Duchenne Muscular Dystrophy: Literature Review

O. Rubina Sajjath[*1,3], P. Neelesh[1,3], A.R Arunesh[1,3], R. Sivasakthi[2,3]

[1.]Department of Pharmacy Practice, Karpagam College of Pharmacy, Coimbatore -641 032, Tamil Nadu, India.
[2.] Professor, Department of Pharmacy Practice, Karpagam College of Pharmacy, Coimbatore -641 032, Tamil Nadu, India.
[3.]The Tamil Nadu Dr. MGR Medical University, Chennai- 600032, Tamil Nadu, India

Correspondence Author :

Rubina Sajjath - rubina200314@gmail.com ph - + 91 88077 08676

Department of Pharmacy Practice,

Karpagam College of Pharmacy,

Coimbatore -641 032,

Tamil Nadu, India.

Co - Author :

Neelesh - nee23464@gmail.com ph - + 91 6383152451

Department of Pharmacy Practice,

Karpagam College of Pharmacy,

Coimbatore -641 032,

Tamil Nadu, India.

Co - Author :

A.R Arunesh - aruneshar6@gmail.com ph - + 91 82484 71094

Department of Pharmacy Practice,

Karpagam College of Pharmacy,

Coimbatore -641 032,

Tamil Nadu, India.

Guide :

R.Sivasakthi - sivasakthimpharm@gmail.com ph - + 91 9965141122

Professor,
Department of Pharmacy Practice,
Karpagam College of Pharmacy,
Coimbatore -641 032,
Tamil Nadu, India.

Abstract

Duchenne muscular dystrophy is a disorder that is passed down through the X chromosome. It happens when there are changes in the DMD gene. These changes mean that the body is missing or has a version of a protein called dystrophin. The disease mostly affects boys. Leads to weak muscles trouble walking and problems with the heart and breathing. Spotting the disease early is very important. The way it is handled includes using medicines like corticosteroids and treatments that target the gene changes. It also includes therapy checking the heart and lungs taking care of nutrition looking after bones and offering support for mental and emotional health. A group of doctors working together can help slow the disease and make life better for those with Duchenne dystrophy.

Keywords: Duchenne dystrophy, corticosteroids; gene-targeted therapy, multidisciplinary management

Introduction

Duchenne muscular dystrophy (DMD) is a progressive neuromuscular disease inherited in an X-linked recessive pattern and therefore affects mainly boys. It is estimated to occur in about 1 in 3,500 to 5,000 male births [1, 16]. The cause is a mutation in the DMD gene, which encodes the protein dystrophin. When dystrophin is absent or non-functional, muscle fibres weaken and break down over time, leading to progressive muscle damage and weakness.

Signs usually appear in early childhood. Parents may notice that a son moves more slowly than his peers and has difficulty running, jumping, climbing stairs or rising from the floor. A characteristic sign is Gowers' manoeuvre, in which the child pushes up from the floor with his hands because the leg muscles are too weak. Most boys are diagnosed at around five years of age, and many lose the ability to walk independently during their early teens [2, 12].

DMD does not affect only the skeletal muscles used for movement. It also involves the heart and the muscles of respiration. Cardiomyopathy and respiratory insufficiency due to weak respiratory muscles are common, and bone problems such as fractures and spinal deformity also occur. These complications strongly influence health and life expectancy [3, 9]. Improvements in care, including corticosteroids, regular monitoring of cardiac and respiratory function, physiotherapy and supportive services, have improved quality of life, and many people with DMD now live into their thirties and forties [16].

The course of the disease varies with the type of mutation and with whether any functional dystrophin is still produced. Related dystrophinopathies such as Becker muscular dystrophy (BMD) generally progress more slowly [13]. Women who carry a DMD mutation usually have no symptoms, although some may develop muscle or cardiac problems [16, 17]. There is currently no cure for DMD, but early diagnosis and management by a team of specialists can slow its effects and improve outcomes, and treatments that target specific gene mutations are being developed [14, 16]. This article reviews current guidance for diagnosing and managing DMD, covering medication, cardiac and respiratory monitoring, rehabilitation, bone health and psychosocial support, with the aim of supporting patients and families through a balanced approach to care.

Duchenne Muscular Dystrophy (DMD)

DMD is a disease of the muscular system with additional involvement of the central nervous system. It is carried on the X chromosome and inherited in a recessive manner. The cause is a mutation in the DMD gene, so that the body either cannot make dystrophin or makes a faulty version. Dystrophin normally stabilises muscle fibres; when it is missing or damaged, muscle fibres break down, become weaker and eventually die. First signs usually appear between two and three years of age [9, 16]. The muscles of the hips, thighs, shoulders and upper arms are affected first, and a child with DMD may find it hard to rise from the floor, climb stairs, keep balance or lift the arms. DMD mainly affects boys; girls can be carriers and sometimes show mild signs. As noted above, about 1 in 3,500 to 5,000 boys is affected [1, 16].

History

Progressive muscle weakness was first described in the nineteenth century. In 1868 the French neurologist Guillaume-Benjamin-Amand Duchenne published a report of the disease that later took his name. In the 1950s the German physician Peter Emil Becker described a milder variant, now called Becker muscular dystrophy (BMD). Duchenne and Becker muscular dystrophy both belong to the group of disorders known as dystrophinopathies, which also includes X-linked dilated cardiomyopathy, a cardiac form of dystrophin deficiency [6, 16].

First Muscular Dystrophy Gene to Be Cloned

The DMD gene was identified by positional cloning, that is, by locating it on the chromosome, and was isolated in 1987 by Koenig and colleagues [5]. It lies on the X chromosome at Xp21. The gene is very large, spanning about 2.5 million base pairs and containing 79 exons [9, 14]. Mutations in the gene cause either Duchenne or Becker muscular dystrophy, depending on how the mutation affects the production or function of dystrophin. Other major forms of muscular dystrophy include congenital, distal, Emery–Dreifuss, facioscapulohumeral (FSHD), limb-girdle (LGMD) and oculopharyngeal (OPMD) muscular dystrophies.

Epidemiology

Pooled DMD overall and birth prevalence

The data summarised in this section are taken from the systematic review and meta-analysis of Crisafulli et al. [1]. Figs. 1–4 were prepared by the authors from the study-level data reported in that review, and Tables 1A and 1B compile those data. The analyses and pooled results described below are those of the original authors.

Of the 22 studies that reported DMD prevalence, 13 (59.1%) were conducted in Europe, four (18.2%) in the Americas, two (9.1%) in Asia and three (13.6%) in Africa [1]. Most studies measured prevalence from existing data sources such as medical charts, administrative databases and patient or disease registries [19]. The only exception was the study by El-Tallawy et al., which used a community survey. Worldwide, reported DMD prevalence ranged from 0.9 cases per 100,000 males to 16.8 cases per 100,000 males. These figures include people from newborns to adults living with DMD. When both sexes were considered together, prevalence ranged from 0.7 to 7.7 cases per 100,000 persons; the lowest figure was reported from Sweden and the highest from Egypt. The pooled prevalence was 7.1 cases per 100,000

males (95% confidence interval [CI] 5.0–10.1) and 2.8 cases per 100,000 persons in the general population (95% CI 1.6–4.6) (Fig. 2) [1].

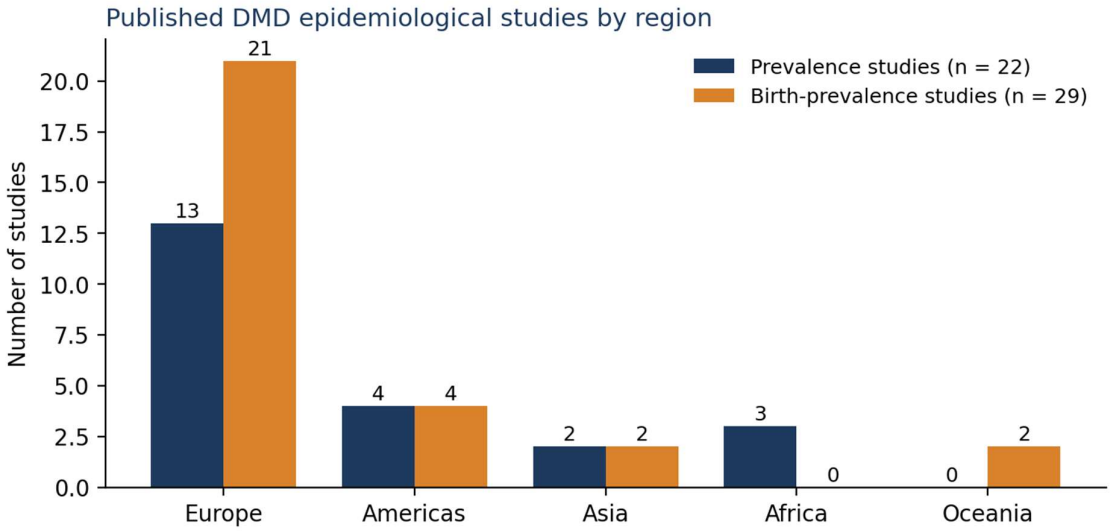


Fig. 1. Number of published epidemiological studies of Duchenne muscular dystrophy by region, for prevalence (n = 22) and birth prevalence (n = 29). Counts are taken from the review by Crisafulli et al. [1]; figure prepared by the authors.

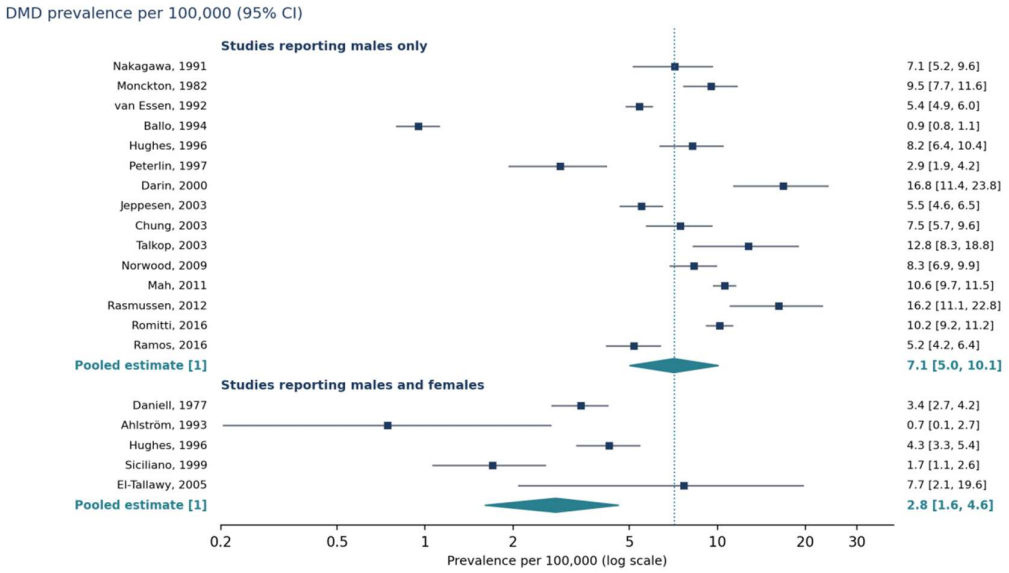


Fig. 2. Prevalence of Duchenne muscular dystrophy per 100,000 with 95% confidence intervals, by study and sex composition. Study case counts and populations are from Crisafulli et al. [1]; study-level estimates and exact Poisson 95% CIs were calculated by the authors, and pooled estimates are those reported in [1].

Results varied considerably between studies. For males, heterogeneity statistics were Cochran's Q = 856.45 and I^2 = 98.5% ($p < 0.001$); for the whole population they were Q = 21.29 and I^2 = 87.4% ($p < 0.001$). The 95% CIs for I^2 were 97.2–99.4% for males and 63.0–99.4% for the whole population. Because only five studies contributed to the whole-population estimate, firm conclusions about heterogeneity are difficult to draw [1].

Of the 27 studies that reported DMD birth prevalence, 21 (72.4%) were from Europe, four (13.8%) from the Americas, two (6.9%) from Oceania and two (6.9%) from Asia. The range of birth prevalence was very wide: 1.5 cases per 100,000 male births in the German study and 28.2 per 100,000 live male births in the Italian study. Eighteen studies (62.1%) used existing data, and the remaining 11 (37.9%) collected data directly through questionnaires, blood sample analysis, muscle biopsy or screening. When all studies were combined, the overall birth prevalence of DMD was 19.8 cases per 100,000 male births (95% CI 16.6–23.6) (Fig. 3) [1].

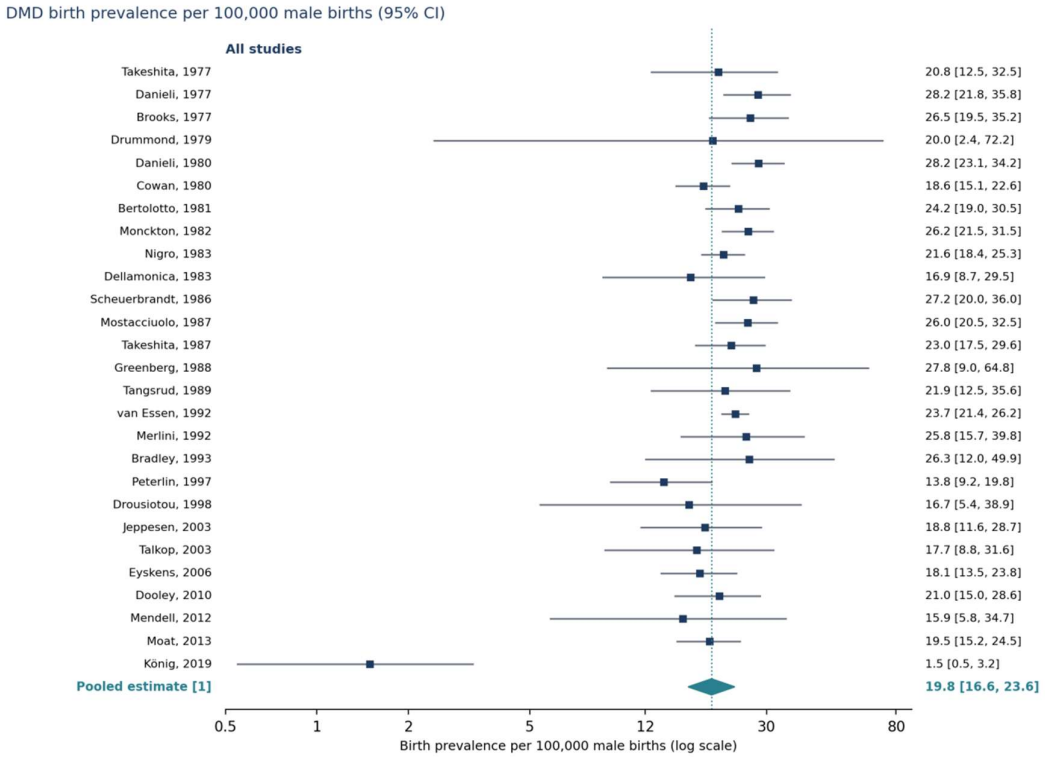


Fig. 3. Birth prevalence of Duchenne muscular dystrophy per 100,000 male births by study. Study case counts and populations are from Crisafulli et al. [1]; study-level estimates and exact Poisson 95% CIs were calculated by the authors, and the pooled estimate is that reported in [1].

There was also notable variation among studies of birth prevalence (Cochran's Q = 82.03; I^2 = 89.8%; p < 0.001; 95% CI for I^2 75.5–95.8%). In the quality assessment, four studies were rated low quality and none high quality; the remainder were rated medium quality. A random-effects meta-analysis restricted to medium-quality studies gave a pooled prevalence of 6.8 cases per 100,000 males (95% CI 4.5–10.2; I^2 = 98.4%) and a pooled birth prevalence of 19.5 cases per 100,000 male births (95% CI 16.3–23.5; I^2 = 90.6%) [1].

On visual inspection of the data, Ballo et al. and Peterlin et al. reported low prevalence values per 100,000 males, whereas Darin et al. and Rasmussen et al. reported very high values (Tables 1A and 1B); no differences in study characteristics explained these extreme results. For birth prevalence, the study by König et al. appeared as an outlier, having had difficulty collecting data in its study year because privacy concerns led to under-reporting of DMD cases. There was no evidence of publication bias on inspection of the funnel plots or with Begg and Mazumdar's rank correlation test for asymmetry (p = 0.771 for prevalence and p = 0.184 for birth prevalence) (Fig. 4) [1, 8].

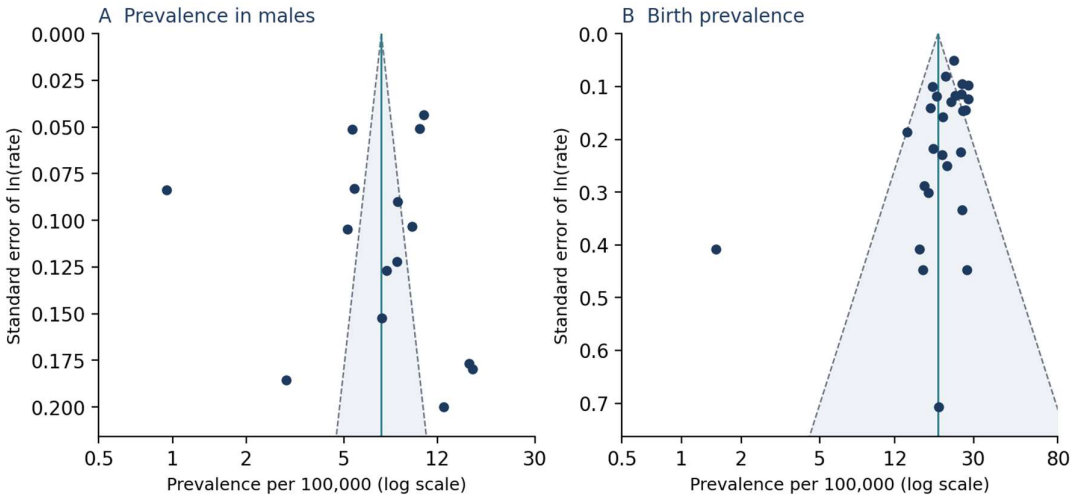


Fig. 4. Funnel plots of study-level estimates for DMD prevalence in males (panel A) and DMD birth prevalence (panel B). Plots were prepared by the authors from the data in [1]; the publication-bias tests (Begg and Mazumdar) and their p-values are those reported in [1].

Table 1A. Study and population details

Author, year	Study area	Data source	Study years / design
Danieli, 1977 [25]	Veneto, Italy	Hospital records	1952–1972; retrospective chart review
Monckton, 1982 [26]	Alberta, Canada	Hospital/clinic records	1950–1979; retrospective chart review
Leth, 1985 [27]	Denmark	Hospital, nursing-home and GP data	1965–1975; retrospective cohort
Radhakrishnan, 1987 [28]	Benghazi, Libya	Hospital records	1983–1985; retrospective chart review
Nakagawa, 1991 [29]	Okinawa, Japan	Hospital records	1989; retrospective cohort
van Essen, 1992 [30]	Netherlands	DMD registries and databases	1961–1982; retrospective cohort
Ahlström, 1993 [31]	Örebro, Sweden	Clinical and administrative records	1974–1988; retrospective chart review
Ballo, 1994 [32]	South Africa	Practitioner and genetic-clinic referrals	1987–1992; observational cohort
Hughes, 1996 [33]	Northern Ireland	Surveys, hospital records and registry	1993–1994; epidemiological survey
Hughes, 1996 [33]	Northern Ireland	Surveys, hospital records and registry	1993–1994; epidemiological survey

Author, year	Study area	Data source	Study years / design
Peterlin, 1997 [34]	Slovenia	Registries and medical records	1969–1984; retrospective cohort
Siciliano, 1999 [35]	Tuscany, Italy	Survey and hospital databases	1997; epidemiological survey
Darin, 2000 [36]	Western Sweden	Registries and biopsy databases	1995; retrospective cohort
Jeppesen, 2003 [37]	Aarhus, Denmark	Medical records	1977–2002; retrospective study
Chung, 2003 [38]	Hong Kong	University hospital records	1985–2001; prospective cohort
Talkop, 2003 [39]	Estonia	Hospital records and registry	1994–1999; epidemiological survey
El-Tallawy, 2005 [40]	Assiut, Egypt	Community survey	1996–1997; cross-sectional study
Norwood, 2009 [41]	Northern England	Genetics databases	2007; retrospective cohort
Mah, 2011 [42]	Canada	Clinical and genetic data	2000–2009; retrospective cohort
Rasmussen, 2012 [43]	South-Eastern Norway	Patient data	2005; prospective cohort

Table 1B. DMD definition and prevalence estimates

Author, year	DMD definition / diagnostic method	Prevalence type	Estimate per 100,000 (95% CI)
Danieli, 1977 [25]	High serum CK levels	Period	3.4 (2.8–4.2), males
Monckton, 1982 [26]	Not specified	Point	9.5 (7.8–11.6)
Leth, 1985 [27]	Histology, EMG, serum CK and family history	Point	6.94
Radhakrishnan, 1987 [28]	Clinical examination, family history, CPK and EMG	Point	6.0
Nakagawa, 1991 [29]	Clinical findings, CK, EMG and immunohistochemistry	Point	7.1 (5.1–9.6), males
van Essen, 1992 [30]	Clinical status, CK, EMG, biopsy and genetics	Point	5.4 (4.9–6.0), males
Ahlström, 1993 [31]	Not specified	Point	0.7 (0.2–2.7)

Author, year	DMD definition / diagnostic method	Prevalence type	Estimate per 100,000 (95% CI)
Ballo, 1994 [32]	CK, EMG and genetic testing	Period	0.9 (0.8–1.1), males
Hughes, 1996 [33]	Not specified	Point	8.2 (6.3–10.4)
Hughes, 1996 [33]	Not specified	Point	4.3 (3.3–5.4), males
Peterlin, 1997 [34]	Clinical findings, enzymes, EMG and biopsy	Point	2.9 (2.0–4.2), males
Siciliano, 1999 [35]	Genetic and dystrophin testing	Point	1.7 (1.1–2.6)
Darin, 2000 [36]	Clinical examination, CK, biopsy and genetics	Point	16.8 (11.4–23.8), males
Jeppesen, 2003 [37]	ICD-8 code 330.39	Point	5.5 (4.6–6.5), males
Chung, 2003 [38]	CK, nerve conduction, EMG, biopsy and genetics	Point	9.8 (7.7–12.6), males
Talkop, 2003 [39]	Not specified	Point	12.8 (8.3–18.8), males
El-Tallawy, 2005 [40]	Electrophysiology, biochemistry, CK and biopsy	Point	7.7 (2.1–19.6)
Norwood, 2009 [41]	Genetic testing of the DMD gene	Point	8.3 (6.8–9.8), males
Mah, 2011 [42]	Clinical phenotypes and genetic reports	Period	10.6 (9.7–11.5), males aged 0–24
Rasmussen, 2012 [43]	Genetic testing and/or muscle biopsy	Point	16.2 (11.5–22.8), males

Data compiled from Crisafulli et al. [1]. Prevalence estimates are per 100,000 persons unless stated as males. Bracketed numbers are the reference numbers used in Crisafulli et al. [1] and should be replaced with this manuscript's own reference numbers. CK, creatine kinase; CPK, creatine phosphokinase; EMG, electromyography.

Etiology

Cause of DMD

Until the 1980s little was known about the cause of muscular dystrophy. In 1986 researchers supported by the Muscular Dystrophy Association identified a gene on the X chromosome that, when mutated, causes Duchenne, Becker and intermediate forms of dystrophy [16]. In 1987 the protein product of the DMD gene was identified and named dystrophin [7]. The gene is located on the short arm of the X chromosome at Xp21.2, a locus being the position of a gene on a chromosome. Most mutations in the DMD gene are deletions, in which one or more exons are missing [9, 14]. DMD results when the mutated gene fails to produce functional dystrophin. In Becker muscular dystrophy, the mutations still allow some functional

dystrophin to be made; this partial protein protects the muscle from damage, so the disease progresses more slowly than Duchenne [13].

During muscle contraction, dystrophin transmits force from inside the muscle cell to the cell membrane. To link the interior of the muscle fibre with its edge, dystrophin is a very long protein: one end binds to the cytoskeleton, and the other end connects to proteins at the cell membrane. The central rod domain consists of repeating spectrin-like units, and many DMD cases arise from mutations in the part of the gene that encodes this region [14]. When dystrophin is lost, muscle fibres become weak and are easily damaged during use. This damage causes inflammation, and over time chronic inflammation leads to replacement of healthy muscle fibres by fibrous and fatty tissue, severely reducing muscle function. Dystrophin also acts as a scaffold that holds signalling molecules in place near the cell membrane; when it is missing, these molecules are displaced and their functions are disrupted, for example reducing blood flow to muscle. The result is ongoing muscle damage and weakness that begins in early childhood [9, 14] (Fig. 7).

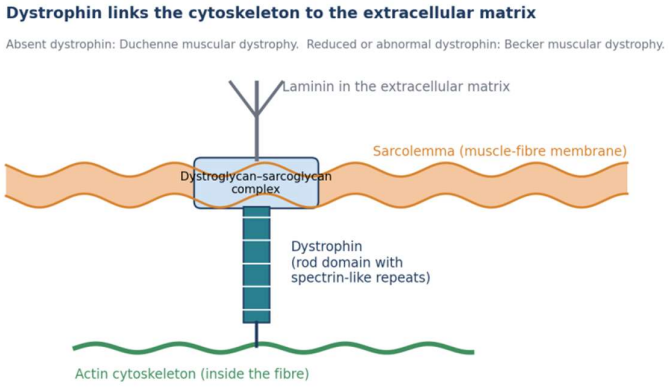


Fig. 7. Schematic of dystrophin in the muscle fibre. Dystrophin links the actin cytoskeleton to the extracellular matrix through the dystrophin-associated complex. Absent dystrophin results in Duchenne muscular dystrophy; reduced or abnormal dystrophin results in Becker muscular dystrophy. Original schematic prepared by the authors.

Inheritance in DMD

DMD follows an X-linked pattern because the responsible gene lies on the X chromosome. Males have one X chromosome, inherited from the mother, and one Y chromosome from the father; females have two X chromosomes, one from each parent. If a woman carries a mutated DMD gene on one of her X chromosomes, each son has a 50% chance of inheriting the mutation and developing DMD, and each daughter has a 50% chance of inheriting it and becoming a carrier. Carriers usually have no symptoms, but some experience mild muscle weakness, cramps or cardiomyopathy [17].

A boy may develop DMD even when there is no family history. This can happen for two reasons. First, the mutation may have been present but unrecognised in the family for generations, because no males were affected or earlier cases were misdiagnosed. Second, a new (de novo) mutation may arise by chance in one of the mother's egg cells; such a mutation is not found in her blood, so standard carrier tests cannot detect it. De novo mutations are estimated to account for about one-third of new DMD diagnoses, and

better genetic counselling and family planning mean that fewer families are now seeing inherited cases [9, 14, 17].

A man with DMD cannot pass the mutation to his sons, because he gives them his Y chromosome. All of his daughters inherit his single X chromosome, which carries the mutation, and are therefore obligate carriers. Each daughter has a 50% chance of passing the mutation to each of her children, so each of her sons has a 50% chance of having DMD, and the pattern can continue through generations [17] (Fig. 8).

Females and DMD

Girls usually have two X chromosomes. If a girl inherits a mutated DMD gene from one parent, she usually has a normal copy from the other parent, which produces enough dystrophin to prevent most symptoms. Boys have a single X chromosome and therefore no backup copy. Early in development, one X chromosome in each cell of a female embryo is randomly inactivated, so in any given cell there is a 50% chance that the maternal or paternal X is switched off. This process is called X-inactivation. If, by chance, the X carrying the healthy gene is inactivated in a large proportion of cells, a girl or woman may show signs of DMD [9, 17].

Most female carriers have no symptoms, but some experience muscle weakness. A small number, called manifesting carriers, have muscles that tire or cramp more quickly, and some develop cardiac problems, which can present as breathlessness or difficulty exercising. Untreated, these cardiac problems may be serious or life-threatening, which is why regular cardiology review is important. Rarely, a female has only one X chromosome or a severely abnormal second X chromosome and makes no dystrophin; she then develops a dystrophinopathy like a male. A female relative of a boy with DMD can be offered diagnostic testing and genetic counselling to learn whether she is a carrier, understand the risks and plan her care. If she is found to be a carrier, regular assessment of muscle strength and close cardiac monitoring can help manage any symptoms that appear [16, 17].

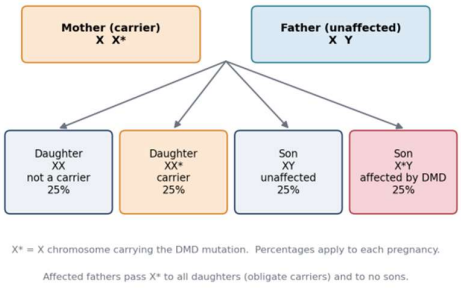


Fig. 8. X-linked recessive inheritance of DMD for a carrier mother and unaffected father. Original schematic prepared by the authors.

Pathophysiology

Mutations in the DMD gene cause the absence of dystrophin in muscle cells. Without dystrophin, the dystrophin-associated protein complex at the sarcolemma becomes unstable, making the muscle membrane vulnerable to mechanical stress and ischaemia. As a result, membrane permeability increases, cell signalling is disturbed and intracellular calcium levels rise. High calcium levels activate proteases, which damage muscle cells (Fig. 9). Mitochondrial dysfunction leads to increased production of reactive oxygen species. Together these factors initiate a cycle of cell necrosis, chronic inflammation and reduced

regenerative capacity of muscle tissue. Over time, muscle fibres are replaced by connective and fatty tissue, which causes progressive loss of muscle function [9, 14].

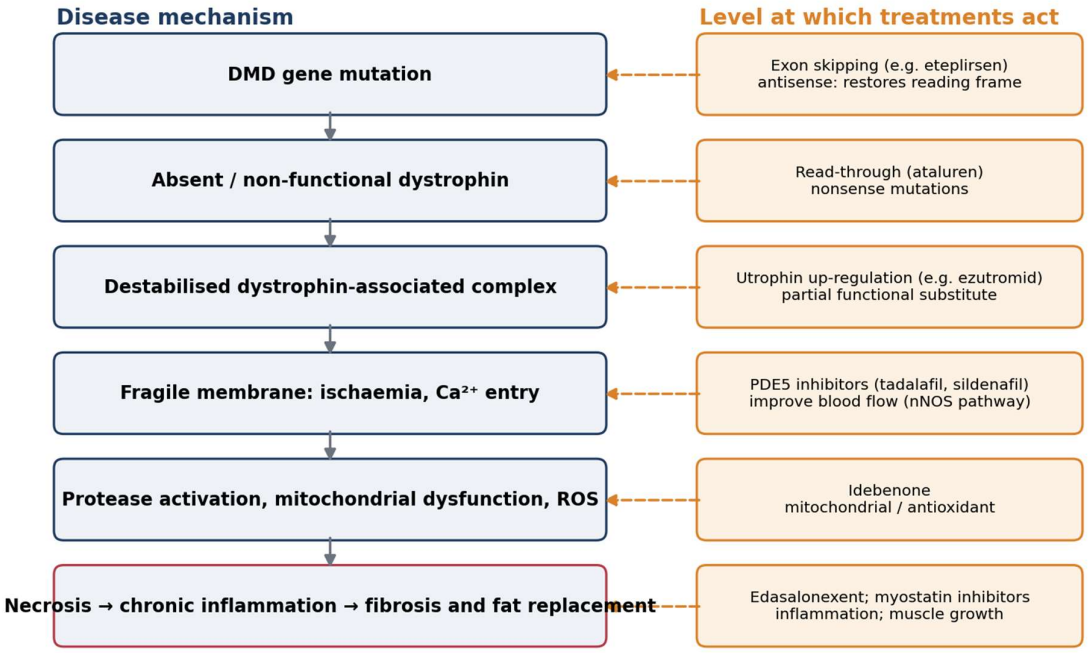


Fig. 9. Schematic of the mechanisms of muscle damage in DMD and the levels at which the therapies discussed in the text act. Original schematic prepared by the authors.

Pathogenesis and Clinical Findings

Pathogenesis

DMD is an X-linked genetic disorder caused by a mutation in the DMD gene at Xp21. The mutation results in absence or severe deficiency of dystrophin, a protein that stabilises the muscle cell membrane and maintains the link between the muscle fibre cytoskeleton and the extracellular matrix. Without dystrophin, muscle fibres are more susceptible to damage and their repair mechanisms are impaired, producing an imbalance between muscle fibre degeneration and regeneration. Over time, damaged muscle fibres are progressively replaced by connective tissue, a process known as fibrosis [9, 14] (Fig. 10).

Clinical findings

Skeletal muscle involvement: Progressive skeletal muscle weakness is a defining feature of DMD. Gait abnormalities usually begin between 2 and 4 years of age. Between 4 and 6 years, children may develop a wide-based or waddling gait, proximal muscle weakness with Gowers' sign, and ankle contractures that may cause toe walking. Wheelchair dependence may occur at around 10–12 years of age in untreated patients [14].

Pseudohypertrophy: The calf muscles may appear enlarged because connective and fatty tissue replace normal muscle fibres [9].

Cardiac complications: Damage to cardiac muscle cells leads to fibrosis and may cause dilated cardiomyopathy. As the disease progresses, congestive heart failure may develop [9].

Respiratory complications: Weakness and degeneration of the respiratory muscles reduce vital capacity and maximal inspiratory and expiratory pressures. Patients may develop pulmonary infections and respiratory failure, which can contribute to premature death [3, 9].

Gastrointestinal complications: Involvement of smooth muscle may reduce gastric motility (gastric hypomotility), leading to problems such as constipation [2].

Musculoskeletal complications: Progressive weakness and contractures may cause increased lumbar lordosis, scoliosis and restricted joint movement, which interfere with walking and daily activities.

Laboratory findings: Creatine kinase (CK) is released into the bloodstream when muscle fibres are damaged, so patients with DMD commonly have markedly elevated serum CK [9, 12].

Cognitive and behavioural findings: Some patients have learning difficulties or behavioural changes related to dystrophin deficiency in the central nervous system (CNS) [9, 18].

Disease progression

The DMD mutation leads to absent dystrophin, membrane instability, repeated muscle fibre damage, progressive degeneration and fibrosis. These changes cause increasing muscle weakness, pseudohypertrophy, cardiac dysfunction and respiratory complications. Respiratory failure and heart failure may contribute to premature death.

Important definitions

Dystrophin: a protein that helps stabilise the muscle cell membrane and links the cytoskeleton to the surrounding extracellular support.

Fibrosis: replacement of damaged muscle fibres with connective tissue.

Gowers' sign: a sign of proximal muscle weakness in which the patient uses their hands to push against their thighs while rising from a sitting or squatting position.

Pseudohypertrophy: enlargement of a muscle due to accumulation of connective tissue rather than an increase in functional muscle tissue.

Abbreviations

DMD, Duchenne muscular dystrophy; BMD, Becker muscular dystrophy; CNS, central nervous system; CK, creatine kinase; CHF, congestive heart failure.

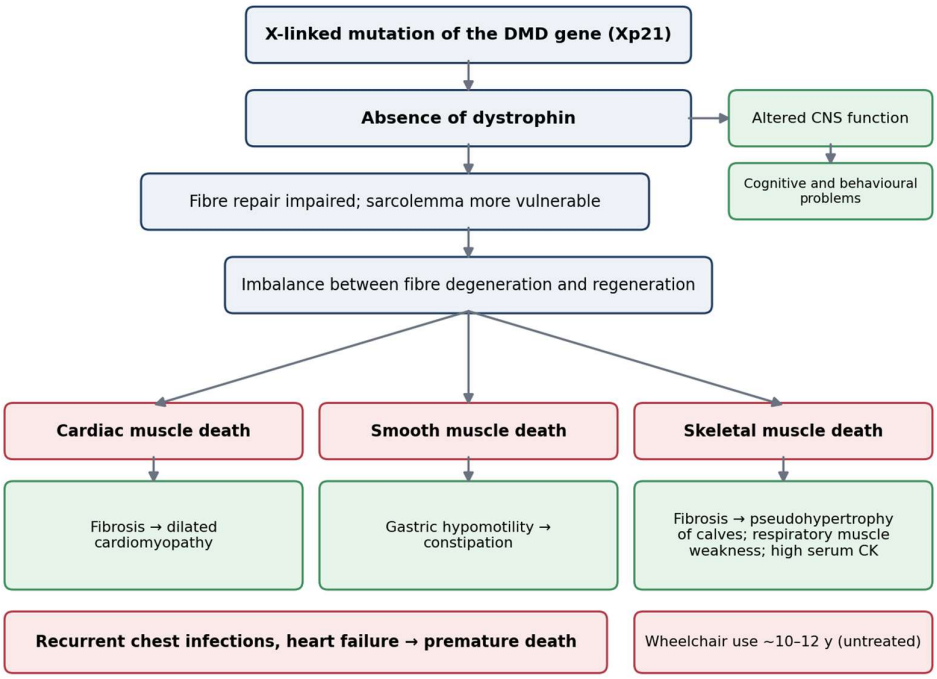


Fig. 10. Schematic of DMD pathogenesis and clinical findings. Original schematic prepared by the authors.

Clinical Presentation and Progression

Early and late ambulatory phase

Symptoms of DMD are not apparent at birth, although some patients show early neurodevelopmental delay. The initial symptoms generally appear within the first three years of life and include difficulty walking, frequent falls, and difficulty climbing stairs and rising from the floor. Patients also tend to walk on their toes (Table 2). Axial muscle weakness, a positive Gowers' sign (Fig. 12), pseudohypertrophy of the muscles and mild Achilles tendon retraction may be found on neurological examination in the early stages, and some patients begin to show cognitive difficulties [2].

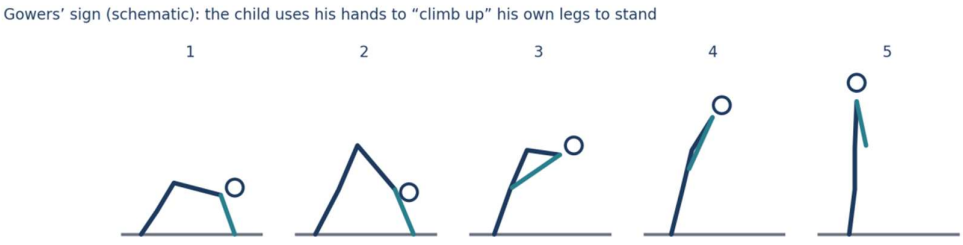


Fig. 12. Gowers' sign (schematic): the child uses his hands to "climb up" his own legs to stand. Original illustration prepared by the authors.

Children have fairly good motor development until 4–6 years of age, after which development slows and plateaus between 4 and 8 years. This is followed by progressive decline, with loss of strength and of previously acquired skills. Contractures and retraction of the least mobile joints also occur in this phase and can impair comfort and motor function. Reduced physical activity and corticosteroid therapy increase

weight gain, which further reduces mobility and increases osteoporosis and fracture risk [11, 12]. Until recently, patients became wheelchair dependent before adolescence, but with improvements in supportive care and corticosteroid therapy, loss of ambulation now occurs later. Because dystrophin isoforms are also expressed in the brain, about 20–34% of patients have some degree of intellectual disability, autism spectrum disorder or other cognitive or behavioural change [9, 12, 18].

Late ambulatory to non-ambulatory phase

Most patients become non-ambulant at 12–14 years of age, after which severe orthopaedic complications appear. Scoliosis, caused by weakness of the paraspinal muscles, affects about 90% of non-ambulant patients. Respiratory and cardiac complications are also seen. Breathing problems occur during sleep: nocturnal hypoventilation leads to periodic apnoea, morning headaches, nausea, tiredness, loss of appetite and cognitive impairment. Poor respiratory function has historically been the main cause of death, but with appropriate respiratory management and ventilatory support, cardiac complications (cardiomyopathy and arrhythmia) have become an important cause of death [3, 9]. Table 2 summarises the main features at each stage. Progression and severity vary between patients, and significant differences have been observed between siblings with the same dystrophin mutation, suggesting that environmental or genetic modifying factors influence the individual phenotype.

Table 2. Summary of the main clinical characteristics of the different stages of DMD

Early ambulatory	**Late ambulatory**
Weakness in lower limbs	Increasing difficulty walking
Gowers' sign	Inability to climb stairs and to get up from the ground
Trendelenburg gait	First symptoms of scoliosis
Toe walking	
Difficulty climbing stairs	
Inability to jump	
Learning difficulties and behavioural problems	

Early non-ambulatory	**Late non-ambulatory**
Loss of ambulation	Progressive upper-limb weakness
Ability to remain standing	Inability to remain seated
Development of scoliosis	Cardiac and respiratory complications

Note: The original table listed "Gait loss" and "Ability to stand" for the early non-ambulatory stage; these have been reworded to match Fig. 13 ("Loss of ambulation"; "Ability to remain standing").

Diagnosis of DMD

The aim of diagnosis is to establish the diagnosis in a timely way, start appropriate treatment and ensure ongoing support, education and genetic counselling. Diagnosis should be led by a physician specialised in neuromuscular disorders, who will assess the child's condition and determine which tests are needed (Fig. 11) [2, 10, 12].

When to suspect DMD

DMD should be considered even without a family history, especially in boys with muscle problems, high serum creatine kinase (CK) or raised transaminases (AST and ALT) of unexplained origin. Early signs include delayed walking, frequent falls, difficulty running or climbing stairs, a waddling gait and a positive Gowers' sign. There may also be delays in learning to walk or in speech. DMD is usually diagnosed at around five years of age. In children with a family history of DMD, CK testing should be performed early [9, 12].

Confirmation of the diagnosis

Genetic testing on a blood sample is required to confirm DMD, even when a muscle biopsy appears to show the disease. Commonly used tests are multiplex PCR, multiplex ligation-dependent probe amplification (MLPA) and DNA sequencing. Multiplex PCR detects deletions, whereas MLPA detects both deletions and duplications. If deletion and duplication tests are negative, DNA sequencing is performed to find point mutations and small insertions or deletions. Identifying the exact mutation supports genetic counselling, prenatal testing and the choice of mutation-specific treatments. A muscle biopsy may be performed if genetic testing is inconclusive or unavailable; the biopsy is examined for the amount and size of dystrophin, and little or no dystrophin makes the diagnosis likely. Genetic testing is still needed after a biopsy result. If genetic testing confirms DMD, a biopsy is not necessary. Electromyography (EMG) and nerve conduction studies are not usually needed to diagnose DMD. Early, accurate diagnosis allows timely care, family support and genetic counselling [2, 9, 12, 15].

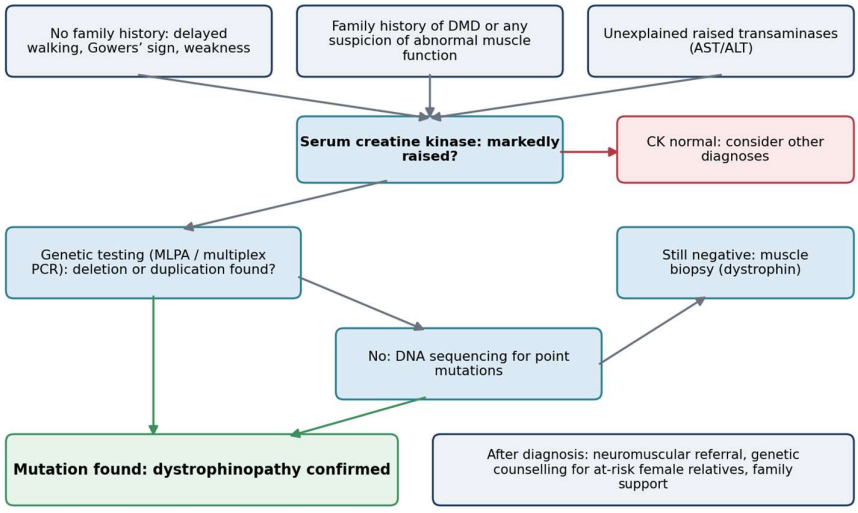


Fig. 11. Diagnostic pathway in DMD, from clinical suspicion to confirmation. Original schematic prepared by the authors.

Adult Care Priorities in Duchenne Muscular Dystrophy: A Guide for Healthcare Providers

The priorities below are consistent with the international DMD care recommendations [2–4, 12].

1. Discuss goals and transition to adult care

Healthcare providers should spend time alone with the patient at every visit, which encourages independence and allows discussion of personal goals. Educational and employment goals should be reviewed regularly, and care planning, including advance directives and an emergency care plan, should be facilitated.

2. Breathing

Pulmonary function should be evaluated every six months, or as advised by a pulmonologist. Cough-assist devices should be discussed when peak cough flow falls below 270 L/min or when weakness increases. A sleep study and non-invasive ventilation (for example BiPAP) should be considered when forced vital capacity (FVC) falls below 50% of predicted or when symptoms of hypoventilation appear, such as frequent awakenings, morning headaches and behavioural changes, and also when end-tidal carbon dioxide (CO_2) rises above 45 mmHg. Immunisations, including annual influenza vaccination, should be kept up to date, and respiratory infections should be treated promptly. Supplemental oxygen must not be given without monitoring carbon dioxide levels.

3. Corticosteroid management

The rationale for corticosteroid therapy should be discussed with the patient, and efficacy and adverse effects should be reviewed at each visit. Corticosteroids must never be stopped abruptly, and the need for stress-dose corticosteroids during illness or surgery must be addressed.

4. Cardiac management

Cardiac assessment by imaging, preferably cardiac magnetic resonance imaging (MRI), should be performed every six months or as advised by a cardiologist; echocardiography can be used when MRI is unavailable. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should be prescribed as appropriate, and standard heart failure treatment should be started when dysfunction appears, such as a shortening fraction below 28% or an ejection fraction below 55%, according to the guideline.

5. Endocrine and bone health

Patients receiving corticosteroids should have 25-hydroxyvitamin D measured and receive vitamin D supplementation as needed, and nutritional counselling should emphasise calcium and vitamin D intake. Bone density should be assessed, and bisphosphonate therapy considered when indicated. Back pain and symptoms suggestive of vertebral compression fractures must be evaluated. Pubertal development should be assessed at each clinic visit until puberty is established, and testosterone therapy should be considered when clinically indicated.

6. Physical and occupational therapy

Specialised physical therapy assessments should be carried out every four to six months using standardised measures of muscle strength and function. Daily stretching should be encouraged when comfortable, to prevent contractures. Exercise, splints and assistive mobility devices (such as scooters, wheelchairs, beds, arm supports and lifts) should be considered according to need, and posture and positioning should be assessed regularly, with appropriate supports to reduce the risk of scoliosis.

7. Nutrition and gastrointestinal management

Body weight should be monitored regularly. Dietary counselling should address healthy eating and adequate calcium and vitamin D intake. Swallowing function should be evaluated to identify the need for intervention, and gastro-oesophageal reflux disease (GERD), constipation and gastroparesis should be treated as necessary. Dental examinations every six months should be encouraged.

8. Emergency preparedness

Patients and their caregivers should carry a copy of the most recent clinical summary, including medication details and neuromuscular contact information, together with a Duchenne emergency card. Special precautions are required during anaesthesia: succinylcholine must be avoided in patients with DMD because of the risk of serious complications, and anaesthesia should be managed by clinicians familiar with the condition.

9. Mental health

Psychological adjustment, coping, behavioural and emotional disorders and social isolation should be assessed at every visit. Individualised personal care and support should be discussed, and relationships, friendships, participation in activities and community engagement should be reviewed to promote well-being and quality of life.

10. Multidisciplinary care and community resources

Patients should be guided to reliable sources of information, and follow-up should be coordinated by a neuromuscular centre with expertise in DMD. Patients and families should be given links to organisations such as Parent Project Muscular Dystrophy and the World Duchenne Organization, and should have opportunities to meet other adults living with DMD.



Fig. 14. Adult care priorities in DMD. Original summary figure prepared by the authors.

Treatment and Patient Follow-up

The course of DMD has improved over recent years because of early multidisciplinary treatment, including careful management of respiratory and cardiac function, nutrition, physical therapy, and bone and joint health [11, 16]. Regular follow-up helps keep the disease stable or slow its progression (Fig. 13 and Fig. 14).

Corticosteroid therapy

Corticosteroids are the mainstay of treatment because of their long-term benefits on motor, cardiac and respiratory function [9, 10, 12]. Treatment is recommended once the child's motor function has reached a plateau (about 4–6 years of age), and functional scales may help identify this point [9, 12]. There is controversy about whether corticosteroids should be continued after loss of ambulation. Recent studies suggest that continuing treatment preserves upper-limb strength, reduces progression of scoliosis and delays cardiac and respiratory involvement [9, 12]. The national vaccination schedule should be completed, and immunity to varicella confirmed, before corticosteroids are started [10, 12].

The corticosteroids used are prednisone and deflazacort. Intermittent regimens are less effective but are associated with fewer adverse effects. The most widely used schedules are (a) prednisone 0.75 mg/kg/day, (b) deflazacort 0.9 mg/kg/day, and (c) prednisone 0.75 mg/kg/day on alternate days, or for 10

consecutive days followed by 10 days off [9, 12]. Both drugs improve muscle strength and function, and more recent studies suggest that continuous treatment with deflazacort is generally better tolerated [10, 12]. Prednisone and prednisolone increase skeletal muscle strength, whereas deflazacort may in addition promote muscle regeneration [12]. A significant proportion of patients do not tolerate long-term corticosteroids and experience adverse effects, while others do not respond satisfactorily. The dose is generally increased as the child grows, provided adverse effects are manageable, until the child weighs about 40 kg. When there are no significant adverse effects, the established dose is maintained during the non-ambulatory phase. If adverse effects are not easily manageable, the dose is reduced by 30% before withdrawal is considered [10, 12]. Dosing decisions should always be made by the treating specialist.

Table 3. Adverse effects of corticosteroids and their management [12]

Adverse effect	Observations and follow-up	Recommended measures
Weight gain and obesity	Increased appetite	Nutritional counselling to prevent overweight
Acne and warts	More pronounced in adolescents	Topical treatment; corticosteroid schedule need not be changed
Cushingoid features	Rounded face and cheeks become more obvious over time	Dietary control and restricted sugar and salt intake
Cataracts	Annual eye examination, especially with deflazacort	Consider switching to prednisone or specific treatment if vision is impaired
Growth retardation and delayed puberty	Monitor height and sexual development every 6 months; untreated DMD patients are usually shorter	Consider endocrinology consultation in severe cases
Immune/adrenal suppression	Consider the risk of mild and severe infections	Assess the need for stress-dose corticosteroid during major surgery or severe illness
Glucose intolerance	Check urine glucose at every consultation	If positive, consider blood glucose testing
Hypertension	Measure blood pressure at every consultation	Weight reduction and salt restriction; consider ACE inhibitors or β-blockers if ineffective
Adverse behavioural changes	Mood swings, attention deficit and hyperactivity; more pronounced during the first 6 weeks	Consider delaying corticosteroid administration; if ineffective, assess for behavioural therapy
Gastritis, gastro-oesophageal reflux and peptic ulcer	Monitor acid reflux and stomach pain; check stool for blood in patients with anaemia	Avoid NSAIDs and consider gastroprotective medicines

Eteplirsen

Eteplirsen is an antisense oligonucleotide that acts at the RNA level. It targets exon 51 of the DMD gene; in some mutations, skipping this exon restores the reading frame so that a shortened but partly functional dystrophin can be produced [9, 15, 16]. It is suitable only for patients whose mutations are amenable to exon 51 skipping, so not all patients qualify. eteplirsen is not a cure and neither halts disease progression, although they may slow it in some patients. The choice of treatment depends on the patient's mutation and general health, and clinicians review each patient's genetic results before deciding whether either is suitable [14, 16].

Musculoskeletal management

Musculoskeletal management aims to keep joints mobile, prevent contractures, protect posture and slow loss of function. Physiotherapy should be used at every stage. While the patient can still walk, regular stretching of the ankles, knees and hips is essential; after loss of ambulation, stretching of the arms and upper limbs becomes very important. Ankle-foot orthoses can support walking during the day and, at night, maintain joint position and reduce the risk of contractures. Knee-ankle-foot orthoses or other standing aids may help patients remain upright for longer. Musculoskeletal assessment every six months is recommended to track contractures, muscle weakness and any signs of spinal curvature. In some patients with progressive scoliosis, spinal fusion surgery may be an option depending on respiratory function and general health [9, 11, 12].

Respiratory management

Respiratory care is critical because the respiratory muscles weaken over time, which can lead to weak cough, frequent chest infections and eventually respiratory failure. Regular lung function checks include forced vital capacity (FVC), oxygen saturation by pulse oximetry and peak cough flow. During the ambulatory phase, lung function should be assessed periodically, and more often as the disease progresses. After loss of ambulation, monitoring should take place at least every six months, or more often if needed. Respiratory physiotherapy and cough-assist techniques help clear secretions and reduce the risk of complications during infections. Non-invasive ventilation may be needed when breathing becomes weak. Influenza and pneumococcal vaccination is important because people with DMD are more vulnerable to complications from these infections [3, 12].

Cardiac management

Cardiac care focuses on detecting and treating heart problems, including arrhythmias, linked to DMD. Cardiac assessment should begin at diagnosis and continue throughout the disease even in the absence of symptoms, using electrocardiography, echocardiography and cardiac MRI as needed. ACE inhibitors or angiotensin receptor blockers may be started when needed and, on expert advice, can be used early. Beta-blockers or mineralocorticoid receptor antagonists may be added depending on cardiac function. Atrial fibrillation and dangerous arrhythmias must be evaluated and treated, and anticoagulants may be needed in some patients to prevent thromboembolism. Regular monitoring is important because cardiac disease can worsen even when the patient feels well [3, 12].

Nutritional and gastrointestinal management

Nutritional and gastrointestinal care aims to maintain a healthy weight, ensure good nutrition and prevent problems such as constipation, swallowing difficulty and acid reflux. Weight should be checked often

because corticosteroids and reduced mobility can lead to weight gain and obesity. A balanced diet with adequate protein, vitamins, minerals and fluids is recommended. Constipation can be managed with fluids, fibre, gentle activity where possible and laxatives when needed. Gastro-oesophageal reflux and oesophagitis can be treated with proton pump inhibitors or H_2-receptor antagonists. As the disease advances, swallowing may become more difficult, leading to reduced food intake and weight loss; nasogastric feeding or gastrostomy may be considered if oral intake is unsafe or insufficient. Dietary counselling and regular nutritional reviews help maintain health [3, 12].

Cognitive and psychological management

Cognitive and psychological care is important because children with DMD may have learning difficulties, speech problems, behavioural changes, anxiety and emotional stress. Neuropsychological evaluation helps identify needs and determine whether speech therapy, school support or psychological intervention is required. Learning support and curriculum adaptation can improve school performance, and psychological counselling helps patients cope with physical limitations and emotional difficulties. Families may also experience stress from caregiving and from watching the disease progress, and support from psychologists, social workers and patient or family support groups is encouraged. A supportive environment and coordinated care across teams can improve health and quality of life [4, 10, 18].

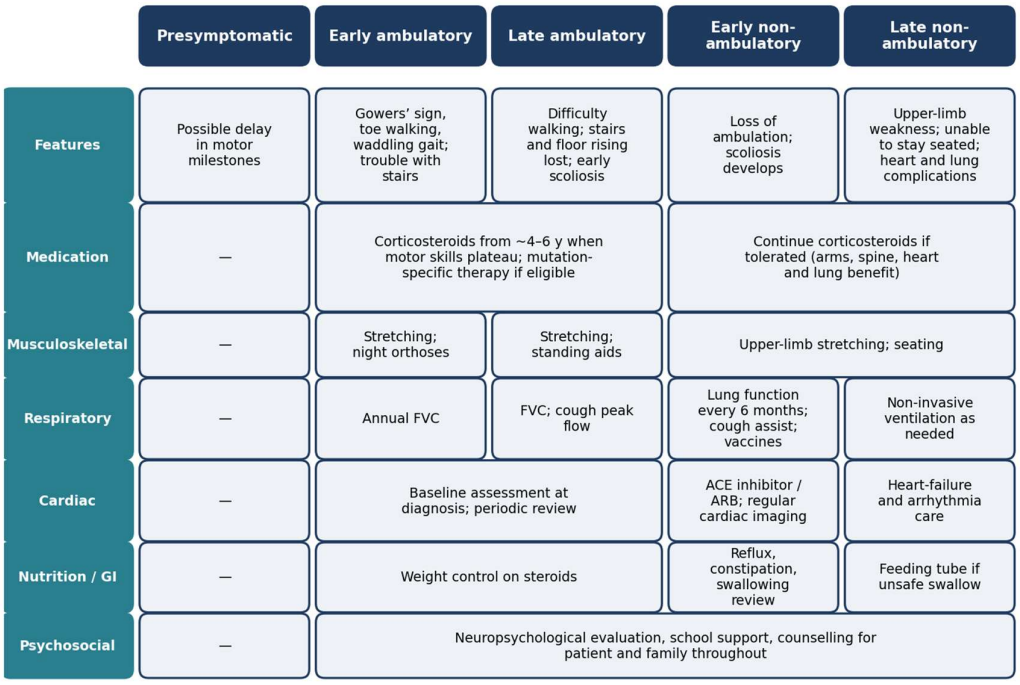


Fig. 13. Stages of DMD and corresponding multidisciplinary management. Original summary figure prepared by the authors.

Conclusion

DMD is a genetic disorder that requires early diagnosis and careful management by a team of specialists. Corticosteroids, therapies that target the underlying mutation and supportive care help preserve muscle function for longer and prevent serious complications. Monitoring of cardiac and respiratory health,

physiotherapy and attention to nutrition are all important in helping patients live better and more comfortably. Further research is needed on gene-targeted therapies to find better treatments and improve long-term outcomes for people living with DMD.

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