point mutations. The striated and cardiac muscles, as well as the brain and retina, all express dystrophins. The distribution in the brain is less than that in the muscle and this does help to explain some of the central nervous system manifestations of DMD [20].

Epidemiology

Dystrophinopathies affects 1 in 5,000 to 1 in 6,000 live male births. DMD prevalence is less than 10 cases per 100,000 males and for BMD is less than 8 cases per 100,000 live male births [21, 22]. DMD in females is very rare (<1 per million) and occurs when they have Turner's syndrome (a translocation involving DMD or those with bi-allelic *DMD* mutations) [23]. Approximately 2.5–19% of carriers have skeletal muscle symptoms and 7.3–16.7% develop dilated cardiomyopathy. Up to 13.3% of female carriers with BMD mutations have skeletal muscle symptoms and dilated cardiomyopathy but respiratory defects do not usually occur in them [24]. 47% deletions and 7% duplications cluster in hotspot regions in *DMD*, which are located at exons 45–55 and 3–9 occurs respectively [25]. The *DMD* gene is the largest known human gene at 2.4 Mb, producing a 14 kb mRNA transcript from 79 exons [26]. DMD is most often passed via the X-chromosome from a mother that carries one mutated copy of the gene to male offspring, but also has a relatively high rate of de novo mutations accounting for roughly 1/3 of all cases [27, 28, 29]. The survival of patients with DMD has improved over time; indeed, a study in France found that the median life expectancy was 25.77 years for those born before 1970 and 40.95 years for those born after 1970 [30]. A review study in Scotland suggested that lifespan was normal in carriers with cardiomyopathy [31]. DMD and BMD are caused by de novo germline mutations in one-third of patients and mothers who are not somatic carriers of DMD mutations but having children with DMD or BMD are at risk of having another child with DMD or BMD owing to germline mosaicism (a percentage of her oocytes carries the mutation). The frequency of germline mosaicism in oocytes or sperms varies per individual but it can be up to 14% [32].

Pathogenesis

DMD is predominantly a disease characterized by muscular necrosis and degeneration. Muscle tissue is designed specifically for contraction and serves as the foundation for breathing, blood pumping, and movement of the body. Additionally, contractile activity produces a significant amount of mechanical stress that, if not adequately controlled, will harm muscle. Unable to control mechanical stress brought on by muscular action is a key element in the etiology of DMD.

Although the heart is the body's most overworked muscle, cardiomyopathy is a late symptom of DMD. This observation is most likely caused by variations in DAPC

composition and dystrophin expression. Particularly, the Dp427m type of dystrophin is solely expressed in t-tubules in the heart [33]. At the Z-discs, dystrophin directly binds to the contractile apparatus (-actin), and it also interacts with the cardioprotective proteins Cypher, AHNAK1, Cavin 1, and CRYAB. DMD is caused by structural and/or functional defects of a sarcolemmal protein owing to mutations in the encoding gene. DMD encodes the muscle-specific dystrophin (Dp427m) in addition to two other full-length isoforms from the promoters Dp427c and Dp427. These isoforms are expressed in cortical neurons and cerebellar Purkinje cells, respectively. Dystrophin interacts directly or indirectly with the muscle membrane, the cytoskeleton (actin microfilaments, medial filaments, microtubules, and other associated structural proteins), channel proteins, and signalling or scaffold proteins in skeletal muscle.

The dystrophin associated protein complex (DAPC) is made up of dystrophin and its binding partners. Since several of its components are glycoproteins, the conventional DAPC-also known as the dystrophin glycoprotein complex, or DGC-was first identified in the early 1990s. The DGC contains 11 proteins: dystrophin, the dystroglycan subcomplex (α-dystroglycan and β-dystroglycan), the sarcoglycan subcomplex (α-sarcoglycan, β-sarcoglycan, γ-sarcoglycan and δ-sarcoglycan), sarcospan, syntrophin, dystrobrevin and neuronal nitric oxide synthase (nNOS).

The DAPC disassembles due to dystrophin insufficiency, and F-actin no longer interacts with the extracellular matrix. Due to the crucial mechanical and signalling functions that the DAPC plays in preserving the structural integrity and contractile activity of muscle cells, the effects of DAPC disintegration on muscle cell function are extensive [34].

Sarcolemma weakening

The cytoskeleton, sarcolemma, and extracellular matrix are connected by the DAPC and integrin complex in healthy muscle, preserving the integrity of the sarcolemma. The DAPC breakdown in DMD makes the sarcolemma more vulnerable to contraction injury. Patients with DMD-related cardiomyopathy are most frequently seen to have sarcolemmal rips and sarcolemma rupture.

Functional ischaemia

The first noticeable muscular lesions in DMD patients are little clusters of muscle degradation and regeneration. As nNOS is anchored to the sarcolemma by dystrophin (particularly, dystrophin spectrin-like repetitions R16 and R17), nitric oxide is produced and released, causing vasodilation in the surrounding vasculature. nNOS is mis localized to the sarcoplasm and the overall cellular nNOS level is decreased in the absence of dystrophin, impairing protective vasodilation, and causing ischemic damage to muscle [35].

Free-radical damage

Due to the absence of the dystrophin-microtubule connection, the microtubule lattice in DMD becomes thick and disordered, dramatically increasing the process of NOX2-mediated ROS generation. Another significant source of free radicals in DMD muscle is reactive nitrogen species, which are produced by the activation of delocalized nNOS in the cytosol [51]. Further free radicals are produced in DMD muscle by mitochondrial failure and invading inflammatory cells. As a result of this free-radical generation, DMD muscle exhibits higher levels of indicators for protein, lipid, and DNA oxidation, indicating persistent and recurrent oxidative damage and therefore the ability to cope with oxidative stress is greatly reduced in DMD muscle.

Regeneration failure

In DMD, muscle atrophy, fibrosis, and fat replacement are all caused by a failure to repair. According to several studies, the DAPC directly affects muscle regeneration. In fact, satellite cells divide asymmetrically to repair injury in healthy muscle, and interactions between DPAC proteins (dystrophin-PAR1b and 1-syntrophin-p38/Carm1) are crucial to this process [56]. Regeneration is hampered by DAPC disintegration because activated satellite cells' myogenic commitment is compromised. Failed regeneration occurs owing to the indirect effects of changes in the microenvironment from the absence of dystrophin, such as matrix remodelling, epigenetic alterations, and chronic inflammation, in addition to the probable failure in myogenic commitment [36].

Membrane Instability

The fundamental problem in DMD is frequently thought to be membrane fragility, which sets off several secondary pathophysiological pathways that cause myocyte death. Skeletal muscle loses the majority of the DGC when dystrophin is lost, but cardiac muscle retains the majority of the other DGC components when dystrophin is absent. Without functional dystrophin, the sarcolemma weakens and exhibits substantial leakiness when the myocyte is put under more strain. Elevated levels of CK, which are primarily attributed to skeletal muscle, as well as cTn from the heart, are serum indicators of this enhanced cellular permeability [60, 61, and 62]. Studies employing genetic models have confirmed that membrane integrity is crucial for the preservation of cardiomyocytes and dystrophic cardiomyopathy. Important participants in membrane preservation and repair have been identified as Dysferlin, MG53, and thrombospondin 4 (Thbs4). In dystrophin-null or sarcoglycan-null animals, it has been demonstrated that gene ablation of any of these causes worsening cardiac and skeletal muscle disease.

Calcium Dysregulation

High membrane permeability causes homeostatic disruption in large part by eroding ion gradients, which helps to explain why intracellular calcium levels are elevated. The increases in cytosolic calcium concentrations observed in dystrophic myocytes may be caused by a multitude of ion channels and calcium handling proteins in addition to passive calcium leak through membrane perforations. In addition to external sources, the sarcoplasmic reticulum (SR) may also contribute to the excess diastolic calcium observed in dystrophic cardiomyocytes. The problem of high calcium leak through the sarcolemma may exacerbate itself if these systems are unable to sequester SR calcium sufficiently to maintain low diastolic calcium levels, leading to substantial myocyte disease. Increased proteolysis, mitochondrial malfunction, and signaling cascades that encourage cell death are all triggered by elevated intracellular calcium, which disrupts a myocyte's normal contractile and electrical activity [37].

Mitochondrial Energetics

To carry out its physiological activities, the heart consumes a significant amount of ATP. The heart has developed an energetic buffer and shuttling mechanism employing phosphocreatine to store and move chemical energy to fulfill these extremely high and dynamic energy needs. When cardiac energy requirements rise, phosphocreatine (PCr) can act as a fuel buffer that is quickly turned into ATP. The dystrophic heart's mitochondria are somehow damaged and unable to supply the energy needs of the dystrophic cardiomyocyte.

Fibrosis

One of the early clinical signs of dystrophic cardiac disease is fibrosis, which first manifests in the hearts of DMD patients before the age of 10. Cardiomyocytes, fibroblasts, endothelial cells, and immune cells are a few of the cell types that contribute to the growth of cardiac fibrosis. The dystrophic heart's fibrosis is most likely brought on by the cellular stress and necrotic death of cardiomyocytes, which contaminate the surrounding tissue with cytokines, chemokines, and debris that draw neutrophils and macrophages. These cells have a variety of phenotypes, and a variety of environmental stimuli may influence their polarization to encourage tissue inflammation or healing via paracrine signalling profiles [67]. Aside from the apparent problem of not aiding in the heart's pumping motion, the buildup of fibrosis may also pose problems. First, by moving the workload demand onto the nearby cardiomyocytes, which will now have to perform excessive contractile work in a stiff, mechanically taxing environment, it probably promotes additional losses of functional myocardium. Second, the scar may disrupt the pathways for electrical conduction in the heart, which could result in several arrhythmias [Figure 1, 2].

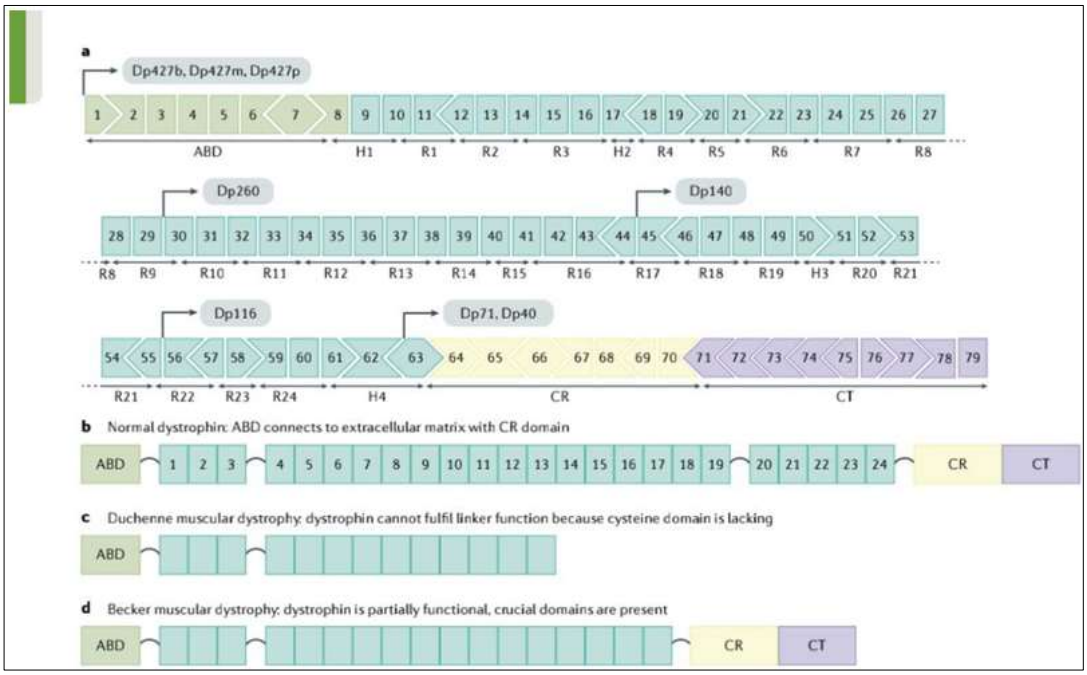

Fig 1: Schematic depiction of DMD and dystrophin protein.

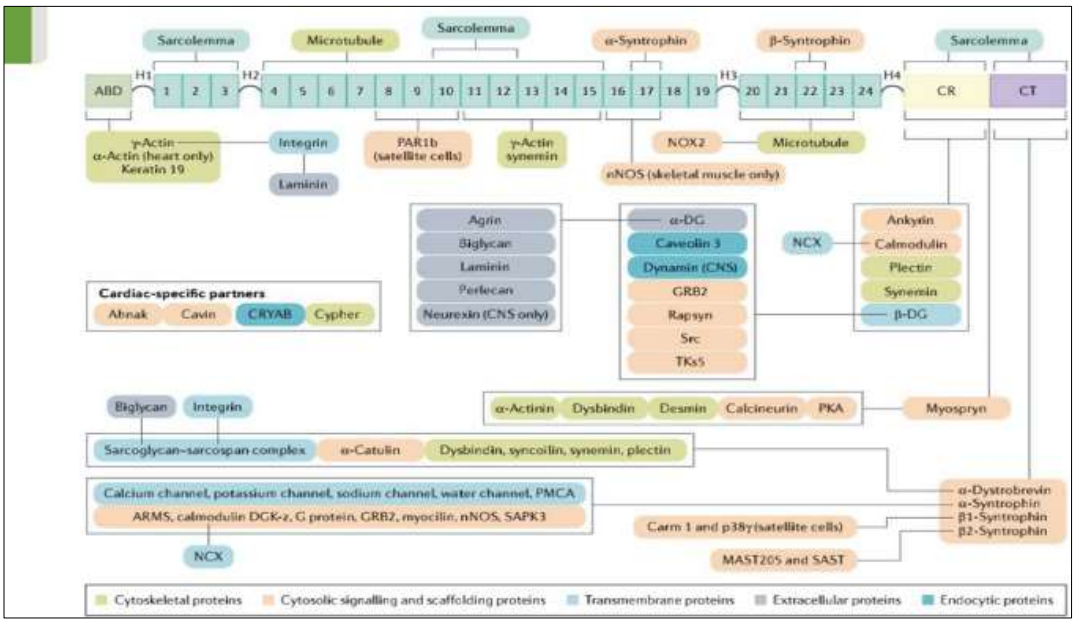

Fig 2: Dystrophin and binding proteins

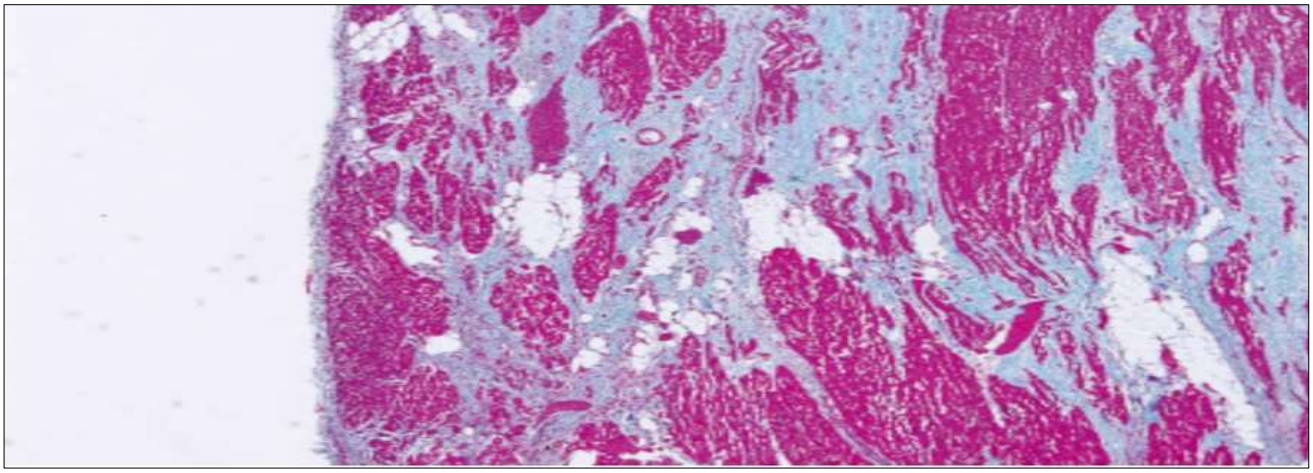

Fig 3: Cardiac fibrosis in DMD

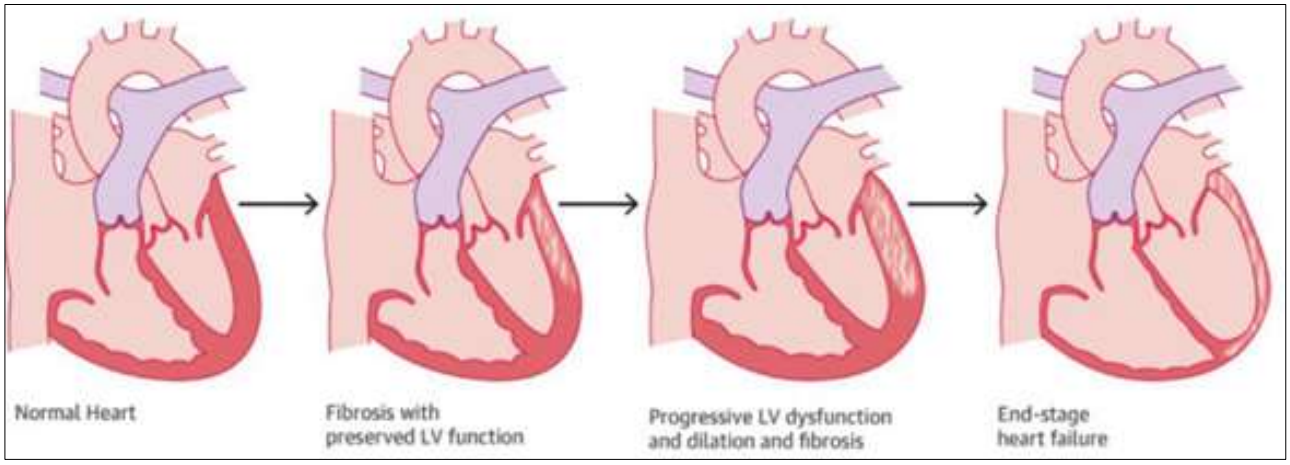

Fig 4: Heart failure due to fibrosis

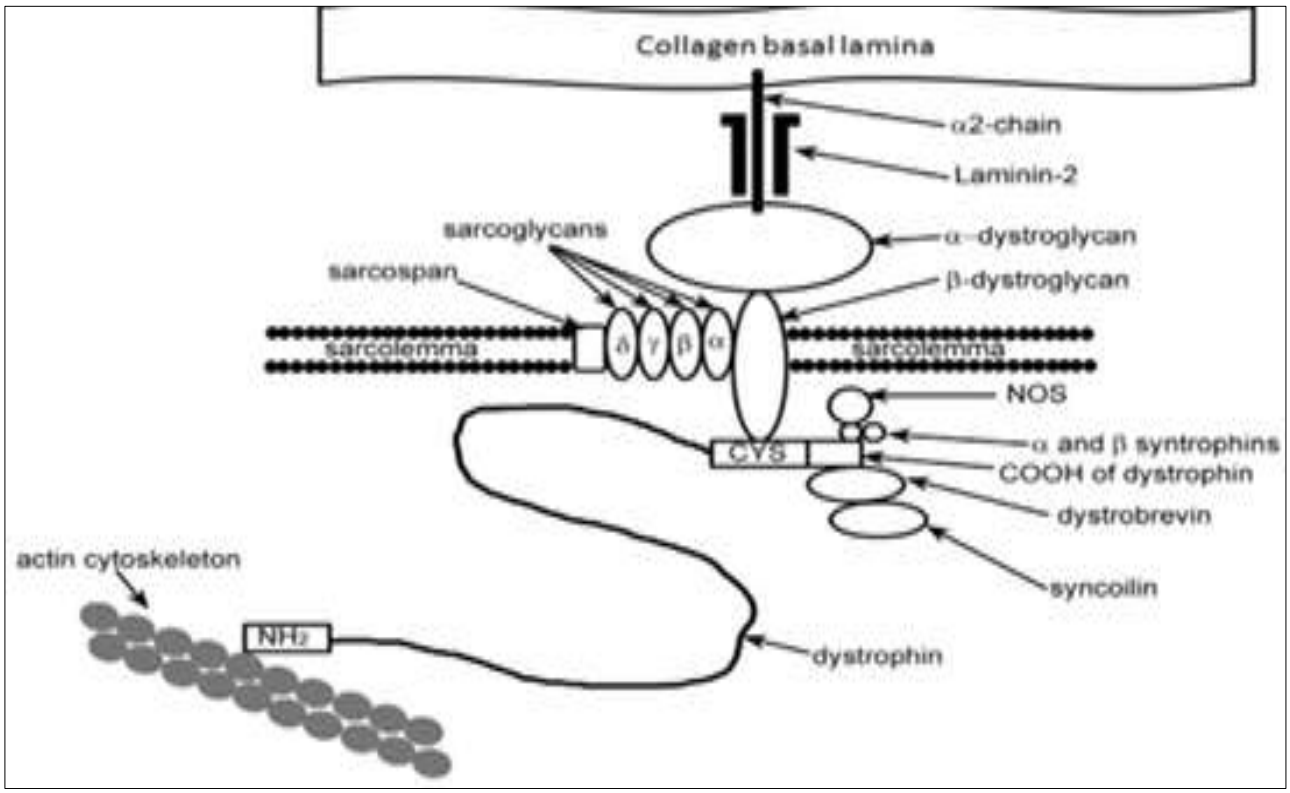

Fig 5: A schematic diagram of the position of dystrophin and its connection with the members of the dystrophin-glycoprotein complex (DGC). Dystrophin acts as a link between the basal lamina and the actin cytoskeleton helping to maintain the integrity of the sarcolemma. The loss of dystrophin compromises the DGC and leads to a more fragile sarcolemma.

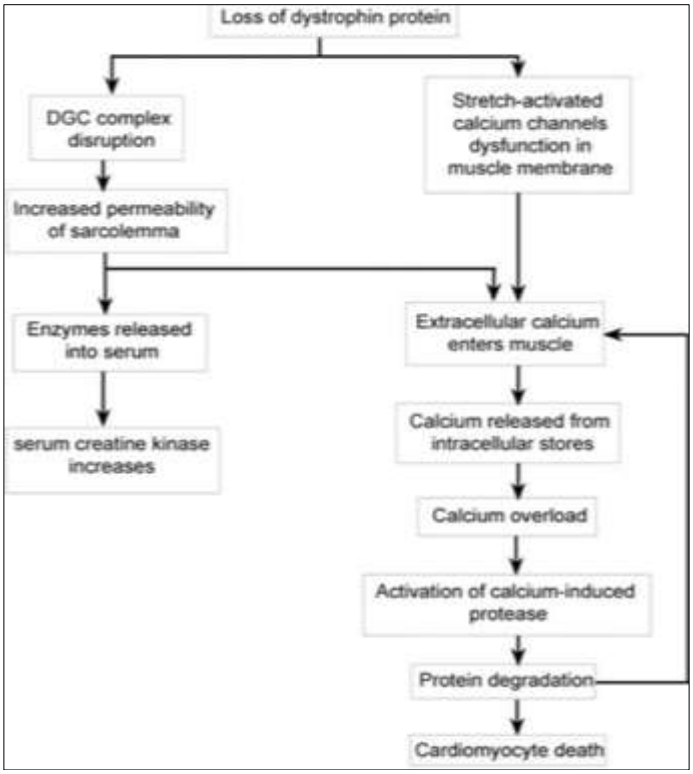

Fig 6: A flow diagram of the known pathways by which the loss of dystrophin or a severely truncated dystrophin leads to the development of cardiomyocyte death.

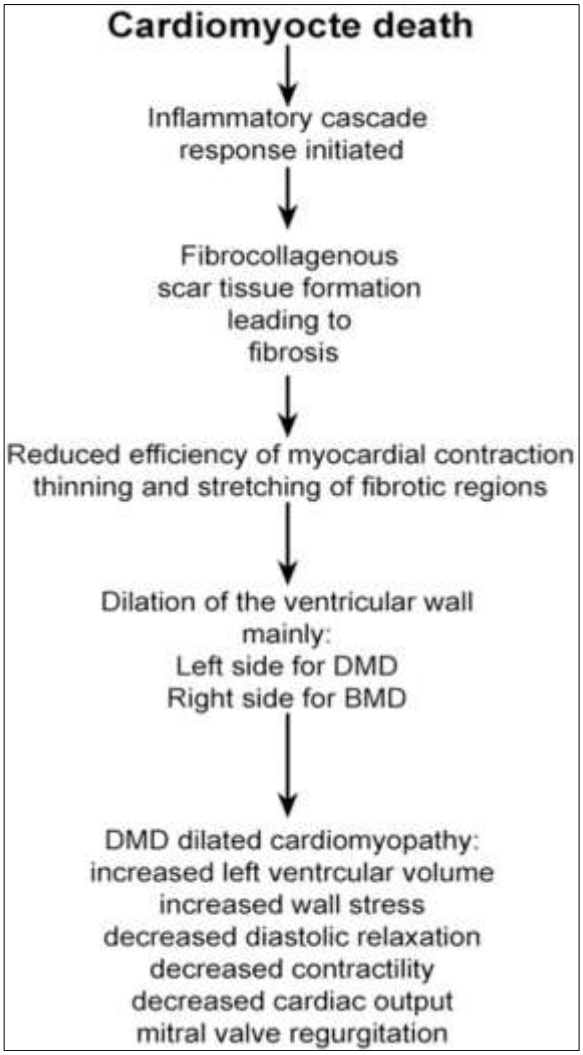

Fig 7: A flow diagram of how the death of the cardiomyocytes caused by the lack of dystrophin then develops into the dilated cardiomyopathy seen in DMD patients.

Diagnosis

A thorough clinical assessment, a thorough review of the patient's medical history, and several specialists testing, including molecular genetic tests and biopsies, are used to determine the diagnosis of DMD. Deoxyribonucleic acid (DNA) is analyzed in molecular genetic testing to look for specific genetic mutations, such as deletions, duplications, or single point mutations. Tests may be performed on blood or muscle cell samples. In some circumstances, muscle biopsy samples can be subjected to a specialized test to ascertain the presence and concentrations of proteins within cells. There are numerous methods that can be utilized, including immunofluorescence, Western blotting, and immunostaining. certain antibodies that react to certain proteins, such as dystrophin, are used in these testing.

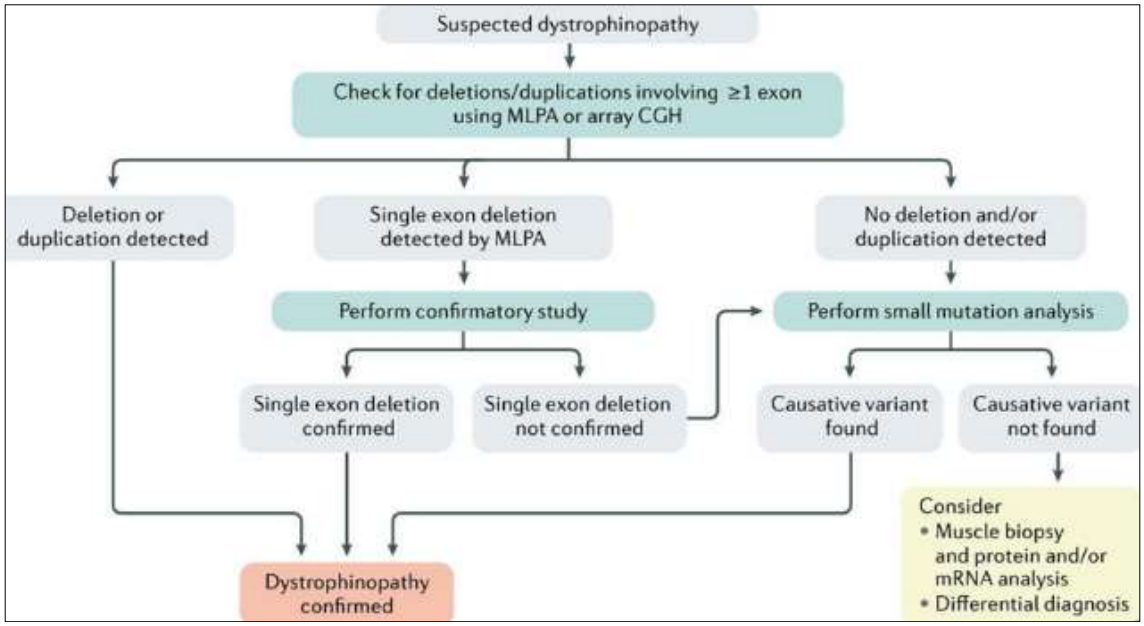

Fig 8: Diagnostic decision tree to confirm the genetic diagnosis of dystrophinopathies.

Although exome sequencing or gene sequencing will likely be routine for all patients with suspected inherited diseases in the future, at present, it is more economical to perform a genetic diagnosis for dystrophinopathies using a stepwise approach [38]. The presence and abundance of the 79 DMD exons are first assessed by multiplex ligation-dependent probe amplification (MLPA) or array comparative genomic hybridization (array CGH). Most genetic diagnostic laboratories employ MLPA because it is easy to implement due to the availability of commercially available kits. Because 75% of patients have DMD deletions or duplications2, MLPA or array CGH will find the causative mutation in most cases. It is vital to note that if MLPA identifies a single exon loss, it is critical to validate this finding with a secondary test to rule out the possibility that one of the probes was unable to bind due to a minor mutation.

If MLPA or array CGH fail to detect a mutation, minor mutation analysis using Sanger sequencing is required, this involves sequencing each of the 79 exons and adjacent intronic regions. MLPA is used in diagnostic laboratories in middle- and high-income countries around the world; nevertheless, minor mutation analysis is often only available in specialized laboratories. Only multiplex PCR may be offered in low-income countries. Multiplex PCR sets that analyse the presence or absence of frequently deleted DMD exons based on how deletions cluster in two hotspots are available. However, because these sets do not include all DMD exons, this study merely shows that certain exons are missing while others are present, and it is unclear which exons are implicated in the deletion. For example, if exons 43 and 46 are known to be present but exon 45 is missing, the deletion can involve only exon 45 (out-of-frame) or exon 44 and exon 45 (in-frame). As a result, this method cannot determine whether the deletion is in-frame or out-of-frame, or whether a patient is eligible for a mutation-specific treatment. Furthermore, this test can only reliably detect deletions and no other types of mutations, hence multiplex PCR is not suggested for the genetic diagnosis of DMD and BMD. If MLPA, array CGH, and minor mutation analyses are not accessible, multiplex PCR is better than no genetic analysis. When analysing the mutation's effect, it is important to remember that clinical symptoms are what determine whether someone has DMD or BMD. In >90% of cases, in-frame mutations will lead to BMD and out-of-frame mutations to DMD; however, exceptions have been reported. In the case of discordance between symptoms and genetic mutations, such as an in-frame mutation and symptoms of DMD, one could consider a muscle biopsy and protein analysis to assess, for example, whether alternative splicing can explain the discordant phenotype. It is important to remember that clinical symptoms are what determine whether someone has DMD or BMD. A muscle biopsy is not required for a diagnosis of DMD for most patients and is indicated only when no mutations are detected using MLPA, array CGH or Sanger sequencing. In these cases, the purpose of muscle biopsy is to assess whether dystrophin is properly localized (using immunofluorescence analysis) or absent/ reduced (using Western blotting and immunofluorescence, absent levels are diagnostic of DMD) or has a altered size (using Western blotting, an altered size is diagnostic of BMD). Often, these cases are caused by deep intronic mutations and mRNA can be isolated from the biopsy for further analysis. Care can be undertaken in patients who do not have a recognized causal mutation; however, genetic counselling is more difficult and

confusing. Notably, due to the large molecular size and low quantity of dystrophin, protein analysis by Western blotting or immunofluorescence is difficult.

Treatment

DMD has no curative treatment. Physical therapy and active and passive exercise should be used to develop muscle strength and prevent contractures. Treatments are tailored to each individual's exact symptoms.

Small Molecule Therapies for the Heart

Small molecule-based therapies are aimed at reducing the symptoms and hindering the mechanisms of disease progression in the heart. The four groups of cardiac small molecule approaches listed here are all currently in use in DMD clinical management.

Angiotensin-Inhibiting Therapies

The renin-angiotensin system inhibitor has become a cornerstone of cardiac-directed therapy efforts in DMD patients, with the goal of ameliorating the deleterious remodelling that follows cardiomyocyte loss. The two primary medication classes utilized to decrease the detrimental effects of angiotensin in heart failure patients in general and DMD patients in particular are angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs). ACEIs are an older drug class that is often used as the first line of therapy for general heart failure and was the first to be used in trials to demonstrate improved cardiac function and survival among DMD patients [39]. In cases of low ACEI tolerance, ARBs are offered as a supplementary option or an alternative. ARBs may have a unique potential to protect cardiomyocytes during acute episodes of increased cardiac workload.

Beta-Adrenergic Receptor Blockers

Tachycardia is a common symptom of DMD, and it reflects autonomic dysfunction in the dystrophic heart, which predisposes it to arrhythmias. Holter monitoring in DMD patients routinely reveals average heart rates >100 beats per minute, reflecting increased activation of the sympathetic nervous system and increased adrenergic signalling in the heart [74]. Activation of cardiac β -AR increases heart rate and contractility by increasing and speeding up calcium transients in the myocyte, which contributes to arrhythmogenesis. Beta-blockers are commonly used to treat acquired heart failure, and they are frequently coupled with ACEIs and diuretics to increase survival and decrease hospitalization rates.

Corticosteroids

Steroids are likely to be protective in the dystrophic heart, according to DMD patient studies, with probable advantages including longer survival, retained ventricular function, and even reductions in fibrosis [40]. Corticosteroids are the standard of therapy for people with DMD. These medications reduce the progression of muscle weakening in patients and postpone the loss of ambulation by 2-3 years. Prednisone and deflazacort are two prominent corticosteroid medications used to treat DMD patients.

Mineralocorticoid Receptor Antagonists

Aldosterone activation of the mineralocorticoid receptor (MR) can contribute to cardiac disease by inducing cardiomyocyte mortality, hypertrophy, and fibrosis in DMD cardiomyopathy and other kinds of heart failure. As a result, MR antagonists such as eplerenone and spironolactone are commonly used to treat heart failure with low EF and are occasionally used to treat DMD cardiomyopathy [41]. Clinical trials later revealed that patients with DMD and preserved ejection fraction who were already receiving an ACEI or ARB showed modest but significant improvements in myocardial strain, ejection fraction, and chamber dilation with eplerenone treatment when compared to those who did not receive eplerenone. The new discovery of vamorolone, an MR antagonist that is as potent to eplerenone and mimics the anti-inflammatory properties of corticosteroids, could be a significant step toward including this MR antagonist as a routine and proactive therapy for DMD cardiomyopathy.

Gene-Targeted Therapies

Gene-targeted therapies aim to induce the production of a functional gene product that will restore normal myocyte physiology. These treatments seek to restore the original cell defect by restoring functional dystrophin expression. Because of the wide range of mutations that cause DMD, many of these therapies must be adapted to specific patient subgroups based on the kind and location of the disease-causing mutation. Because the heart cannot be routinely biopsied to assess the efficacy of dystrophin re-expression, physicians will rely on more sensitive measures such as myocardial strain to examine patient hearts at early stages of the disease.

Stop Codon Read through

Approximately 10% of DMD patients have a nonsense mutation, which substitutes a typical amino acid triplet with a premature stop codon and causes the ribosome to interrupt translation, preventing the remaining protein from being synthesized [42]. The basic idea behind stop codon read-through, also known as nonsense suppression, is to get the ribosome to keep translating the mRNA through the premature stop codon and the rest of the transcript. The results in human patients are more unclear, with no demonstrable effect on heart function in a small cohort of non-ambulatory DMD patients, even though cardiac function remained stable across the 20–24-month therapy period.

Antisense-Mediated Exon Skipping

The most prevalent type of DMD mutation is a deletion, with many of them resulting in dystrophin loss due to the disruption of the open reading frame. When the open reading frame of a gene is displaced by a deletion or insertion, it frequently results in a downstream premature stop codon that stops translation; thus, the assumption of exon skipping is to sacrifice one exon to restore the open reading frame of the rest of the gene. To hide the splice site, antisense oligonucleotides (AON) bond to the premature mRNA at the splice acceptor site of the mutant exon. This leads the spliceosome to move on to the next available splice acceptor site, resulting in the mutant exon being excluded from the final mRNA transcript. In patients with frameshift deletions, the goal of this method is the creation of a shortened dystrophin protein that still has a deletion but preserves the majority of its functions. AON treatments, which were frequently administered in the form of a phosphorodiamidate morpholino oligomer (PMO), were

more likely to be trapped in cardiomyocyte endosomes than in skeletal muscle [43, 44, 45]. Following preclinical research, it was found that adjusting the dose and altering the delivery mechanism might overcome this problem in the heart, resulting in improved cardiac muscle dystrophin. However, tissue penetration and PMO lifespan have been a source of concern, and there is no indication of considerable eteplirsen uptake or advantages in the heart. Other AON delivery systems are also being researched to identify alterations that can maximize cellular penetration and systemic safety, with a strong emphasis on PPMOs. Because these agents only work at the level of premature RNA and have limited longevity in the cell, it will be important to set appropriate guidelines for dosing frequency to reflect sufficient efficacy in the heart to minimize the risk of XLCM-like heart failure.

Micro-dystrophin Viral Gene Therapy

Based on its theoretical ability to completely replace the missing gene product, viral gene replacement therapy is the only approach currently in clinical development that offers hope to all DMD patients, regardless of the underlying dystrophin mutation, and is the only available therapy for patients with mutations that span critically important dystrophin regions. The broad lessons learned from this vast body of work are 1) viral gene therapy is feasible and can even be efficiently systemically delivered, 2) only adeno-associated virus (AAV) is currently safe enough to use as a gene therapy vehicle in human patients, and 3) the safety and efficiency of viral gene therapy depend upon many factors that are unique to particular species and also the individual biology of the patient. While most preclinical research with AAV-delivered micro dystrophin has focused on skeletal muscle, substantial evidence of the cardiac benefits of systemic treatment includes significant decreases in histology and improvements in function, supporting their progression into clinical trials. Trials [46, 47, 48]. In the setting of an otherwise moderate BMD-like phenotype, AAV gene therapy for DMD may result in the persistent need for further small molecule-based cardiomyopathy treatment.

CRISPR-Cas9 Gene Editing

CRISPR-Cas9 is a highly adaptable genome-editing method discovered at the heart of a bacterial self-defence mechanism against viral infection, giving rise to a potential new tool for fixing genetic disorders. A single guide RNA (sgRNA) molecule detects a genomic sequence and signals an endonuclease to induce a double-stranded break in the DNA at specific recognition sites. Because the editing takes place at the genomic level and myocyte nuclei do not split further, this technique has the potential to treat DMD by restoring dystrophin expression with a single dose of the therapeutic drug. Because the CRISPR-Cas9 treatment strategy relies on systemic delivery and expression of foreign genes, this therapeutic approach has frequently used AAV-mediated gene delivery in preclinical work to achieve adequate transduction *in vivo*, with promising results from many separate studies [82]. Despite its considerable promise, this strategy is not without drawbacks. Additional preclinical studies with longer post-treatment monitoring in dog and/or non-human primate DMD models will be required to confirm the safety and efficacy of this genome-editing therapy, but current findings inspire hope that CRISPR-Cas9 treatment will reach clinical trials [49, 50].

Conclusion

Duchenne muscular dystrophy (DMD) associated cardiomyopathy is a serious and potentially fatal consequence of this deteriorating neuromuscular condition. An overview of the pathophysiology, clinical symptoms, diagnostic methods, and prospective treatment options for treating DMD-related cardiomyopathy has been presented in this review. In those with DMD, cardiomyopathy is a major cause of death. It is necessary to intervene early with medical and technological remedies. In DMD, cardiac involvement is linked to Dp116. Many of the regularly prescribed medications for HF have shown to be highly successful, particularly when started in the very early stages of the illness before heart failure is even noticeable. To detect heart issues early and begin ACE-I therapy, recent recommendations emphasize the significance of routine cardiac examination since the diagnosis of DMD. CMR is important due to its sensitivity in detecting early areas of fibrotic replacement of the cardiac muscle in this preclinical stage of DMD-DCM, CMR plays a significant role. The most frequent type of mutation underlying DMD is deletion. A significant improvement in the quality of life of DMD patients has been made possible by the current treatment options and regular monitoring. The cardiomyopathy that develops in DMD patients is a serious health problem that needs to be addressed, however, as evidenced by the extended life expectancy of these individuals. The most common cause of death in people with DMD is cardiomyopathy with systolic heart failure, and decreased LVEF is an independent predictor of mortality at younger ages. Regarding pharmacological therapy for heart failure, DMD patients seem to be undertreated. The most common cause of death in people with DMD is cardiomyopathy with systolic heart failure, and decreased LVEF is an independent predictor of mortality at younger ages. Regarding pharmacological therapy for heart failure, DMD patients seem to be undertreated. Cardiomyopathy has become a brand-new issue when under anaesthesia. Preoperative cardiac state should be thoroughly assessed. To forecast end organ involvement in DMD patients, the cardiologist and pulmonologist should collaborate. Maintaining end organ perfusion through appropriate left ventricle function is the aim of anaesthesia. The only available therapies are palliative, and there is no known cure for the illness. It comes at a time when palliative care doctors and nurses are required. The most crucial goal is to make sure that the patients live respectable lives. Regarding heart failure, patients with DMD tend to be undertreated. Treatments that are harsh might cause more harm than good. Even though DMD-associated cardiomyopathy is still a difficult and life-limiting condition, continuous research and developing treatment options provide afflicted people hope for better outcomes and a higher quality of life. The continuous fight against this severe effect of Duchenne muscular dystrophy relies heavily on early diagnosis, interdisciplinary treatment, and cutting-edge medicines. We must do further studies and clinical trials if we are to keep learning more about DMD-related cardiomyopathy and developing effective therapeutic options.

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