Chapter

Clinical Management of DMD-Associated Cardiomyopathy

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Abstract

Over the past decade, cardiomyopathy has become the leading cause of mortality among patients with Duchenne muscular dystrophy (DMD). The majority of DMD patients over the age of 18 experience some degree of cardiac involvement. The primary cardiac manifestations of DMD include progressive left ventricular (LV) wall stress leading to LV dilatation and wall thinning, and the development of cardiac fibrosis, all of which culminate in decreased LV contractility and reduced cardiac output. Mortality in these patients is predominantly related to pump failure and fatal arrhythmias leading to sudden cardiac death. While basic guidelines for the management of cardiomyopathy in DMD patients exist, these recommendations are by no means comprehensive, and this chapter aims to provide further insight into appropriate clinical diagnosis and management of DMD-associated cardiomyopathy. Notably, earlier and more frequent cardiac assessment and care can allow for better outcomes for these patients. Pharmacological treatments typically include an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, beta-adrenergic receptor blockers, mineralocorticoid receptor antagonists, and corticosteroids. Non-pharmacological therapies include automated implantable cardioverter defibrillators and left ventricular assist devices, as well as in rare cases cardiac transplantation. Additionally, many emerging therapies show great promise for improving standards of care. These novel therapies, based primarily on applied gene therapy and genome editing, have great potential to significantly alter the DMD care landscape in the near future.

Keywords: DMD-associated cardiomyopathy, Duchenne muscular dystrophy, dystrophinopathy, heart failure

1. Introduction

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disorder diagnosed during childhood and characterized by skeletal muscle wasting, diaphragmatic weakness and scoliosis resulting in chronic restrictive lung disease, and progressive cardiomyopathy. As an X-linked recessive disorder, DMD disproportionately impacts males compared to females and affects approximately 1 in every 3500 to 5000 live male births [1–3]. The disease is caused by mutations in the dystrophin gene located on the Xp21 chromosome, resulting in a lack of a functional dystrophin protein [4, 5]. While other dystrophinopathies result in a truncated but

partially functional dystrophin protein, the total absence of functional dystrophin protein in DMD patients leads to a myriad of devastating clinical outcomes.

Over the past several decades, significant progress has been made in treating and managing many of the complications in DMD. Although respiratory failure was historically the leading cause of morbidity and mortality in this population, advancements in nocturnal ventilatory support and spinal stabilization therapy have dramatically improved clinical outcomes and increased the average life expectancy of DMD patients [6]. As a result, more patients are living into adulthood where cardiomyopathy begins to manifest and now accounts for the majority of deaths [1, 4, 6, 7]. Although there is ongoing research in gene therapy and genome editing techniques to improve skeletal muscle function in DMD patients, cardiomyopathy among DMD patients remains a problem of paramount clinical significance, with the current focus on reducing cardiac involvement and mitigating the effects of the cardiomyopathy. This chapter will highlight the genetic and molecular pathology underlying DMD and provide insight into the clinical manifestations, diagnosis, treatments, and therapies for DMD-associated cardiomyopathy.

2. Genetics and the molecular basis underlying cardiac dysfunction in Duchenne muscular dystrophy

The dystrophin gene is the largest protein-coding gene in the human genome at 2.5 Mb, located on chromosome Xp21.1 [1, 5, 8]. With 79 exons and a 14-kb encoding transcript, the gene has four promoters which produce different isoforms of the dystrophin protein in various organs, but primarily in skeletal muscle, cardiac muscle, and the brain (**Figure 1A**) [8]. Frame shift mutations resulting in deletions of one or more exons of the gene are the most common cause of DMD, accounting for at least 65-75% of DMD cases [9, 10]. Duplications, deep intronic changes, nonsense mutations, and missense mutations can also disrupt dystrophin expression and lead to DMD [9], though these mutations occur less commonly. The phenotypic manifestations of DMD occur when these mutations result in a complete lack of functional dystrophin protein. While most instances of DMD are inherited, around 30% of cases are caused by spontaneous mutations in the gene [1, 11].

The dystrophin protein plays an integral role in maintaining myocyte membrane stability, connecting the dystrophin-associated glycoprotein complex (DGC) to the intracellular contractile apparatus and extracellular matrix of the cell (**Figure 1B**) [1, 4, 12, 13]. An absence of dystrophin protein destabilizes this complex and promotes sarcolemmal fragility. In the skeletal muscle of DMD patients, this leads to the loss of the majority of the DGC. In contrast, cardiac muscle retains the remainder of the DGC despite the absence of dystrophin. Despite these pathophysiological differences, both skeletal and cardiac muscle are drastically impacted by the absence of dystrophin protein. Specifically, in cardiac muscle the absence of dystrophin impacts the ability of myocytes to function properly and leads to many secondary pathophysiological mechanisms of cell degradation [1, 4, 14].

One such mechanism contributing to myocyte degradation involves the disruption of ion gradients. As the myocyte membrane weakens due to the absence of dystrophin, calcium passively leaks through the membrane; the activation of sarcolemmal stretch-activated channels during myocyte contraction causes intracellular calcium levels to further increase [4, 15]. Additionally, transient receptor potential (TRP) channels and L-type calcium channels (LTCC) have been shown to contribute to increased intracellular calcium in DMD murine studies [16–18]. Increased intracellular calcium ultimately results in myocyte degradation through two distinct pathways. First, electrical and contractile activities of myocytes are interrupted by

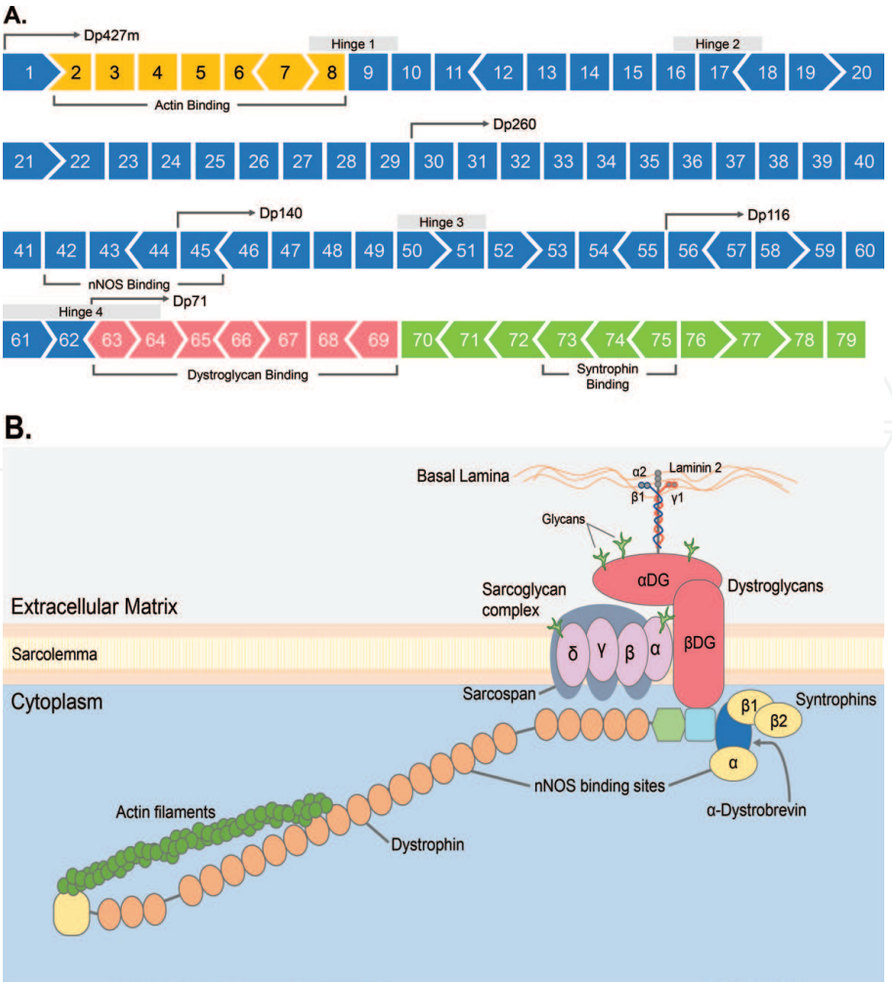

Figure 1.
Dystrophin structure and cellular location within a myocyte. (A) the dystrophin gene map composed of 79 exons and the essential regions highlighted in various colors. (B) Schematic of the dystrophin-associated glycoprotein complex (DGC). Adapted from Zhang et al. Physiolo. Rev 2018 98:1205-1240.

the inappropriate influx of calcium, promoting proteolytic activity via proteolytic enzymes and calpains, which eventually leads to cell death [15–17]. A secondary degradation pathway is triggered when excess cytosolic calcium begins to accumulate inside mitochondria, resulting in mitochondrial swelling and dysfunction that triggers separate apoptotic pathways [17]. Cardiac physiological studies on DMD^{mdx} mice have demonstrated elevated levels of mitochondrial calcium and mitochondrial swelling, leading to a disruption in mitochondrial ATP production in DMD^{mdx} hearts long before any fibrotic changes or reductions in left ventricular (LV) systolic function are detectable [4, 15–17].

In addition to calcium gradient disruption, increased generation of reactive oxygen species (ROS) and nitric oxide dysregulation also contribute to the development of DMD-associated cardiomyopathy. NADPH oxidase 2 (NOX2) is a membrane-bound isoform of the NOX enzyme, and it is the suspected source of increased ROS production in DMD patients. Elevated expression of NOX2 has been demonstrated in studies of both skeletal muscle and cardiomyocytes of DMD^{mdx} mice [19]. It has additionally been speculated that ROS produced by NOX2 may contribute to calcium leakage from the sarcoplasmic reticulum leading to mitochondrial dysfunction [4, 19, 20]. Activation of NOX2 leads to the production of an extracellular superoxide, which is then converted to hydrogen peroxide (H_2O_2). H_2O_2 is able to permeate through the myocyte membrane and results in the oxidation of various intracellular macromolecules, eventually leading to secondary

pathways contributing to cell death [4, 21]. Finally, angiotensin II receptor type I (AT1R) is believed to be involved in redox pathways involving the stimulation of NADPH oxidases, such as NOX2, and so the overproduction of ROS can lead to the overstimulation of AT1R. These events lead to further oxidative stress resulting in increased cardiomyocyte cell death [21].

Nitric oxide synthases (NOS) are a family of enzymes that catalyze the production of nitric oxide. There are three isoforms of NOS: neuronal NOS, endothelial NOS, and inducible NOS. In skeletal muscle, dystrophin interacts with neuronal NOS to control vasculature [22]. The relationship between dystrophin and NOS is less clear in the myocardium, especially since all three isoforms of NOS are expressed within cardiomyocytes and the molecular mechanisms and interactions have not been well elucidated to date [4]. It is speculated that NOS may play a similar role in cardiomyocytes as in skeletal muscle, and that in affected DMD patients nitric oxide diffusion is impaired. Researchers believe that inducible NOS may play a key role in the development of cardiac dysfunction in DMD, since its expression is high in immune cells and studies have found elevated inducible NOS levels and decreased neuronal NOS levels in cardiac tissue, while endothelial NOS levels and activity were reported to remain fairly constant [4, 22].

Collectively, these mechanisms involving altered ion gradients, mitochondrial dysfunction, and impaired nitric oxide activity contribute to pathways that promote cardiomyocyte dysfunction and cell death. The inflammatory responses to these processes ultimately lead to the development of myocardial fibrosis and maladaptive ventricular remodeling [9, 23]. Fibroblasts, endothelial cells, immune cells, and cardiomyocytes all contribute to the development of fibrosis by promoting profibrotic cytokines and chemokines. Fibrotic infiltration typically begins in the posterobasal and lateral left ventricular walls [4, 23]. As cardiomyocytes undergo apoptosis, they are replaced by the extracellular matrix (ECM). Subsequently, matrix metalloproteinases promote the degradation of ECM proteins, including collagen [24]. The increase in cytokines, chemokines, and degraded ECM debris stimulates an immune response, attracting neutrophils and macrophages which eventually leads to myocardial scarring and fibrotic patches [4, 24]. In the heart, LV volume and wall stress progressively increase as fibrotic tissue causes thinning and stretching of the ventricular walls, decreasing contractility and cardiac output. These processes eventually lead to either clinically decompensated heart failure, pump failure, and/or sudden cardiac death due to ventricular arrhythmias [4, 9, 23].

3. Clinical manifestations and diagnosis

Initially, DMD presents very early in childhood and therefore it is paramount to diagnose and initiate treatment as early as possible. Symptoms of DMD can arise in patients as young as three years of age and typically involve progressive muscle weakness, often manifesting as difficulty with ambulation, gait instability, difficulty climbing stairs, and enlarged calf muscles (or calf pseudohypertrophy). Additional presenting symptoms include scoliosis with or without back pain, fatigue, dyspnea secondary to diaphragmatic muscle weakness and/or cardiomyopathy, and arrhythmias [4, 25, 26]. The Gower's sign, the act of a child using their hands to help prop themselves up into a standing position, is also a very common indicator of DMD [9, 25, 26]. These signs and symptoms suggest the possibility of underlying DMD and necessitate further diagnostic testing.

Key initial diagnostic tests include measurements of serum creatine kinase (CK) and liver transaminases (such as alanine aminotransferase, aspartate aminotransferase) [27]. When levels of these biomarkers are elevated, DMD should be

suspected, and confirmatory genetic testing should be pursued. Genetic analysis via multiplex ligation-dependent probe amplification (MLPA) and genetic sequencing can help verify the presence and type of neuromuscular disorder [9, 27]. This is a critical step in diagnosis and is essential in informing which genetic therapies might be viable therapeutic options. On occasion, genetic testing yields no mutations in the DMD gene, or false negatives. In these instances of strong clinical suspicion of DMD with negative genetic test results, a muscle biopsy should be performed to assess for the absence of the dystrophin protein by immunohistochemistry [9]. Diagnosis of DMD occurs once genetic analysis and/or the biopsy confirms the absence of DMD.

However, diagnosing cardiac involvement in DMD is somewhat more challenging. Many of these patients are wheelchair-dependent and non-ambulatory well before adulthood, and as a result, patients are often asymptomatic until they have developed advanced disease [9, 28]. Studies report that approximately 25% of DMD patients develop cardiomyopathy by 6 years of age, and that percentage grows to almost 60% by age 10 [9, 29, 30]. Progression of cardiomyopathy often accelerates as patients age and nearly all DMD patients are expected to have clinical cardiac involvement by age 18 [7, 30]. Recognition and treatment of cardiomyopathy early in the disease course correlate with improved outcomes and more favorable ventricular remodeling, rendering it crucial to identify cardiac involvement as early as possible [1, 9, 23]. For this reason, guidelines strongly suggest including a cardiologist as a member of the care team from disease onset [4, 25, 31]. The 2018 DMD Care Considerations, presented by the Center for Disease Control and Prevention, recommends that cardiac care and assessment are essential at the time of diagnosis [25, 31]. While previous guidelines have recommended consulting with cardiologists every two years, it is now strongly recommended that DMD patients receive cardiac assessment and screening at least every year starting from diagnosis [25, 31].

Development of myocardial fibrosis along with ventricular dilation reflects myocyte destruction and progression in the underlying cardiomyopathy. Fatigue, nausea, dyspnea, palpitations, tachycardia, and chest discomfort may all represent symptomatic manifestations of DMD-associated cardiomyopathy, though many patients remain asymptomatic until later stages in life [31]. Therefore, the use of standard cardiac tools as well as high fidelity cardiac imaging are essential to accurately diagnose cardiac involvement in patients with subclinical disease [1, 25].

Electrocardiograms (ECG) should be among the first tests performed, and results are often abnormal in DMD patients, correlating with morphological changes in cardiac muscle [23]. Screening ECG usually reveals tall R waves and deep Q wave irregularities in the anterolateral leads, which typically suggest lateral wall scarring (**Figure 2A–C**) [29, 32].

The ECG may be suggestive of cardiac involvement; however, cardiac imaging is essential to diagnose and monitor progression of cardiac involvement in DMD patients. While echocardiography has been a mainstay in diagnostic cardiac imaging for years, studies in patients with DMD have demonstrated that echocardiograms often underestimate both LV cavity volume and function and are much less sensitive compared to cardiac magnetic resonance imaging (cMRI) in detecting wall motion abnormalities and overall cardiac function [9, 25, 32]. cMRI has been shown to be more accurate in assessing cardiac abnormalities in the setting of altered body habitus in DMD patients due to scoliosis, and it is considered the gold standard for cardiac imaging in DMD patients [25, 32]. The presence of late gadolinium enhancement (LGE) on cMRI indicates various degrees of myocardial inflammation, fibrotic scarring, and myocyte damage [25, 32]. In addition, LGE is often present before there is any clinically detectable deterioration in cardiac function or

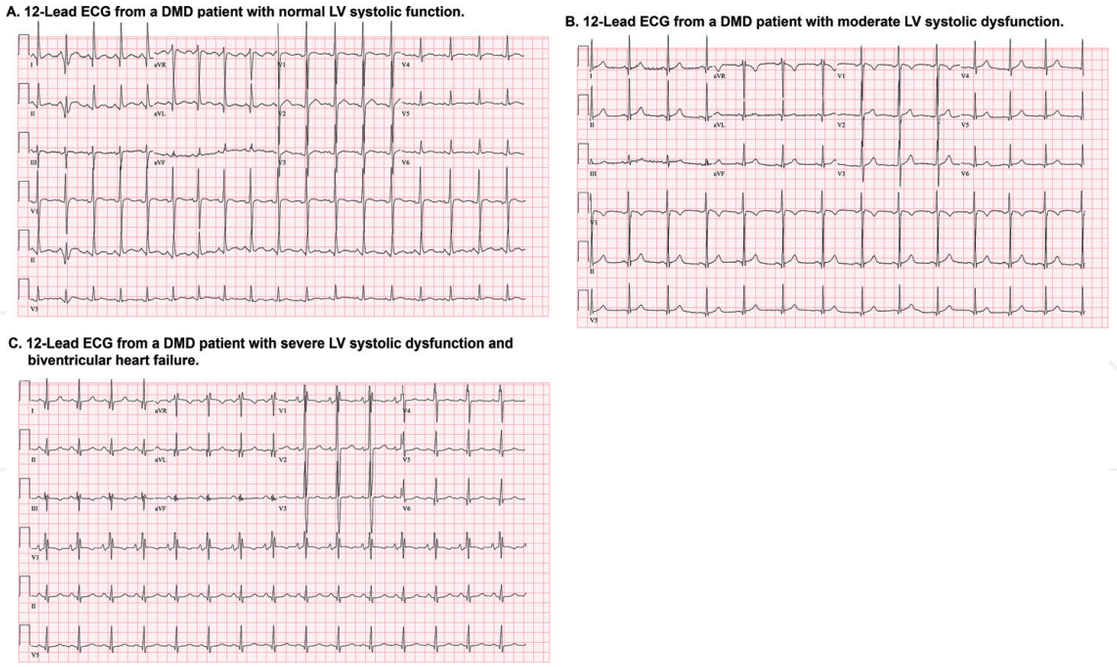

Figure 2.
ECG changes at various stages of DMD-associated cardiomyopathy. (A) DMD patient with normal cardiac function. (B) DMD patient with moderate LV systolic dysfunction. (C) DMD patient with severe LV systolic dysfunction and biventricular heart failure.

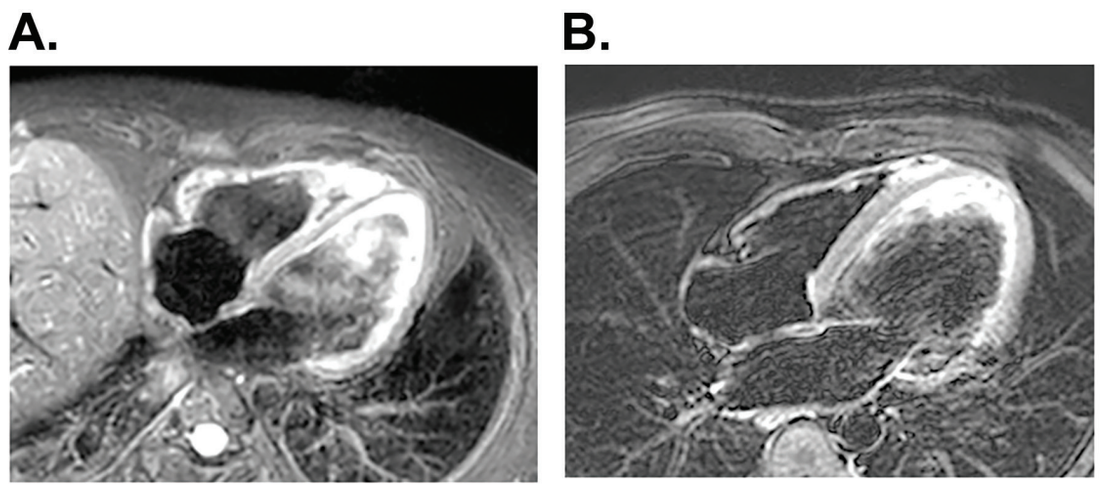

Figure 3.
Structural differences in DMD-associated cardiomyopathy. Representative 4-chamber cMRI images in (A) a DMD patient and (B) a healthy age-matched control patient.

symptoms of cardiomyopathy [25, 32]. When LGE is present, its distribution and change over time can be particularly effective in tracking cardiomyopathy progression [25, 32]. Finally, cMRI provides the most sensitive assessment of cardiac size, mass, and function, which can similarly be serially monitored to assess for progression of cardiac damage and response to medical therapy. Current DMD guidelines recommend a baseline cMRI to be performed between 8 and 10 years of age and repeated approximately every 2 years thereafter [25, 31]. **Figure 3** depicts representative cMRI images in a DMD patient and an age-matched healthy control patient.

In cMRI, the technique of strain imaging has also been shown to be highly sensitive in gauging LV ejection fraction (LVEF) and cardiac dysfunction, especially when circumferential strain imaging is used [33]. Deviations in strain imaging can be indicative of cardiac dysfunction, and these abnormalities are common in DMD patients, even when LVEF measures are normal. Use of cMRI strain imaging, along

with the presence of LGE, can provide valuable diagnostic and prognostic information about a patient's cardiac condition beyond simple measurements of contractile function [9, 33].

While cMRI has become the preferred imaging modality in DMD patients, there are still barriers to widespread adoption and utilization of cMRI. High procedural cost limits accessibility of cMRI, and the procedure can be challenging for younger patients and patients with claustrophobia [1, 25]. Furthermore, muscular weakness, spinal abnormalities, and restrictive lung disease can often make it difficult to fully assess cardiac structure and function using any of the available imaging techniques, but especially echocardiogram (ECHO) [9, 25, 32]. Therefore, if a cMRI can not be obtained the next ideal cardiac imaging tool that can be used is a cardiac CT scan with IV contrast, followed by 3D-ECHO with contrast.

The need for comprehensive cardiovascular assessment in DMD patients is undisputed, but there is also a significant risk for cardiovascular disease in DMD carriers [9, 25]. Mothers and sisters of patients who have been diagnosed with DMD should undergo both genetic testing to determine carrier status and evaluation by a cardiologist, preferably a heart failure specialist, to determine presence of heart disease. Recent studies have shown an increased risk of cardiac involvement in approximately 50% of DMD carriers, despite the presence of a functional *DMD* gene [9, 23, 34, 35]. For this reason, mothers and sisters of patients who have been diagnosed with DMD should undergo both genetic testing to determine carrier status and evaluation by a cardiologist, preferably a heart failure specialist, to determine presence of heart disease.

4. Pathophysiology underlying DMD-associated cardiomyopathy

Prior studies of DMD patients have demonstrated early cardiac involvement, with cardiac manifestations present in approximately 25% of DMD patients by 6 years of age and nearly universal cardiac involvement by 18 years of age [29, 30, 36]. These DMD patients go on to develop progressive cardiomyopathy as loss of dystrophin within cardiomyocytes results in ongoing cell death, leading to cardiac fibrosis and impaired cardiac function.

The pathologic mechanism underlying heart failure in the DMD population has not been fully elucidated. It is proposed that pathologic remodeling of the heart occurs as a result of both structural and metabolic abnormalities [37]. The mechanism underlying both ischemic and non-ischemic cardiomyopathy is the development of pathological cardiac hypertrophy, which eventually leads to paradoxical maladaptive cardiac remodeling [38]. Overtime, this compensatory mechanism fails and leads to cardiac dilatation and clinical heart failure [38]. Today, significant strides have been made in treating congestive heart failure (CHF), particularly systolic heart failure. Blockade of the renin-angiotensin-aldosterone system and inhibition of sympathetic activation have largely been the primary modes of treating a cardiomyopathy and inducing reverse cardiac remodeling. At least in non-ischemic cardiomyopathy patients on optimal medical therapy, approximately one third of patients will achieve normalization of the LV ejection fraction (LVEF), one third of patients will have improvement in the LVEF and the latter one third of patients will have progression in the LVEF requiring assessment for advanced heart failure therapies [i.e. implantation of a LV assist device (LVAD) or a heart transplantation]. Thus, the standard of care for treatment of a cardiomyopathy is based on the development of pathological cardiac hypertrophy, which eventually leads to a dilated cardiomyopathy when left untreated. This approach to treating a cardiomyopathy has been extrapolated to the treatment of DMD-associated cardiomyopathy.

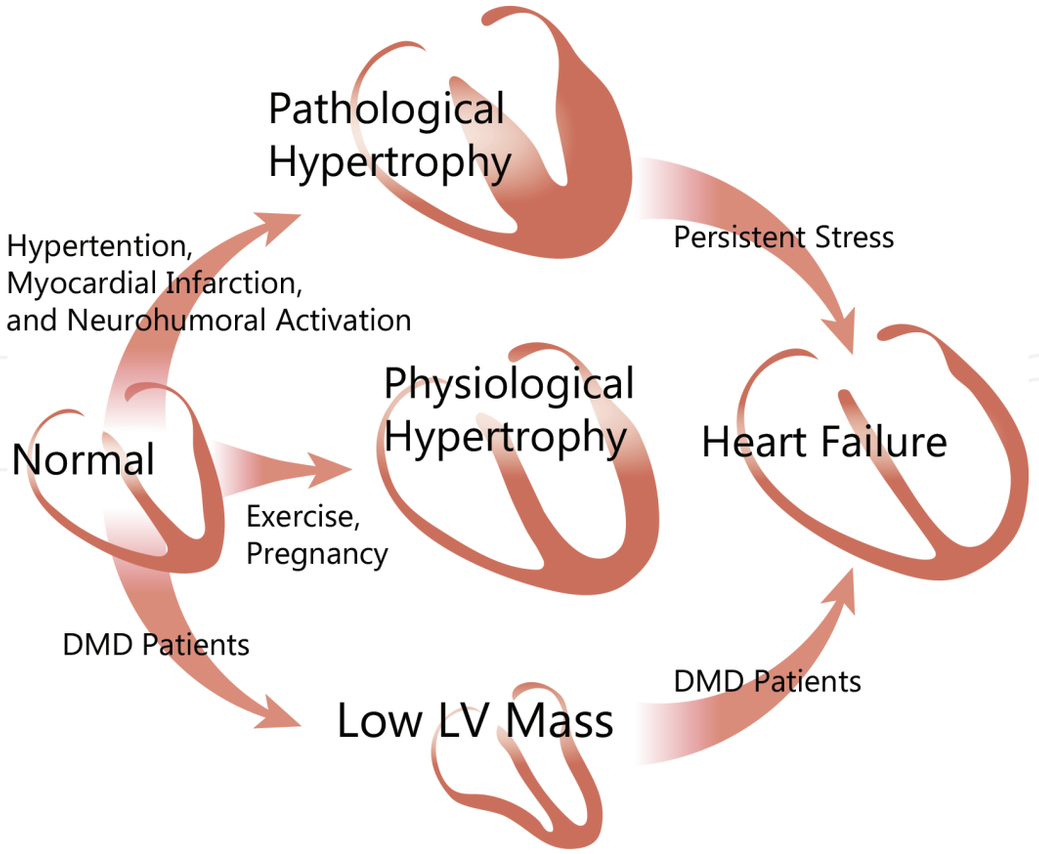

Figure 4.
Proposed mode of maladaptive cardiac remodeling leading to DMD-associated cardiomyopathy.

Although pathological cardiac hypertrophy has been assumed to be the primary mode of maladaptive cardiac remodeling in DMD-associated cardiomyopathy, clinical data suggests the use of guideline-directed medical therapy is not as effective in DMD-associated cardiomyopathy as it has been in other forms of cardiomyopathy with a reduced ejection fraction. Despite the increasing utilization of current standard of care heart failure therapies and device therapies, DMD-associated cardiomyopathy poses greater morbidity and mortality than other dilated cardiomyopathies and remains the leading cause of mortality in the DMD population [32]. Accordingly, the mechanism of maladaptive cardiac remodeling has been increasingly called into question. A cMRI study recently completed at UT Southwestern Medical Center suggests that adult DMD patients have small, atrophic hearts as compared to age-matched and weight-matched patients with non-ischemic cardiomyopathy or healthy patients enrolled in the Dallas Heart Study and this manuscript is currently under scientific review [39]. In an effort to further elucidate the mechanism leading to cardiac remodeling in DMD patients, the Mammen Laboratory at UT Southwestern Medical Center has discovered a proliferative defect in cardiomyocytes lacking dystrophin as early as four days postnatally in DMD^{mdx} mice. This work was presented at the 2019 American Heart Association Scientific Sessions meeting and the manuscript is also currently under scientific review [40]. The mechanism into how a proliferative defect within neonatal DMD cardiomyocytes leads to the eventual development of a DMD-associated cardiomyopathy in adult DMD patients is actively being investigated. These studies provide supportive data that the mode of maladaptive cardiac remodeling leading to DMD-associated cardiomyopathy, as illustrated in **Figure 4**, may be substantially different as compared to the mechanisms underlying non-ischemic cardiomyopathies. Once the signaling pathways governing these processes are better understood, appropriate

targets for pharmacotherapy can be identified and allow for the development of novel drugs that can substantially improve the overall morbidity and mortality in the DMD population.

5. Management and treatment of DMD-associated cardiomyopathy

The majority of current therapies for DMD-associated cardiomyopathy collectively induce reverse cardiac remodeling and alleviate symptoms of the disease. Recent guideline documents have attempted to shift the focus of care to more proactive measures over the past decade [9, 25, 32, 41, 42]. These treatments include both pharmacological and non-pharmacological approaches.

5.1 Pharmacological treatments

The four major drug classes used to treat DMD-associated cardiomyopathy include angiotensin-converting-enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), beta-adrenergic receptor blockers, mineralocorticoid receptor antagonists (MRA), and corticosteroids (**Table 1**).

ACE-inhibitors are a first line class of medications used to treat DMD-associated cardiomyopathy [1, 43]. Studies have shown that the use of ACE-inhibitors in DMD patients specifically can delay the onset and progression of DMD-associated cardiomyopathy [23, 43, 44]. In addition, teenage DMD patients started on a beta-blocker and an MRA along with an ACE-inhibitor have significantly increased LVEF compared to untreated control subjects [43, 45]. Therefore, as outlined in the 2017 scientific statement by the American Heart Association, as well as by the DMD Care Considerations Working Group in 2018, it is strongly recommended that all DMD patients should be treated with an ACE-inhibitor beginning by the age of 10, regardless of the presence of LV dysfunction [4, 41, 43, 46]. However, at the discretion of the physician and the family, an ACE-inhibitor may be started earlier depending on the results of cMRI studies [25, 32, 46]. The most commonly prescribed ACE inhibitors in this population include enalapril and lisinopril [4, 43, 44].

Drug Class	Examples
Beta-Adrenergic Receptor Blockers	Carvedilol, Metoprolol Succinate, Bisoprolol
Angiotension-Converting-Enzyme Inhibitors	Perindopril, Enalapril, Lisinopril
Angiotension II Receptor Blockers	Candesartan, Losartan, Valsartan
Mineralocorticoid or Aldosterone Receptor Antagonists	Spironolactone, Eplerenone
Steroids	Prednisone, Deflazacort
Angiotension II Receptor-Neprilysin Inhibitor	Sacubitril/Valsartan
Vasodilators	Isosorbide Dinitrate/Hydralazine
Diuretics	Furosemide, Bumetanide, Torsemide
Cardiac Glycosides	Digoxin
Sodium-Glucose Co-Transporter-2 Inhibitors	Canagliflozin, Dapagliflozion, Empagliflozin
Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel Blockers	Ivabradine

Table 1.
Pharmacological medications used in the treatment of DMD-associated cardiomyopathy.

While ACE-inhibitors are still widely prescribed, their use may be limited by side effects in certain patients, including dry cough and the development of hyperkalemia. The use of an ARB is an effective and safe alternative medication to an ACE-inhibitor and its mechanism of action is also mediated by inhibiting the renin-angiotensin aldosterone signaling pathway [4, 23]. Thus, ARBs are often prescribed as alternative cardioprotective class of medications in DMD patients who experience adverse reactions to ACE-inhibitors [1, 47, 48]. These data are in line with large double-blind randomized clinical trials looking at the efficacy of ARBs versus ACE-inhibitors in patients with either non-ischemic or ischemic cardiomyopathies [49].

MRAs are another class of medications that have been shown to have beneficial effects specifically in DMD-associated cardiomyopathy. The combined use of a MRA and an ACE-inhibitor has been shown to improve cardiac function in DMD patients in a randomized clinical trial [1, 4, 23]. In particular, eplerenone administered in conjunction with an ACE-inhibitor has been demonstrated in a clinical trial to significantly decrease ventricular circumferential strain in the treatment group compared to placebo [4, 50]. While spironolactone is a more potent MRA, eplerenone interferes less with the androgen receptor and has a more favorable side effect profile as compared to spironolactone [4].

Beta-adrenergic receptor blockers are another drug class frequently utilized in treating DMD-associated cardiomyopathy. Beta blockers, are commonly used in conjunction with ACE-inhibitors/ARBs and MRAs to improve clinical cardiac outcomes and induce reverse cardiac remodeling in DMD [4, 23]. Although there is no double blind clinical trial demonstrating the beneficial effects of combination therapy in DMD-associated cardiomyopathy, there are several non-randomized clinical studies in the DMD population supporting the use of combination therapy [51–54]. In one particular study, survival rates of those on carvedilol was found to be higher than the control group, data consistent with many large randomized clinical trials on the beneficial effects of beta-blockers [55]. The beneficial effects of this combinatorial therapy are both additive as well as synergistic in regards to inducing reverse cardiac remodeling and delaying cardiomyopathy progression in DMD-associated cardiomyopathy [23].

Corticosteroids are also very commonly used in DMD patients to improve ambulation, and are initiated early in the disease course, typically between 2 to 5 years of age [56–58]. Corticosteroids are primarily used to manage skeletal muscle wasting and are intended to improve muscle strength and ambulatory capacity in DMD patients [56]. However, long-term corticosteroid use is associated with significant adverse effects in DMD patients, including delayed puberty, decreased bone density, weight gain, development of type II diabetes, and risk of developing systemic infections [42, 59–61]. A recent retrospective study, revealed DMD patients on a corticosteroid had a higher LVEF and greater chance for survival, though study limitations prevent one from drawing a direct correlation between corticosteroid use alone and mortality benefit given the confounding effect of co-administration of ACE-inhibitors in this study [62]. Further research is warranted to determine whether the clinical benefit of continued corticosteroid therapy outweighs the known significant side effect profile. Current guidelines recommend continuation of corticosteroid therapy except in patients who develop severe systemic infections or clinically significant osteoporosis [42, 60, 61].

Digoxin, a cardiac glycoside, comprises another class of medications used to treat DMD-associated cardiomyopathy. Digoxin has been used in conjunction with beta-adrenergic receptor blockers, ACE-inhibitors/ARBs, MRAs, and corticosteroids to reduce morbidity associated with DMD-associated cardiomyopathy [23, 63]. However, digoxin has fallen out of favor recently due to its adverse side effect profile and the lack of available data demonstrating clear clinical mortality benefit of digoxin administration in DMD patients [23].

Other guideline directed therapies for heart failure (i.e. diuretics, isosorbide dinitrate/hydralazine, ivabradine, sacubitril/valsartan, and sodium-glucose co-transporter-2 inhibitors) have been shown to reduce morbidity and in some cases also mortality in patients with non-ischemic and ischemic cardiomyopathies (**Table 1**) [49, 64, 65]. The use of these medications in the treatment of DMD-associated cardiomyopathy have not yet been studied, so the impact on morbidity and mortality is unclear in the setting of DMD patients. However, some of these medications are being judiciously used in select DMD patients with progressive, refractory DMD-associated cardiomyopathy.

5.2 Non-pharmacological treatments

As is the case in the treatment of non-ischemic cardiomyopathy, a number of non-pharmacological therapies exist for the treatment of DMD-associated cardiomyopathy. These therapies include automated implantable cardioverter-defibrillators (AICD) with or without biventricular pacemaker capability, implantable left ventricular assist devices (LVAD) and heart transplantation. These treatments are most appropriate for DMD patients with end-stage heart failure who display signs of refractory disease, poor cardiac output, and/or severe conduction abnormalities. With the exception of AICDs, there is currently a lack of objective data regarding the benefits of LVAD implantation or heart transplantation in improving the morbidity or mortality in this unique patient population. As such, current guidelines do not recommend routine incorporation of these non-pharmacological therapies in treating DMD-associated cardiomyopathy.

In multiple large clinical trials, AICDs have demonstrated a mortality benefit by decreasing the incidence of sudden cardiac death in non-ischemic and ischemic cardiomyopathy patients with a LVEF less than 35% [49]. In addition, AICD implantation has been shown to reduce mortality rates in patients with sustained ventricular tachycardia or patients who have been resuscitated from sudden cardiac arrest [49]. The addition of cardiac resynchronization therapy to AICD implantation in patients with cardiomyopathy and a wide QRS complex has demonstrated improved morbidity and mortality in this patient population [66–68]. Therefore, the guidelines as set forth by the American College of Cardiology and the American Heart Association gave a Class I indication to the implantation of an AICD in patients with advanced heart failure and an LVEF less than 35% [49, 69]. These guidelines have been applied to DMD patients with cardiomyopathy and LVEF less than 35%, but in this unique population, special care and consideration must be taken into account when implanting an AICD given the high likelihood of significant muscle atrophy in the left upper portion of the chest [23, 25, 70]. It is generally recommended that these patients be referred to an electrophysiologist with extensive experience in implanting devices in muscular dystrophy patients.

A LVAD is a form of mechanical circulatory support device that can be implanted into patients with advanced DMD-associated cardiomyopathy, either as a destination therapy or as a bridge to heart transplantation. While LVADs have been demonstrated to improve mortality in patients with advanced end-stage non-ischemic and ischemic cardiomyopathy, approximately 20–30% of LVAD patients experience some complication within a year of implantation including infection, bleeding, and stroke [71–73]. Although LVADs have been implanted in DMD patients with advanced cardiomyopathy, the majority of these patients died within one year of LVAD implantation [74, 75]. As noted by Stoller et al., there are several essential or key factors that determine the long-term success of implanting a LVAD into DMD patients with advanced end-stage dilated cardiomyopathy (**Table 2**) [76].

Heart transplantation has been successfully undertaken in patients with muscular dystrophy. Both short and long term survival rates are very favorable

Key Factors Determining the Long-Term Success of a LVAD in a DMD Patient
Use of a multidisciplinary team pre- and post-LVAD implantation.
Appropriate candidate selection. While restrictive pulmonary physiology will be present, the DMD patient should not be on mechanical ventilatory support either pre-LVAD. In addition, the DMD patient should not have a GT-tube or PEG tube for supplemental feeding pre-LVAD.
Recognition of end organ dysfunction. DMD patients have very low baseline serum creatinine due to low muscle mass and even mild elevations are indicative of renal dysfunction. Conversely, liver function tests may be borderline elevated although further elevation, especially with evidence of volume overload, suggest right-sided heart failure in DMD patients.
An experienced cardiothoracic surgeon with significant expertise implanting LVADs into critically ill patients with advanced cardiomyopathy.
Selection of a LVAD that would not disrupt the diaphragm and thus further weaken the diaphragmatic muscle strength. This criteria is perhaps the most important factor that will determine the long-term success of a LVAD in a DMD patient and decrease the risk of any major medical complication.
Early extubation post-LVAD implantation with aggressive pulmonary toilet.
Aggressive care provided by physical, occupational, and respiratory therapy teams post-LVAD.
Very supportive and involved family.

Table 2.
Essential factors determining the long-term success of an LVAD in DMD-associated cardiomyopathy. Adapted from [76].

and comparable to age- and weight-matched cardiomyopathy patients without muscular dystrophy [77, 78]. However, there were only three DMD patients in both of these studies assessing the survival outcomes post-transplant. Due to significant skeletal muscle wasting in many DMD patients with advanced heart failure and restrictive lung disease, heart transplantation has only been undertaken in a limited number of DMD patients with advanced dilated cardiomyopathy, thus impairing the ability to draw conclusions regarding outcomes post-transplant specifically in this patient population.

6. Emerging therapies and future directions

Despite the many gaps that still exist in cardiac care in patients with DMD, much progress has been made over the past two decades, and recent developments have paved the way for future therapies. In particular, gene-replacement and genome-editing therapies hold significant promise due to the potentially corrective nature of these treatments by targeting the disease at the genetic level and restoring normal dystrophin levels.

Gene-replacement therapy using recombinant adenoviral virus vectors (rAVV) is one corrective method that has been proposed to treat DMD. This therapeutic approach is an especially promising therapy because this treatment modality has the potential to treat any underlying mutation within the dystrophin gene resulting in DMD disease and can therefore be applied to every DMD patient [4]. Since the full-length DMD gene is too large to package within a rAVV, micro-dystrophins, which contain only the most essential parts of the gene, can be successfully packaged into a rAVV [79]. While this approach has had some success in preclinical and early clinical trials, there are still several drawbacks that have been observed, including heightened immune responses to the rAVV [79, 80]. Additionally, it is uncertain if the truncated micro-dystrophin protein will sufficiently improve cardiac function and reduce the burden of cardiomyopathy in DMD patients [4].

Antisense-mediated exon skipping using antisense oligonucleotides (ASO) is one type of genome editing therapy, which strives to restore the open reading frame caused by a frame-shift mutation [4, 81]. The restoration of the open reading frame is accomplished by targeting a specific mutated exon via an ASO, and then removing the mutated exon with spliceosomes. By sacrificing the single exon, the remainder of the gene can be restored and a functional, truncated dystrophin protein is expressed, with a phenotype more similar to that of Becker muscular dystrophy (BMD) [4]. While preclinical and clinical studies have demonstrated promising results and have led to the FDA approval of some of these therapies, clinical trials have shown only minimal restoration of dystrophin and limited effects on cardiac physiology due to inadequate delivery to and correction of cardiomyocyte dysfunction [81, 82]. However, recent research suggests that optimizing dosage and personalizing treatment may yield more promising results for treating DMD-associated cardiomyopathy, so it remains a potential option [23, 81]. As of March 2021, there are four ASO therapies (eteplirsen targeting exon 51, golodirsen targeting exon 53, viltolarsen targeting exon 50, and casimersen targeting exon 45) that have received FDA approval for the treatment of DMD. However, it remains unclear the long term benefits of these ASO therapies in treating the skeletal muscle dysfunction, the diaphragmatic weakness, and the cardiomyopathy that plague all DMD patients.

Genome editing utilizing clustered regularly interspaced short palindromic repeats (CRISPR) with CRISPR-associated protein 9 (Cas9) has emerged as another novel and exciting genetic approach to permanently treating DMD patients [83–90]. The clear advantages of CRISPR-Cas9 technology over antisense-mediated exon skipping are two-fold. First, using CRISPR-Cas9 mediated genome editing offers a one time permanent treatment for DMD. Second, CRISPR-Cas9 technology provides highly sensitive and specific gene editing. This novel therapeutic method proposes delivery of the CRISPR-Cas9 machinery via adenoviral virus vectors (AVV). As such, this treatment also has the potential to trigger an undesired immune response [89, 90]. The pre-clinical data demonstrates CRISPR-Cas9 mediated genome editing remains a very promising and permanent correction to dystrophin deficiency in DMD patients [89–91].

Although all three of the above mentioned novel genetic therapeutic modalities have generated significant enthusiasm by scientists, clinicians, and patients, there remains a fundamental flaw of these proposed therapies in relation to DMD-associated cardiomyopathy. This flaw relates to the fact that they serve to functionally convert a DMD patient into a phenotype more closely resembling that of a BMD patient, rather than completely correcting or curing the DMD patient entirely of the disease process. While it is true that patients with BMD suffer less debilitating disease, approximately 70% of BMD patients over their lifespan still eventually develop advanced cardiomyopathy. Thus, while these novel genetic therapeutic modalities will surely improve the lives of DMD patients with improved skeletal muscle strength and mobility, challenges related to treating disease-related cardiomyopathy will persist [4].

Several other promising molecular therapies are also currently under investigation. Ataluren, an aminoglycoside-derived compound that functions as a stop-codon readthrough, is an investigational drug that has recently been approved by the European Medicine Agency, and is still being reviewed by the FDA [4, 92]. This therapy works to continue translation of the gene past a premature stop codon. While results in preclinical trials have shown modest improvements in cardiac dystrophin levels, there has been little evidence so far of any actual cardiac benefit derived from this therapy in clinical trials [92, 93]. Stem-cell therapy holds significant potential as a therapeutic modality in treating DMD patients. In particular, induced pluripotent stem cells have shown promise, though there are barriers in terms of successful engraftment of these cells into DMD muscle as well as the process of differentiation

in-vivo [94]. Many potential future therapies such as these have focused on restoring dystrophin levels in skeletal muscle and while this may improve skeletal muscle weakness and ambulation, it is essential to consider whether these therapies will also improve the accompanying cardiomyopathy.

Along with emerging therapies, new diagnostic measures have also been studied. One such diagnostic tool includes newborn screening (NBS), which involves measuring the creatine kinase (CK) levels among neonates [95, 96]. The CK levels are often markedly elevated in newborns with DMD. The utilization of a two-tier system for testing, a cost-effective and accurate application of NBS, has been shown to have promising potential as a diagnostic tool to identify patients with DMD at an even earlier age [95].

In addition to these emerging therapies, there are many questions that have yet to be answered about existing treatments and therapies. Exact timing of initiation and dosage of first and second-line medications is still uncertain and remains disputed, though there is a broad consensus that earlier, anticipatory treatment is recommended for DMD patients [25, 43]. There is also a lack of supporting literature on beta-adrenergic receptor blockers, and more studies are needed to determine their exact benefits with and without the concurrent use of ACE-inhibitors or ARBs as well as MRAs [23].

Finally, DMD carriers are a relatively understudied and underappreciated group within this unique population of patients. DMD carriers are at significant risk for developing advanced cardiomyopathy, but the mechanisms underlying this phenomenon are unclear. The primary hypothesis is that skewed X chromosome inactivation occurs selectively within the cardiomyocytes of these patients, and one of the two X-chromosomes in the DMD female carrier becomes transcriptionally inactive [1, 34]. DMD carriers have an estimated 50% lifetime risk for developing cardiomyopathy [34, 97]. Researchers believe that the degree of X inactivation is correlated with the severity of cardiac manifestations in these patients, but better designed studies are required to understand the various mechanisms involved in the development of DMD-associated cardiomyopathy in DMD carriers [1].

7. Conclusion

Over the past two decades, tremendous progress has been made in understanding the pathophysiology and treatment of DMD-associated cardiomyopathy. Due to advances in neurologic, pulmonary, and orthopedic care provided to DMD patients, there has been a significant increase in the life expectancy in these patients. Therefore, more DMD patients are living into adulthood resulting in cardiomyopathy as the primary mode of death in the majority of DMD patients in 2021. Current cardiovascular guidelines directed specifically towards DMD patients are now available and provide a more solid foundation for evaluating and treating affected patients. Importantly, earlier recognition and management of the disease and its cardiac manifestations has great potential in slowing the progression of DMD-associated cardiomyopathy. Part of this success is due to the incorporation of heart failure cardiologists into the multidisciplinary team approach to DMD care and the aggressive application of guideline directed medical therapy at an early age. Though there is much progress to be made, advancements in potential novel therapies and the growing body of research in this field have created a promising future for cardiac care in DMD.

Conflict of interest

Dr. Pradeep Mammen declares the following conflicts of interests: American Heart Association (member of the AHA Career Development Research Grant

Committee), AveXis Inc. (member of the Data Monitoring and Safety Committee), California Institute of Regenerative Medicine (member of the Grants Working Group), CareDx Inc. (Site PI for the SHORE Registry), Catabasis Inc. (research grant), Dyne Therapeutics (consultant and member of the DMD Advisory Board), National Institute of Health (research grants and ad hoc grant reviewer for the NIH SMEP and MOSS Study Sections), and PhaseBio Inc. (research grant and member of the Scientific Advisory Board). The other authors have declared that no conflicts of interest exist as it pertains to the subject of the current study.

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