Chapter

Current Pathophysiological and Genetic Aspects of Dilated Cardiomyopathy

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Abstract

Dilated cardiomyopathy is the most common form of cardiomyopathy and the second leading cause of left ventricular dysfunction with highly variable clinical presentation and prognosis. The clinical courses vary and are strongly heterogeneous, ranging from asymptomatic patients to those suffering from intractable heart failure or sudden cardiac death due to arrhythmias. Previous studies have reported a 10 years cardiovascular mortality up to 40% in developed countries, due to advanced heart failure or sudden cardiac death. However, the prognosis of dilated cardiomyopathy patients is variable and depends on multiple risk factors. This chapter provides a review of dilated cardiomyopathy with specific focus on the pathophysiological aspects and genetic etiology of the disease.

Keywords: dilated cardiomyopathy, pathophysiology, etiology, diagnostics, therapy

1. Introduction

Dilated cardiomyopathy (DCM) is one of the most common cardiomyopathies causing heart failure (HF) worldwide. Although it is less common than coronary artery disease (CAD), it affects mainly young adults and presents the most frequent reason for cardiac transplantation in young age [1, 2]. According to the European Society of Cardiology (ESC), the current definition of DCM includes the presence of a dilated and poorly functioning left ventricle or of both ventricles [3]. A heterogeneous group of myocardial and systemic conditions may cause left ventricular dilatation in combination with dysfunction. In fact, identifying the etiology of DCM can be very challenging, which often leads to the common terminology of idiopathic dilated cardiomyopathy (IDC). Furthermore, DCM has a highly variable clinical presentation. While signs and symptoms of HF are most common, some patients are incidentally, for instance, by diagnosing cardiomegaly in chest X-ray. Other symptoms include arrhythmias, conduction disturbances, thromboembolic complications, or sudden cardiac death (SCD). In the last decades, major advances have been made in the understanding of molecular and genetic issues, as well as in the pathophysiology and clinical assessment of cardiomyopathies. Especially, understanding the genetic basis of DCM has improved considerably with the availability of genetic analysis. In addition, other important diagnostic approaches, particularly imaging methods are more widely available. This allows early diagnosis

and the initiation of adequate therapy, which already has led to an improvement of the prognosis in the last years. Data have shown that approximately 25% of DCM patients with recent onset of HF (<6 months) have ameliorated in symptoms or even have complete cardiac function recovery [4, 5]. However, the overall prognosis in patients with symptomatic HF and DCM is still poor. In order to further improve the prognosis of our patients, it is important to regularly gather the knowledge about the current state of DCM and adapt the appropriate diagnostic workups. Therefore, this chapter provides the reader with a comprehensive overview of the current state of DCM from definition over etiology including the genetics aspects to management for cardiovascular specialists.

2. Dilated cardiomyopathy: a frequent cardiac disease

2.1 Definition

In 1980, the World Health Organization (WHO) defined cardiomyopathies as "heart muscle diseases of unknown cause" [6]. The definition was established to distinguish cardiomyopathies from cardiac diseases with known entities such as hypertension, ischemic, or valvular heart disease. About 15 years later, the WHO/International Society and Federation of Cardiology (ISFC) Task Force classified cardiomyopathies according to anatomy and physiology into dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and unclassified cardiomyopathies. The definitions and classifications of cardiomyopathies changed over the years. The American Heart Association (AHA) presented a new scheme in 2006 that combined genetic and clinical criteria [7]. In contrast to that, the ESC defined in 2008 cardiomyopathies in a more clinically oriented classification system according to the WHO scheme as myocardial disorders with structurally and functionally abnormities of the heart muscle in the absence of coronary artery disease, hypertension, valvular disease, or congenital heart disease [3]. As mentioned above, right ventricular dilatation and dysfunction may be present but are not necessary for the diagnosis. Further, DCM is classified into familial/genetic and nonfamilial/nongenetic forms [3]. Recently, a revised definition of DCM was presented by the ESC working group on myocardial and pericardial diseases [8]. This position paper did not modify the above-mentioned definition, it rather added the important value of diverse etiologies and clinical manifestations with an introduction of a novel concept of a continuous phenotypic DCM spectrum, ranging from the subclinical mutation carriers to fully expressed DCM phenotypes.

2.2 Prevalence

The prevalence of DCM in the general population is unknown. The reported numbers considerably vary due to inhomogeneous study methodologies, which are mainly related to inconsistent definitions and classifications of DCM. In addition, the prevalence of DCM varies according to geographic and ethnic differences. One of the first reports was derived from an epidemiological study conducted in Olmsted County, Minnesota, from 1975 to 1984. For the diagnosis of DCM, the authors implemented echocardiography, angiography, and autopsy cases [9]. They presented a prevalence of 36.5/100,000 individuals or 1 in 2700 with a male to female ratio of 3:4 in a European-American population. A much higher prevalence with 1:250 was reported recently by a study from Hershberger et al. The authors estimated the DCM prevalence based on the known ratio of idiopathic DCM to

HCM of ≈2:1. In addition, clinical data of HF patients and left ventricular dysfunction were used as a surrogate for DCM [10]. In Western countries, 25–40% of DCM patients have been described with evidence of familial DCM with predominantly autosomal dominant inheritance [4, 11–13]. In general, epidemiologic studies have stated a rate of 20 up to >50% of familial DCM in patients, who were initially diagnosed with IDC [9, 11, 14–18].

2.3 Clinical presentation

The first presentation of patients with DCM is often characterized by signs and symptoms of HF, such as dyspnea, ankle swelling, fatigue, elevated jugular venous pressure, pulmonary rales, and peripheral edema (**Table 1**). These result from reduced cardiac function with low output and/or elevated intracardiac pressures. Other clinical manifestations include chest pain caused by reduced coronary blood flow or congestion, palpitations, and syncope or sudden cardiac death (SCD). Arrhythmia results from multifactorial reasons, which are present in DCM and include structural changes with myocardial fibrosis and left ventricular dilation as well as electrophysiological changes [19]. The risk of SCD is highly heterogeneous and depends on etiologies and risk factors [20]. Some genetic constellations may be associated with arrhythmias out of proportion to the degree of left ventricular dysfunction (e.g., pathogenic variants in DES, LMNA, and SCN5A) [21]. This is described later in this chapter (see Sections 2.7.3 and 2.8). Furthermore, patients might present with pulmonary and systemic thromboembolism [22]. Possible clinical findings are summarized in **Table 1**.

	Cardiac	**Pulmonary**	**Gastrointestinal/ urogenital**	**Other**
Symptoms	Chest pain Palpitations Syncope	Dyspnea Wheeze Blood-tinged sputum Cough	Reduced appetite Epigastral pain Bloating Obstipation Diarrhea Swollen abdomen Nycturia Reduced libido Erectile dysfunction	Dizziness Lightheadness Concentration disturbances Fatigue Fainting Sweating Leg swelling Symptoms of multisystem disease Skin alterations Visual and hearing impairment Gait disturbance
Clinical signs	Hypotonia Tachycardia Pulsus alternans Arrhythmia Third heart sound Loud 2nd heart sound Displaced apex beat Elevated jugular venous pressure Eedema	Tachycardia Tachypnoea Low oxygen saturation Hemoptysis Rales Obstructive lung auscultation Diminished lung sounds due to pleural effusions Pulmonary edema	Hepatomegaly Ascites Jaundice in terminal liver failure Cachexia	Intellectual disability Deafness Myotonia Hyperpigmentation Palmoplantar keratoderma Woolly hair Dysmorphic appearance Polyneuropathic symptoms Carpal tunnel syndrome

Table 1.
Clinical findings in dilated cardiomyopathy.

2.4 Pathophysiological aspects and etiology

As a consequence of the definition, the etiology of left ventricular dilatation and dysfunction is heterogeneous. In developed countries, CAD is the most common cause of left ventricular dilatation and dysfunction, and responsible for approximately 50–70% of HF patients. Therefore, potentially reversible myocardial ischemia must always be excluded for the diagnosis of DCM. The following section describes in detail the possible causes of the DCM (**Figure 1**). However, the current literature underscores that the cause of DCM remains unknown, that is, IDC, in half of the patients [23].

2.4.1 Non-genetic causes of DCM

2.4.1.1 Inflammatory cardiomyopathy

DCM can occur after a cardiac infection or inflammation as an early (e.g. giant-cell myocarditis) or late stage disease. Typically, the active or fulminant myocarditis appears with preserved left ventricular size, while in contrast inflammatory DCM is defined as the presence of chronic inflammatory cells in association with left ventricular dilatation and reduced fraction [3]. The inflammatory myocarditis can result from an infection or may be mediated by autoimmune mechanisms. The infectious myocarditis is commonly caused by viral pathogens as an acute or chronic disease [24]. In the developed countries until the 1990s, the most frequently reported viruses were adenoviruses and enteroviruses. Recently, parvovirus B12 and human herpes virus-6 are increasingly reported causing DCM [25]. In the acute phase, the virus replicates actively within the myocardium. This leads to dysfunction of cardiomyocytes and endothelial cells, and thus triggering the immune response [23]. Commonly, the innate immune system clears the viral load whereas insufficient immune response results in viral persistence and progressive myocyte destruction [25]. The secondary effect is triggered by primed T-cells. In addition, some host myocardial cellular antigens may share epitopic similarities with viral antigens and induce an autoimmune response with further destruction of cardiomyocytes [23].

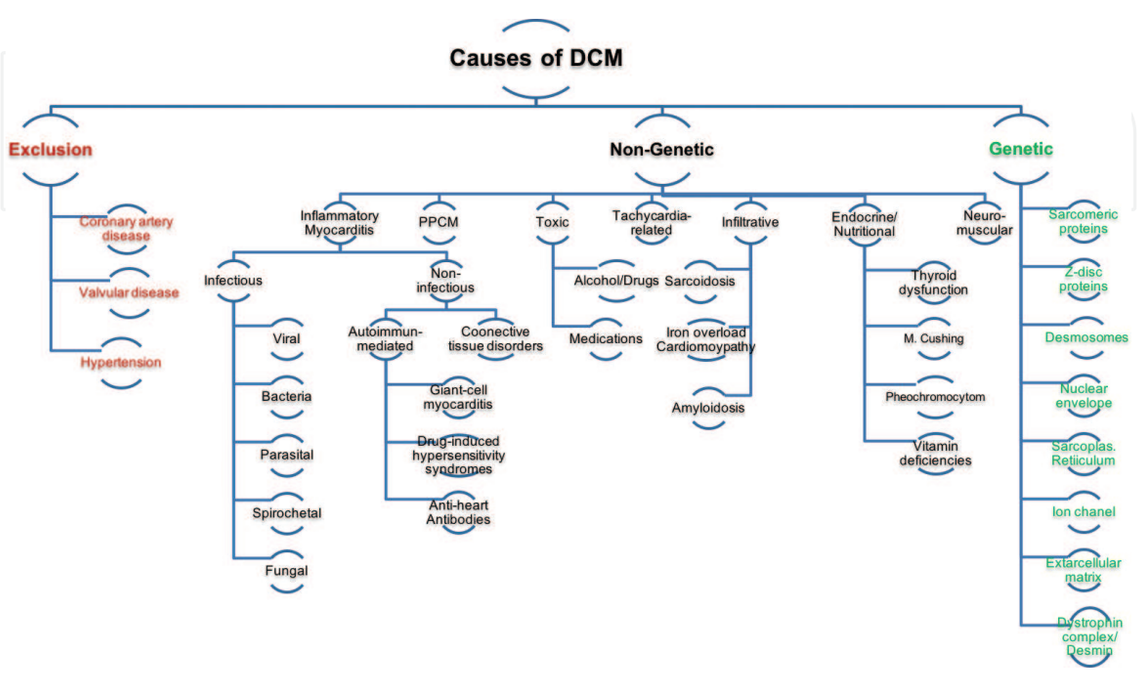

Figure 1.
Etiologies of the dilated cardiomyopathy.

Another important viral-related form of DCM is HIV syndrome. DCM in HIV patients is called HIV-associated cardiomyopathy. Autopsies demonstrated histological evidence of myocarditis in around 50% of patients, who died of AIDS-related illness [26]. Bacterial infections such as brucellosis, diphtheria, psittacosis, and typhoid fever are also known to cause (peri-) myocarditis [27–30]. In addition, E. coli bacteraemia have been described to induce myocarditis [31]. Spirochaetal myocarditis may be encountered in the setting of the Lyme disease (Borrelia burgdorferi), the Weil disease (Leptospirosis), and syphilis (Treponema pallidum) [32]. In endemic areas, the protozoan parasite Trypanosoma cruzi is a typical cause of DCM due to acute cardiac infection (perimyocarditis), as well as chronic myocardial fibrosis leading to DCM [33]. There are several proposed mechanisms leading to DCM in autoimmune disorders. These include immune-mediated myocarditis, progressive fibrosis, apoptosis with resultant restrictive and dilated phenotypes, and progressive atherosclerosis with subsequent ischemic cardiomyopathy [26]. Other causes for a non-infectious myocarditis are: Kawasaki disease in children with coronary vasculitis and systemic lupus erythematosus, which can affect the myocardium without involvement of the pericardium. In rare cases, connective tissue diseases such as scleroderma, rheumatoid arthritis, and polyarteritis nodosa may lead to DCM [26]. The non-infectious etiologies of myocarditis include drug-induced hypersensitivity and hypereosinophilic syndromes, as well as giant-cell myocarditis, which is one of the most aggressive non-infectious autoimmune disorders with rapid and devastating outcome if not treated appropriately [24, 26].

2.4.1.2 Peripartum cardiomyopathy

Peripartum cardiomyopathy (PPCM) affects predisposed teenagers and older women during the last month of pregnancy or within 5 months of delivery with typical signs and symptoms of HF [34, 35]. Suspected etiological factors include inflammatory myocarditis, autoimmunity caused by chimerism of hematopoietic lineage cells from the fetus, hemodynamic stress during pregnancy, and toxicity caused by an abnormal cleavage product of prolactin [3, 36]. Furthermore, genetic predisposition seems to be important [37].

2.4.1.3 Toxic cardiomyopathies

A number of chemical compounds are responsible for DCM. In western and developing countries, alcoholic cardiomyopathy (ACM) represents one of the most common forms of secondary cardiomyopathies resembling IDC with an estimated prevalence of 23–40% [24, 38]. More than women, men are affected by ACM and the occurrence correlates with a daily level and the duration of alcohol consumption [39]. However, the prevalence of ACM is variable and the mean daily amount of alcohol consumption, duration of regular intake, and patients' individual characteristics, including genetic susceptibility, are all related to the development of a respective cardiomyopathy [26]. Alcohol may result in both acute and chronic depression of myocardial contractility. Street drugs such as cocaine and methamphetamines are potent sympathomimetic drugs that induce inotropic and chronotropic effects. Mechanisms of cardiac toxicity include myocardial ischemia from increased oxygen consumption, prothrombotic effects, coronary vasospasms, and acceleration of coronary atherosclerosis [24]. Anthracycline-based chemotherapeutic agents are known to induce cardiac dysfunction. Acute or subacute injury can occur immediately after treatment with transient arrhythmias, pericarditis, and myocarditis [38]. The time course of chronic development of HF varies from an early onset (<1 year) to late onset (>1 year) or chronic progressive cardiomyopathy,

which can occur 10–30 years after exposure. Both chronic forms tend to be irreversible, are dosage dependent and are associated with ultrastructural changes in the cardiac myocytes [40]. Trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2), is wildly used and very effective for the treatment of HER2-positive breast cancer. HER2 receptors are also localized on the cardiomyocyte. The inhibition of the Her2:Her4 signaling process in the myocardium is principally responsible for the cardiotoxicity [26]. In addition, a number of other, non-chemotherapeutical medications are associated with DCM, such as cyclophosphamide, phenothiazines, antidepressant drugs, carbon monoxide, lead, lithium, pseudoephedrine, ephedrine, cobalt, anabolic steroids, hydroxychloroquine, clozapine, and catecholamines [38, 41]. Possible causes of toxic cardiomyopathy are summarized in **Figure 2**.

2.4.1.4 Arrhythmia-induced DCM

Tachycardia-induced cardiomyopathy was described more than 100 years ago by Gossage et al. as a reversible form of systolic dysfunction caused by long-lasting supraventricular or ventricular arrhythmias [42]. Ongoing rapid atrial or ventricular pacing may result in systemic changes by neurohormonal activation, characterized by reduction in serum sodium, activation of the renin-angiotensin system, and an increase of plasma atrial natriuretic peptide, aldosterone, and norepinephrine. Abnormal myocardial and cellular remodeling occurs, which may result in DCM. Furthermore, epinephrine can also lead to abnormal myocardial and cellular remodeling, which further result in biventricular dilatation, decreased contractility, and elevation of left and/or biventricular filling pressure [26].

2.4.1.5 Infiltrative diseases

Several, systemic diseases may infiltrate the myocardium and result in DCM. Sarcoidosis, iron overload, and amyloidosis represent the most common clinical entities. Sarcoidosis is a multisystem inflammatory disease of unknown origin characterized by non-caseating granulomas in multiple organs. Sarcoidosis can progress to a fibrotic stage leading to DCM [26]. In the setting of iron overload, such as hereditary hematochromatosis, high blood volume, or parenteral iron infusions,

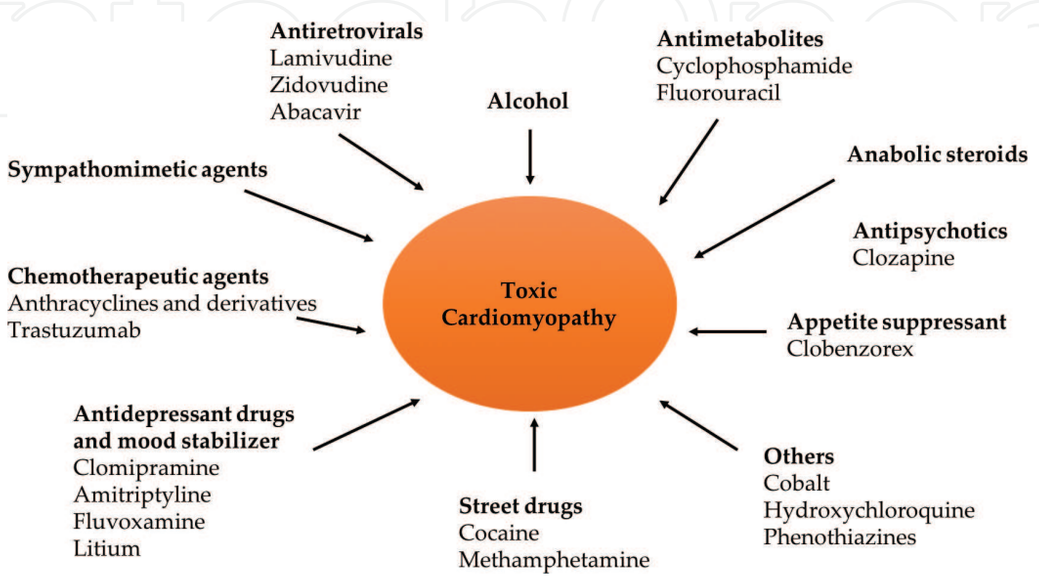

Figure 2.
Reasons for toxic cardiomyopathies.

DCM may occur due to iron-induced reactive oxygen species with cellular oxidative stress and fibrosis [43]. Cardiac amyloidosis is the most common cause of infiltrative cardiomyopathy with poor prognosis. Amyloid is an extracellular tissue deposition of misfolded amyloid protein-fibrils [44]. Cardiac amyloidosis usually presents as a cardiomyopathy with restrictive pathophysiology and can progress to severe cardiac dysfunction and to DCM in very advanced stages [26].

2.4.1.6 Endocrine/metabolic disorders

Endocrinologic disorders rarely lead to the phenotype of DCM. Especially thyroid hormones have a significant impact on cardiac function and structure via regulation and expression of key structural and regulatory genes like myosin heavy chain and phospholamban. Therefore, excess or deficiency of triiodothyronine (T3) may lead to DCM in a late stage [45]. Growth hormone disorders, pheochromocytoma, and Cushing's disease are also very rare causes of DCM [26, 46]. Furthermore, the literature names nutritional deficiencies of thiamine (beriberi disease), selenium (Keshan disease), and L-carnitine being responsible for DCM [47, 48].

2.4.1.7 Neuromuscular disorders

Neuromuscular disease like Duchenne's muscular dystrophy, Becker muscular dystrophy, and Emery-Dreifuss muscular dystrophy can affect the heart and induce DCM. Patients with DCM and muscular dystrophy commonly show X-linked mutations or autosomal recessive inheritance [24]. Further information is summarized in the following section on genetic causes of DCM.

2.4.2 Genetic causes of DCM

In up to 30% of the cases, a gene mutation may be identified as the main cause of DCM [49]. Thanks to advances in next-generation sequencing technologies more than 40 genes have already been identified causing DCM [50]. Most commonly, familial DCM is inherited as an autosomal dominant pattern. Autosomal recessive, X-linked, and mitochondrial inheritance patterns are less common [24]. Most of the genes involved in the development of DCM encode structural elements of the cardiomyocytes. Mutations in genes encoding sarcomeric, cytoskeletal, desmosomal, nuclear membrane, mitochondrial, and RNA-binding proteins have all been linked to DCM [51]. Interestingly, several of the gene mutations linked to autosomal dominant DCM encode the same contractile proteins that are also responsible for the development of HCM [38]. As well, other affected genes are described in ARVC and left ventricular non-compaction cardiomyopathy (NCCM). In the following, we will describe the most investigated gene mutations and their consequences on the cardiomyocyte functioning.

2.4.2.1 Sarcomere protein location: force generation and transmission

The sarcomere is the contracting unit of the myocyte. The thin filaments of the sarcomere emanate from the Z-disc. They consist of filamentous α-actin (gene name ACTC 1) and calcium-sensitive troponin-tropomyosin regulatory apparatus (encoded by TPM1), which includes the three troponin subunits (encoded by TNNT2, TNNC1, and TNNI3) [52, 53]. The thick filament core is formed by the β-myosin heavy chain (encoded by MYH7), the molecular motor of the thick filament, and the myosin-binding protein C (β-MYBPC3) [52, 53]. Titin (encoded by TTN), which is the largest human protein, spans the half length of the sarcomere,

where it acts as a stretch sensor and myofibril stabilizer. It limits sarcomere stretch in early diastole and restores resting sarcomere length after contraction [52, 53]. Titin (TTN) mutations are the most prevalent genetic cause of idiopathic DCM (15–20%). In fact, DCM patients with TTN mutations have a worse outcome due to a higher arrhythmic risk and progressive functional deficits [54]. Mutations in human genes encoding protein components of the sarcomere cause either HCM or DCM. Deficits of force production and transmission are the two main mechanisms that lead to DCM due to sarcomere mutations [55]. Mutations of genes encoding myosin proteins (MYH 6, MYH7, and MYBPC3), actin proteins (ACTC 1 and ACTC 2), and tropomyosin protein (TPM 1) result in alterations of coupling-uncoupling mechanisms of actin to myosin [50]. Specifically, TPM1 mutations are associated with destabilization of actin interactions and compromise force transmission to neighboring sarcomeres. ACTC mutations impair the binding of actin to the Z-disc compromising force propagation [55]. Impaired contractile force may also occur from troponin mutations. Because troponin molecules modulate calcium-stimulated actomyosin ATPase activity, the mutation causes inefficient ATP hydrolysis and decrease contractile strength [55].

2.4.2.2 Cytoskeleton protein location: force transmission and structural integrity

The Z-disc is an electron-dense structure, in which titin and the thin filaments anchor. Critical components include α-actinin, which aligns actin and titin from neighboring sarcomeres and interacts with muscle LIM protein (MLP encoded by CSRP3). Telethonin (encoded by TCAP) is another Z-disc component interacting with titin and MLP to support overall sarcomere function. In addition, Cipher/Z-band alternatively spliced PDZ-motif protein (Cipher/ZASP encoded by LDB3), which interacts with α-actinin-2 through a PDZ domain, an abundant protein interaction modules that recognize short amino acid motifs of the C-termini of target proteins, and couples to protein kinase C (PKC)-mediated signaling via its LIM domains [55, 56]. Gene mutations of multiple Z-disc proteins like MLP, cardiac ankyrin repeat protein (CARP), myopalladin, α-actinin 2, TCAP, and nexilin may result in DCM [52]. Cipher/ZASP mutations have been associated to isolated left ventricular dilatation or DCM with NCCM phenotype [50]. Metavinculin (encoded by VCL) attaches the thin filaments to the plasma membrane and plays a key role in force transmission. Gene mutations in metavinculin cause DCM by disruption of disc structure and actin-filament organization [55]. The costamere, a rib-like structure of the cytoplasmatic and transmembrane proteins, interconnects the cytoskeleton to the plasma membrane and the extracellular matrix. Dystrophin and its associated proteins, sacroglycans and dystroglycan, enrich at the costamere and protect against contraction-induced injury [52]. The integrity of the dystrophin complex is critical for mechano-transduction and loss of function mutations trigger instability of the plasma membrane and myofiber loss. This mechanism leads to Duchenne and Becker muscular dystrophy [57]. Desmin, another intermediate filament in cardiomyocytes, forms a 3D scaffold that extends across the entire diameter of the cardiomyocyte, surrounds the Z-discs and interlinks them together and integrates the contractile apparatus with the sarcolemma and the nucleus. Desmin helps to sense mechanical stretch and transduces downstream signals from extracellular to the nucleus. In addition, desmin plays a crucial role during myogenesis. Inhibition of desmin expression blocks myoblast fusion and myotube formation [58]. Mutations in the desmin genes are associated with an autosomal dominant skeletal myopathy, cardiac conduction block, and DCM [59]. Prevalence of desmin mutations in familial DCM have been reported in 1–2% [60].

2.4.2.3 Desmosomes: cell-cell adhesion and intracellular signaling/mechano-signaling

Desmosomes are organized cell membrane structures that provide functional and structural contact between adjacent cells. Mutations in protein components of desmosomes like plakoglobin, desmoplakin, and plakophilin-2 can cause syndromic and non-syndromic ARVC as well as DCM due to disruption of intercellular junction [55, 61].

2.4.2.4 Sarcoplasmic reticulum: calcium homeostasis

Calcium enters the myocyte through voltage-gated L-type Ca^{2+}-channels. This triggers the release of calcium from the sarcoplasmic reticulum (SR) via the ryanodine receptor 2 (RyR2). At low intracellular calcium concentrations, troponin I and actin interactions block actomyosin ATPase activity. With increasing intracellular concentration, calcium binds to troponin C, which releases troponin I inhibition and stimulates contraction. Calcium dissociates from troponin C in cardiac relaxation. Calcium concentration decreases by calcium reuptake in the SR through the phospholamban-regulated cardiac sarcoplasmic reticulum CA^{2+}-ATPase (SERCA2a) [55]. Mutations of phospholamban precipitate DCM by altering calcium homeostasis [54]. Specific phospholamban mutation R14del is associated with high risk of malignant ventricular arrhythmias and end-stage HF. Further, it is described in a phenotype of ARVC [62].

2.4.2.5 Nuclear envelope: maintain structural organization

The nuclear membrane protein complex contains emerin and lamin A/C (LMNA) [52, 55]. These two lamina proteins and nesprin-1 are part of the LINC complex that links the nucleus to the cytoplasm. Stress signals in the cytoplasm are hypothesized to act with the LINC complex, affecting gene expression in the nucleus. The LINC complex is crucial for an appropriate transcriptional response of the cell to mechanical stress [52]. Defects in emerin proteins can induce X-linked Emery-Dreifuss muscular dystrophy, joint contractures, conduction system disease, and DCM. Dominant lamin A/C (encoded by LMNA) mutations exhibit a more cardiac-restricted phenotype with fibrofatty degeneration of the myocardium and it is conducting system. More than 200 different lamin A/C (LMNA) mutations are associated with inherited cardiomyopathy, primarily DCM that may be associated with conduction system disease prior to the evidence of ventricular dilatation due to fibrofatty degeneration of the myocardium and conducting cells [52, 55]. Other diseases caused by lamin A/C mutations are Charcot-Marie-Tooth neuropathy, Dunningan partial familial lipodystrophy, progeria and other overlapping syndromes, all known as laminopathies [63].

2.4.2.6 Ion channel

The function of sarcolemmal transmembrane cardiac voltage-gated sodium channel is crucial in the generation of cardiac action potentials. Some mutations in the encoding gene SCNA5 are implicated in DCM. SCN5A mutations causes high burden of arrhythmias. There are also many allelic variants in SCN5A, including those leading to Brugada syndrome, idiopathic ventricular fibrillation (VF), familial atrial fibrillation (AF), left ventricular non-compaction cardiomyopathy, and long QT syndrome type III [54, 59, 64].

2.4.2.7 Extracellular matrix-cell-adhesion and signaling

Extracellular matrix proteins such as laminin alpha-4 (LAMA4) and Fukutin (FKTN) have been described in relation to DCM. They may lead to DCM phenotype by disrupting signaling pathways and modifying cell-surface molecules [50].

The genetic evaluation of DCM is summarized in **Table 2**.

Genetic evaluation of DCM	Gene screening of DCM	Genotype correlations of DCM
Sarcomere protein related genes	• Titin (TNN) • α-Cardiac actin (ACTC 1 and ACTC 2) • α-Tropomyosin 1 (TPM 1) • Cardiac troponin subtypes (TNNT2, TNNC1, TNNI3) • Myosin heavy chains (MYH 6, MYH7) • Myosin-binding protein C (MYBPC) • Troponin I-interacting kinase (TNNI3K)	• 12–25% of genetic related DCM are associated with titin (TTN) mutations • α-Tropomyosin 1 (TPM 1) mutations are described in 1–2% of DCM • Myosin heavy chain (MYH7)-mutations in 3–4% of DCM • 3% of DCM are linked to cardiac troponin T (TNNT2) mutations • Gene defects in sarcomere proteins are associated with defects in force generation and transmission • TNNI3K-mutations may cause conduction defects and atrial fibrillation
Cytoskeletal protein related genes: Z-disc Dystrophin complex Cytoskeleton	• α-Actinin 2 (ACTN 2) • Muscle LIM protein (MLP) • Cysteine- and glycine-rich protein 3 (CSPR3) • Telethonin (TCAP) • Cypher/Z-band (LDB3) • PDZ LIM domain protein 3 (PDLIM3) • Cardiac ankyrin repeat protein (CARP) • Myopalladin (MYPN) • Nexilin (NEXN) • Metavinculin (VCL) • Dystrophin (DMD) • Sacroglycan (SGCA, SGCB, SGCD, and SGCG) • Desmin (DES)	• Metavinculin (CVL) mutations are related to 1% of DCM • Dystrophin (DMD) mutations are associated with Duchenne/Becker muscular dystrophy • Sacroglycan (SDC) mutations can cause Limb-girdle-muscular dystrophy Prevalence of *Desmin (DES)* mutations in genetic related DCM is about 1–2%, the mutations are often related with myofibrillar myopathy, ARCV and cardiac conduction blocks
Desmosomal protein related genes	• Plakoglobin (JUP) • Desmoplakin (DSP) • Desmocollin 2 (DSC2) • Desmoglein 2 (DSG2) • Plakophilin-2 (PKP2)	• Mutations in desmosomal genes are frequent in patients with advanced DCM undergoing cardiac transplantation • Desmosomal gene mutations are also linked to ARVC • Desmoplakin (DSP) causes 2% of genetic related DCM • Plakoglobin (JUP)-mutations are also associated with Naxos syndrome • Desmocollin 2 (DSC2) mutations may lead to mild palmoplantar keratoderma
Sarcoplasmic reticulum related genes	• Ryanodine receptor 2 (RyR2) • Phospholamban (PLN) • SR proteins, Ca-ATPase pump (SERCA2a)	• Specific mutations are associated with high risk of malignant ventricular arrhythmias and end-stage heart failure • Ryanodine receptor 2 (RyR2) correlates with cathecolaminergic polymorphic ventricular tachycardia and ARVC • Phospholamban (PLN) mutations can cause ARVC • Some other genes encoding for sarcoplasmic reticulum and cytoplasm related proteins like PTPN11, RAF1 and RIT1 are also associated with Noonan and Leopard Syndrome

Genetic evaluation of DCM	Gene screening of DCM	Genotype correlations of DCM
Nuclear envelope and nucleus protein related genes	• Emerin (EMD) • Lamin A/C (LMNA)	• EMD mutations can lead to X-linked Emery-Dreyfuss muscular dystrophy, joint contractures and conduction system disease • Prevalence of genetic-related DCM due to LMNA mutation is described in 4–8% • LMNA-related heart failure is often more resistant to heart failure therapy and has a high risk for arrhythmias and sudden cardiac death • Mutations in LMNA can cause a severe and progressive DCM and can also lead to Charcot-Marie-Tooth neuropathy, Dunningan partial familial lipodystrophy, Emery-Dreyfuss muscular dystrophy and progeria
Ion channel protein related genes	• Sodium channel, voltage-gated, type V, alpha subunit (SCNA5) • Potassium channel (KCNQ1)	• *SCN5A* mutations account for 2–3% of DCM, mutations are associated with Brugada syndrome, Long QT syndrome, atrial fibrillation and conduction defects • KCNQ1 mutations may induce atrial fibrillation, Long QT 1, Short QT1 and Jervell and Lange-Nielsen syndrome
Extracellular matrix protein related genes	• Laminin alpha-4 (LAMA4) • Fukutin (FKTN)	• Extracellular matrix protein relation has been described to DCM • FKTN and LAMA2 mutations can also cause congenital muscular dystrophy

Table 2.
Genetic aspects of dilated cardiomyopathy.

2.5 Diagnosis

Establishing the etiology is of great importance as it may influence treatment and prognosis of patients with DCM. Beside the conventional clinical tools, modern imaging and genetic tools are available to elucidate and ensure the correct diagnosis. The recently published statement for the diagnostic workup on DCM from the ESC working group on myocardial and pericardial diseases recommend the following steps: first the diagnostic evaluation should be start with in-depth personal and family history, followed by physical examination, an electrocardiogram (ECG), and echocardiography [8]. These steps often sufficiently differentiate between acquired and familial DCM. If there is no suspicion of an acquired DCM and if 'red flags' are recognized, the second-level diagnostic work-up should be added. 'Red flags' are defined as signs and suspicion on a specific etiology. Biochemical analyses, cardiac magnetic resonance imaging (CMR), endomyocardial biopsy (EMB), and genetic testing are recommended in a second step. However, the patient's age plays a crucial role in the decision-making during the diagnostic procedure and should be rated against the potential benefit of dedicated investigations. The detailed diagnostic workup and possible red flags are presented in **Table 3**.

2.6 Screening

In common, DCM is a slowly progressive disease and screening is essential for an early diagnosis of asymptomatic family members. Currently, screening all first-degree family members of patients with genetic proven or non-genetic forms of DCM with a positive family history is recommended. The screening comprises

Diagnostic tool	Look for	Red flags for specific disorders
Personal and familial history	Degree of symptoms Travel history Inheritance pattern Toxin exposition Involvement of other organs	Intellectual and sensorineural disabilities Muscle weakness Myotonia Gait disturbances Skin abnormities, for example, hyperpigmentation and palmoplantar keratoderma, butterfly-shaped face rash Woolly hair
Electrocardiogram		Low P-wave amplitude Atrioventricular block Repolarization disorders with non-coronary distribution Low QRS amplitude Bundle branch block Long QTc Ventricular arrhythmias
24 h electrocardiogram	Relevant brady- and tachyarrhythmias	Relevant tachyarrhythmias
24 h ambulatory blood pressure monitoring	Exclude persistent hypertension	
Biochemistry	Blood count Electrolytes Renal function Cardiac biomarkers TSH HbA1c Serum iron, ferritin and electrophoresis Urine chemistry and proteinuria Serum free light chains HIV and hepatitis serology Other specific serology tests in accordance symptoms and clinical suspicion	High levels of creatine kinase Myoglobinuria Increased serum iron & ferritin levels Leucopenia or neutropenia Free light chains for amyloidosis Diabetes and lactatacidosis Thyroid disorders Infectious etiologies
Echocardiography	Ventricular dilatation Valve diseases Right ventricular pathologies	Left ventricular hypertrabecularisation Segmental dysfunction with noncoronary distribution
Coronary angiography	Exclude coronary artery disease	
CMR	Late Gadolinium Enhancement Intramyocardial edema Intramyocardial iron deposit Right ventricular morphology Molly sequence	Patchy or inferobasal late gadolinium enhancement (LGE) distribution “Midwall sign” septal wall LGE distribution
EBM	Giant cell myocarditis	
Genetics	Screening familial DCM	

Table 3.
Diagnostic workup and possible red flags in dilated cardiomyopathy.

physical examination, 12-lead ECG and transthoracic echocardiography as well as measurement of CK levels. The CK levels may help to identify subclinical skeletal muscle abnormalities and to provide supportive evidence for the presence of an inherited myopathy. If DCM is suspected in first-degree relatives, the screening should be repeated anually. Otherwise, asymptomatic first-degree relatives should be rescreened at three- to five-year intervals because of possible late onset of DCM phenotype [21].

2.7 Therapy

Specific treatment is applicable in syndrome associated DCM, for example, infectious etiologies and infiltrative disorders. However, specific treatment is not available for most DCM patients. Therefore, the therapy focuses on improvement of clinical symptoms as well as on the control of disease progression and potential complications such as sudden cardiac arrest.

2.7.1 Heart failure treatment

Guidelines recommend the following treatment for acute HF, not including non-cardiogenic shock: oxygen, non-invasive ventilation (NIV), intravenous diuretics (20–40 mg bolus furosemide at admission), and intravenous nitrates. Intravenous nitrates have long been described to improve hemodynamic and dyspnea in HF patients by many ways: decrease in systemic blood pressure and left ventricular afterload, substantial reduction preload and therefore of in right and left ventricular filling pressure, an increase in cardiac output, and little or no change in heart rate [65]. Improvement in cardiac output by intravenous nitrates is mostly related to the reduction in left ventricular afterload, but is also influenced by a decrease in pulmonary vascular resistance, improvement in myocardial oxygenation, and a reduction of mitral regurgitation. Administration of inotropes and/or vasopressors is recommended in patients with signs of low cardiac output [66]. However, application of inotropes and/or vasopressors is associated with an increased long-term mortality risk [67–69]. Additional treatment includes the optimal dosing of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). ACEI have been shown to reduce cardiovascular mortality and prevent rehospitalization in patients with HF in two key randomized controlled trails (CONSENSUS and SOLVD-Treatment) [70]. Likewise, ARB improve long-term outcome in HF patients [71]. Another essential component of HF therapy is spironolactone. The RALES study has shown a reduction in mortality after addition of 25 mg of spironolactone to the standard treatment in HF patients with an LVEF <35% [72]. The international guidelines recommend spironolactone in all patients presenting with moderate to severe HF symptoms. In the PARADIGM-HF trial, the use of angiotensin receptor-neprilysin inhibitor (ARNI) (sacubitril/valsartan) showed a reduction of the composite endpoint of cardiovascular death or HF hospitalization by 20% compared with enalapril alone in symptomatic HF patients with reduced LVEF [73]. These study results are implemented in the updated ACC/AHA/HFSA guidelines on management of HF, which recommend to replace ACEI or ARB by sacubitril/valsartan in patients with reduced LVEF and ongoing symptoms [74]. Betablockers reduce mortality in HF patients even without reduced ejection fraction as has been demonstrated by multicenter placebo-controlled studies [75–77]. Because of the negative inotropic effect of betablockers, patients should not be treated in the very acute presentation with signs or symptoms of decompensation and initial doses should be low. Long-term goal is a heart rate below 70 bpm in sinus rhythm. If this is not obtainable with the maximum, or maximum tolerated dose of betablockers, the current European heart failure guidelines recommend the addition of Ivabradine [66]. In addition to pharmacological medication cardiac resynchronization therapy (CRT) has been shown to improve cardiac performance, to reduce symptoms, morbidity, and mortality [78, 79].

2.7.2 Anticoagulation

The role of anticoagulation in DCM with sinus rhythm is unclear [80]. The prospective randomized trials were either underpowered or with a too short

follow-up. At present, there are no trial data to guide anticoagulant treatment regime in DCM. Due to two studies (WATCH and WARCEF trial) showing a slight advantage of warfarin over aspirin, anticoagulation with warfarin is advised in patients with a history of thromboembolism or evidence of intracardiac thrombus [81, 82]. Current ACC/AHA HF guidelines do not recommend anticoagulation in reduced left ventricular function and sinus rhythm without prior thromboembolic events or known cardioembolic source [83]. Studies testing the non-vitamin K antagonist oral anticoagulants (NOACs) in patients with reduced left ventricular function are currently ongoing. In DCM patients with documented AF, oral anticoagulant is recommended with CHA_2DS_2-VASc score ≥ 2, as a class I indication and in men with a CHA_2DS_2-VASc score of 1 as class IIa with level of evidence B [66, 77, 83, 84].

2.7.3 Arrhythmias

The most common arrhythmia in DCM is AF, which increases the risk of thromboembolic complications, impairs cardiac function and worsening HF symptoms. Therefore, evaluation of rate control and anticoagulation in order to preserve LV-function and prevent thromboembolic events is crucial. In the acute setting betablockers, digoxin and their combination may be used to control ventricular rate. In the chronic stage, rhythm control has been shown to be superior to rate control alone in reducing mortality [85]. Because of the commonly reduced left ventricular function, the only therapeutic option is type III antiarrhythmic drug such as amiodarone. Alternatively, electrical cardioversion can be performed. Recently, the CASTLE-AF study demonstrated the superiority of AF catheter ablation in certain patients with HF as compared to medical therapy. The ablation was associated with a significantly lower rate of death and hospitalization for worsening HF [86]. DCM patients may suffer from ventricular arrhythmias (VA), which are mainly caused by myocardial damage, fibrosis and/or loss of cell-to-cell conjunctions, that are described by three mechanisms: reentry, trigger activity, and automatism [87]. Monomorphic ventricular tachycardias (VTs) are frequently induced by macro-reentry mechanism, which is best treated by ablation. The main trigger mechanisms are electrolyte imbalance, mostly secondary to diuretic treatment, antiarrhythmic drugs, and bradycardia. The therapeutic options are a combination of antiarrhythmic drugs like betablockers and type III antiarrhythmics and/or implantation of an implantable cardioverter defibrillator (ICD). The indications for ICD treatment are described later [4].

2.8 Prognosis and risk stratification

Although there has been a significant improvement in prognosis of DCM patients over the last decades, mortality is still high. The prognosis is mainly influenced by HF symptoms and more relevant by the appearance of VTs. Survival data of adults with DCM have shown a one-year mortality of 25–30% and a 50% survival at 5 years. Sustained VT or VF presents the main cause for SCD, which occurs in up to 12% of DCM patients [4, 88]. In general, the prevalence of sustained VT (monomorphic or polymorphic) is estimated as less than 5% [89]. Recently, the Pediatric Cardiomyopathy Registry presented a 5-year incidence rate of SCD in children with DCM of 3% [90]. An age at diagnosis below 14 years, LV dilation, and posterior wall thinning were identified as the most important risk factors. In contrast, the mortality in adults is mostly associated with age and male gender, reduced New York Heart Association (NYHA) functional class, impaired LVEF, and the presence of specific cardiac biomarkers as well as myocardial fibrosis in CMR [91–94]. Furthermore,

genetic aspects play an important role for detection of high-risk patients. Most commonly the pathogenic mutation in the lamin A/C (LMNA) gene is associated with atrial and ventricular arrhythmias. LMNA mutation has been identified as the most malignant and penetrant condition with worse outcomes compared to other forms of DCM [95]. Beside risk models such as the Seattle Heart Failure Model for the prediction of prognosis in the general population of HF patients, there exist no specific risk tools for DCM patients [96]. For the identification of high-risk DCM patients, a personalized and precise approach is required (**Table 3**). This should include the personal and familial history, measurement of LVEF, detailed search for VA and proof of fibrosis using CMR. Other promising approaches are expected to be helpful in decision-making in high-risk DCM patients, determination of microvolt T-wave alternans analysis and detection of autonomic dysfunction using nuclear imaging. In addition, detection of LMNA gene mutation has been described to identify the high-risk DCM population. However, all these approaches need further research.

2.9 Prevention of sudden cardiac death

The most effective therapy of malignant VTs and thus prevention of SCD in DCM patients is the implantation of an ICD. Current ESC guidelines recommend the implantation of a defibrillator in patients who experienced VT or VF (secondary prevention of sudden cardiac death), as well as in high risk patients for primary prevention. The latter are patients with symptomatic HF NYHA class II–III and LVEF ≤35% after ≥3 months of optimal medical therapy who are expected to survive for at least 1 year [97]. Similarly, the American College of Cardiology and American Heart Association guidelines recommend ICD therapy in patients with LVEF ≤35% due to prior myocardial infarction (MI), at least 40 days post-MI, or non-ischemic DCM and NYHA class II or III [98]. However, existing guidelines lack sensitivity and specificity for the selection of patients with DCM for primary prevention ICD implantation. A recently presented meta-analysis by Golwala et al. has demonstrated a 23% reduction in all-cause mortality with ICD therapy compared with optimal medical therapy alone (HR, 0.77; 95% CI, 0.64–0.91) [99]. Although ICD implantation seems to be the best possible option for SCD prevention in DCM, there remain potential complications. Inappropriate shocks, risk of infection, device or lead replacement have to be considered and discussed in detail before an ICD is implanted.

3. Conclusion

DCM includes a heterogeneous group of myocardial and systemic conditions causing left ventricular dilatation and dysfunction. DCM is one of the most common cardiomyopathies worldwide. Yet, the real prevalence is unknown. The etiology contains non-genetic (e.g. myocarditis, peripartum, toxics, arrhythmia, infiltrative etiologies, endocrine, nutritional, and neuromuscular) and genetic causes. Literature on genetic mutations being responsible for DCM has increased exponentially. Today, up to 30% of the DCM cases are described to be caused by a gene mutation, the majority of which occur in autosomal genes that encode for a wide range of proteins of the cardiomyocyte's structural elements. Mutations in genes encoding sarcomeric, cytoskeletal, desmosomal, nuclear membrane, mitochondrial, and RNA-binding proteins have all been linked to DCM. However, the most common mutations occur in genes encoding sarcomeric proteins and in genes related to the nuclear envelope and the

cytoskeleton. Therefore, the diagnostic workup of DCM should involve the clinical tools as well as imaging and gen-technologies. Specific treatment is only available for syndrome-associated DCM. The majority of the DCM patients are treated for HF symptoms, prevention of thromboembolic events, and malign arrhythmias. The prognosis of DCM patients is variable and depends on multiple risk factors. Some, for example, LVEF and NYHA functional class are known for years as risk factors of SCD, others need further research before they can be established in clinical routine.

Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

ACEI	angiotensin converting enzyme inhibitors
AF	atrial fibrillation
AIDS	acquired immune deficiency syndrome
AHA	American Heart Association
ARB	angiotensin receptor blockers
ARVC	arrhythmogenic right ventricular cardiomyopathy
CAD	coronary artery disease
CARP	cardiac ankyrin repeat protein
CK	creatine kinase
CMR	cardiac magnetic resonance imaging
DCM	dilated cardiomyopathy
DES	desmin
ECG	electrocardiogram
EMB	endomyocardial biopsy
ESC	European Society of Cardiology
HCM	hypertrophic cardiomyopathy
HF	heart failure
HIV	human immundeficiency virus
ICD	implantable cardioverter defibrillator
IDC	idiopathic dilated cardiomyopathy
ISFC	International Society and Federation of Cardiology
LAMA4	laminin alpha-4
LINC	links the nucleus to the cytoplasm
LMNA	lamin A/C
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MLP	muscle LIM protein
MYH	myosin proteins
NCCM	non-compaction cardiomyopathy
NIV	non-invasive ventilation
NOAC	non-vitamin K antagonist oral anticoagulant
NYHA	New York Heart Association
PPCM	peripartum cardiomyopathy
RCM	restrictive cardiomyopathy
RNA	ribonucleid acid
RyR2	ryanodine receptor 2

SCD	sudden cardiac death
TPM	troponin-tropomyosin
TNN	cardiac troponin
VA/VT/VF	ventricular arrhythmia/ventricular tachycardia/ventricular fibrillation
WHO	World Health Organization

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