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Cardiovascular complications in patients with idiopathic inflammatory myopathies: does heart matter in idiopathic inflammatory myopathies?

Aleksandra Halina Opinc[1] · Marcin Adam Makowski[2] · Zuzanna Małgorzata Łukasik[1] · Joanna Samanta Makowska[1]

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Abstract
This review presents a detailed study of original researches and previously published reviews concerning cardiovascular involvement in idiopathic inflammatory myopathies (IIM). We aimed to summarize the current knowledge on the cardiac involvement in IIM, evaluate its impact on mortality and indicate areas still awaiting to be investigated. We searched MEDLINE database (until January 2019) and the reference lists of articles. Selection criteria included only published data, available in English, both original researches and reviews. Articles related to cardiovascular involvement in IIM were selected and analysed. The references were also screened, and relevant articles were included. Cardiovascular involvement is frequent in IIM but typically remains subclinical. Among far less prevalent symptomatic forms, congestive heart failure is the most common. Myocardium and conduction system seems to be predominantly affected. High rate of left ventricular diastolic dysfunction was observed. Non-specific changes of ST-T segment were the most common abnormalities in electrocardiography. Patients with IIM were more frequently affected by atrial fibrillation as compared with other autoimmune diseases. Increased risk of myocardial infarction was observed; furthermore, patients often develop comorbidities that enhance cardiovascular risk. Since cardiovascular disorders remain one of the major causes of death and subclinical involvement is frequent, active screening is justified. Growing availability of the novel imaging techniques may facilitate diagnosis. Correlation between myocardial involvement and the type of autoantibodies and impact of different therapeutic options on the progression of cardiovascular lesions require further studies.

Keywords Idiopathic inflammatory myopathy · Dermatomyositis · Polymyositis · Inclusion body myositis · Heart failure · Cardiac

Introduction

Idiopathic inflammatory myopathies (IIM) are rare connective tissue diseases with mean global prevalence ranging from 4.27 to 7.89/100,000 [1]. This group of diseases used to be typically divided into several subtypes such as dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), immune-mediated necrotizing myopathy (IMNM) and overlapping syndromes, common feature of which is muscle inflammation leading to their progressive weakness; however, the skin and internal organs may be affected as well [1–3]. The autoimmune origin is suspected as myositis-specific autoantibodies are detected in the serum of 50–70% patients [2].

Review methodology

A literature search was conducted until January 2019 with the usage of the MEDLINE database. Terms used for searching included 'cardiac' OR 'cardiovascular' OR 'heart' AND 'myositis' OR 'idiopathic inflammatory myopathy'. Only published data were considered including both original studies and reviews available in English. Due to limited published

✉ Joanna Samanta Makowska
joanna.makowska@umed.lodz.pl

Aleksandra Halina Opinc
aleksandra.opinc@gmail.com

Marcin Adam Makowski
drmarmak@gmail.com

Zuzanna Małgorzata Łukasik
zuzanna.lukasik@stud.umed.lodz.pl

[1] Department of Rheumatology, Medical University of Lodz, ul. Pieniny 30, 92-115 Łódź, Poland

[2] Department of Intensive Care, Cardiology, Medical University of Lodz, ul. Pomorska 251, 92-213 Łódź, Poland

data on cardiovascular involvement in patients with idiopathic inflammatory myopathies, authors did not narrow the literature searches to certain years of publication. Abstracts and full articles were read, and the relevant articles with study groups consisting of patients with idiopathic inflammatory myopathies were selected. Articles describing other types of myopathies were excluded. Authors screened also the references in the selected articles, read the relevant articles and included selected publications that filled the inclusion criteria.

Clinical pattern of idiopathic inflammatory myopathies

The most typical symptom of IIM is symmetric muscle weakness, affecting predominantly proximal parts of extremities as well as the neck flexors and the back muscles [2, 4]. Patients report difficulties with daily activities such as climbing stairs, getting up from sitting position and lifting heavy objects [2]. Approximately 1 in 3 patients suffer from myalgia and muscle tenderness [2]. Dyspnoea, as a consequence of respiratory muscle weakness, might emerge with the IIM progression [2, 4–6]. Pharyngeal, laryngeal and oesophageal muscles might also be affected, resulting in dysphagia, dysphonia, dyspnoea, aspiration pneumonia and motility disorders [2, 4, 6]. On the contrary, blurred vision and diplopia due to extraocular muscle weakness are less frequently observed [4]. General symptoms such as febrile states, weight loss and fatigue are frequently reported and so are cases of arthritis and arthralgia, usually affecting distal joints [2, 4, 6]. The most common symptoms of IIM are presented in Fig. 1. Table 1 summarizes the subtypes of inflammatory idiopathic myopathies.

Diagnosis of IIM

The initial diagnosis is usually based on clinical symptoms and additional tests including elevated levels of muscle enzymes such as creatine kinase (CK), myoglobin, lactate dehydrogenase (LDH) and features of muscular damage in electromyography [2, 4, 6]. The final diagnosis is based on both clinical symptoms and the results of additional tests including muscle biopsy, which allow distinguishing between the subgroups of IIM (Table 1); however, it needs to be stressed that it can be falsely negative if the biopsy is taken from non-affected muscle [3, 6, 8]. Magnetic resonance is a novel, promising tool enabling to detect subtle lesions at early-stage myositis and select the area of the potential biopsy. At the early stage of inflammatory myopathy, muscle oedema can be noticed (in PM water retention is limited to muscle tissue itself, in DM can be observed also in the subcutaneous tissue and myofascium), over time muscular tissue is replaced by fatty tissue [7]. Magnetic resonance is also advised as a useful tool to detect cardiac involvement in autoimmune diseases, as it enables to demonstrate myocardial ischaemia, vasculopathy, microvascular abnormalities, myocardial fibrosis, pericardial lesions and myocarditis as well as to determine the aetiology of cardiac dysfunction and distinguish the acute from the chronic phase [10].

Detection of antinuclear antibodies (ANA), especially the so-called myositis-specific autoantibodies like anti-Mi-2, anti-SRP and antisynthetase antibodies (anti-Jo-1, PL-7, PL-12, EJ, OJ, KJ, and Zo), can facilitate the diagnosis of IIM [2, 11]; however, autoantibodies are detected only in 50–70% of the patients [2]. Until the latest discovery of antibodies against cytosolic 5′-nucleotidase (anti-cN1A) in sera of patients with sporadic IBM there was no serum biomarker proving the immune-mediated mechanism of IBM [12].

Some autoantibodies are related to clinical pattern i.e. patients with Jo-1 antibodies often develop interstitial lung disease [2, 5]. Moreover, the type of antibodies may be considered as a prognostic factor as patients with anti-SRP are more resistant to treatment than the patients with anti-Mi-2 autoantibodies [11].

Prevalence of cardiac involvement

Not only skeletal muscles but also the cardiac muscle can be affected in the course of myositis [2, 5]. Although more than 100 years have passed since Oppenheim reported the first case of a PM patient with cardiac muscle involvement, still little is known about the pathogenesis and prevalence of cardiovascular complications in IIM [13, 14]. Recent data suggest a high prevalence of cardiac involvement, as out of 1715 IIM cases reported in the EuroMyositis Registry, the heart was affected in as many as 9% of patients [15]. Noteworthy, according to this registry cardiac complications were observed mostly in overlapping syndromes (12% out of 230 CTD-overlap myositis patients), with the highest prevalence observed in patients with myositis and systemic sclerosis (18%). Contrary, patients with IBM were the least frequently affected by cardiac involvement out of all IIM subtypes, as it occurred only in 4% out of 185 patients with this subtype [15]. Numerous studies indicate that subclinical cardiac involvement in PM/DM patients could be far more frequent than its symptomatic manifestation, as, depending on the study and method used for assessment, prevalence from 13 up to even 72% of patients was reported [14, 16]. Figure 2 summarizes the most common manifestations of cardiac involvement in patients with IIM.

Myocardium and conduction system

In various publications, depending on the method used for assessment, the involvement of the myocardium extends from 9 to 81% of the examined patients [17, 18]. Such discrepancies may result from diversified and often limited number of patients in the study groups, different inclusion criteria to both study and

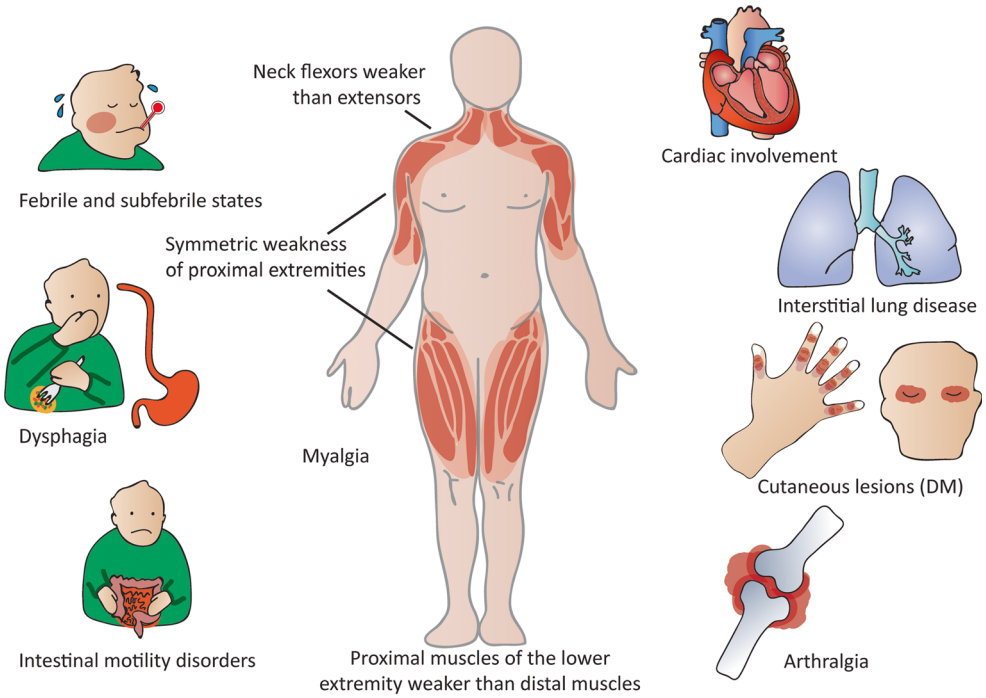

Fig. 1 The most common symptoms of idiopathic inflammatory myopathies. Presented manifestations result from the involvement of both musculoskeletal system and internal organs

control groups, other accepted definition of myocardial involvement or facilitated access to non-invasive methods assessing cardiovascular system as compared with the past years and thus greater recognition of some pathologies in newer studies [19].

Myocarditis

Diagnosis of myocarditis is usually based on clinical and biochemical features, additional examinations and excluding other comorbidities leading to myocardial damage, yet the definite diagnosis can be made based on histopathological findings [20]. In post-mortem studies, inflammation of cardiac muscle was detected in 25–30% of patients with IIM or IIM with concomitant disorders. Interestingly, 67–100% of the patients with IIM or IIM with concomitant disorders, who were diagnosed with myocarditis in post-mortem studies, presented symptoms of congestive heart failure before death, yet it needs to be highlighted that in some cases features of myocarditis were found even if patients did not present cardiac symptoms before death. However, as some of the patients were affected by more than one disease we cannot exclude the possibility that concomitant disorders other than IIM contributed to observed results. Autopsies revealed mononuclear cell infiltrates in the endomysium and myocardial perivascular area as well as degenerative and necrotizing lesions [21, 22]. So far no correlation between PM and DM activity and the presence of myocarditis was stated [20–22]. Magnetic resonance imaging is emerging as a useful and, most of all, a non-invasive tool facilitating the diagnosis of myocarditis [10, 20, 23]. Myocardial enhancement in MRI was found to reflect subclinical involvement of myocardium in patients with myositis more precisely than cardiac muscle scintigraphy or echocardiography [7, 23]. Late gadolinium enhancement (LGE) in cardiac magnetic resonance (CMR) imaging, indicating myocardial fibrosis, was detected in 62.3% of examined patients with PM and DM, mostly in lateral and inferior segments [23]. LGE was confirmed in every patient with reduced ejection fraction but noteworthy also in 54.5% of patients with preserved left ventricular ejection fraction, suggesting that LGE is a more appropriate tool than echocardiography for detecting subclinical lesions [23].

Cardiomyopathy and cardiac remodelling

Cardiomyopathy in the course of IIM manifests typically with left ventricular diastolic dysfunction (LVDD), and echocardiographical lesions indicating diastolic impairment can be found in even 76.5% of patients [24, 25]. Statistically significant correlation was observed between the development of LVDD and the disease duration as well as with the patient's age, the presence of myositis-specific autoantibodies and high uptake of the scintigraphy marker [24]. Dilated cardiomyopathy in the course of IIM can result in the need of myocardial transplant [26]. Increased cardiac load forces adaptive response in a form of myocardial remodelling to uphold the perfusion of the peripheral tissues. However, myocardial remodelling also contributes to progressive dysfunction of the cardiac muscle [10, 23]. Cardiac remodelling leads to hypertrophy and enlargement of heart chambers, which can be observed in electrocardiography (ECG) or echocardiography. Left ventricular hypertrophy or enlargement was reported by non-invasive

Table 1 Comparison between subtypes of idiopathic inflammatory myopathies

Feature	DM	PM	IBM
Muscle weakness	Symmetrical progressive muscle weakness, accompanied by myalgia; proximal muscles of shoulder and pelvic girdle mostly affected, neck flexor muscles weaker than extensors, can affect pharyngeal and oesophageal muscles [2, 4, 6]	Symmetrical progressive muscle weakness, accompanied by myalgia; proximal muscles of shoulder and pelvic girdle mostly affected, neck flexor muscles weaker than extensors, can affect pharyngeal and oesophageal muscles [2, 4, 6]	Distal muscles affected, can be asymmetrical, knee extensors weaker than hip flexors, deep finger flexors, quadriceps muscles, vasti, distal sartorius and medial gastrocnemius are typically affected; later can affect also finger extensors, proximal arm muscles, anterior thigh and ankle flexors; can affect paravertebral, pharyngeal and respiratory muscles, muscle atrophy earlier and more intense than in DM and PM [3, 6, 7]
Skin lesions	Frequent, can include heliotrope rash on eyelids, Gottron papules, erythema localized on upper chest (V-sign, shawl sign) or lateral part of the hips (holster sign), Raynaud's phenomenon, mechanic hands [2, 4, 6]	Possible but not as frequent as in DM [6]	Not observed
Muscle biopsy	CD4+ lymphocytes in the endomysium, perivascular B lymphocytes infiltrates, endothelial hyperplasia of intramuscular vessels, necrosis of muscular fibres, perifascicular atrophy, C5b–9 membrane attack complex in vessel walls leading to vasculopathy, vessels obliterated by thrombi, reduced capillary density [3, 6]	CD8+ cytotoxic T lymphocytes and macrophages infiltrates in the endomysium and perimysium, diffused necrotic and regenerating muscle fibres, possible involvement of non-necrotic muscle fibres, increased expression of MHC I on the surface of myocytes [3, 6]	CD8+ cytotoxic T lymphocytes infiltrates in the endomysium of non-necrotic fibres, vacuolated muscle fibres with accumulation of basophils (rimmed vacuoles), degenerative lesions such as protein and b-amyloid aggregation, mitochondrial lesions, p62 deposits [3, 6, 8]
Muscle MRI	Patchy muscle oedema, oedema also in subcutaneous and myofascial area, followed by degenerative lesions such as fatty infiltrates and muscular atrophy; quadriceps femoris, ileopsoas and the pectineus affected more frequently than in PM [6]	Diffuse muscle oedema, followed by degenerative lesions such as fatty infiltrates and muscular atrophy [6]	Fatty infiltrates and muscular atrophy located in distal parts of limbs, the most affected are: the quadriceps muscle with a "melted" image (but rectus femoris muscle not affected), flexor digitorum profundus muscle, the medial gastrocnemius muscle; typically anterior compartment affected more than posterior in the distal part of thigh [8]
Response to treatment	Various	Various	Poor [9]

DM dermatomyositis, *PM* polymyositis, *IBM* inclusion body myositis, *MHC I* major histocompatibility complex I

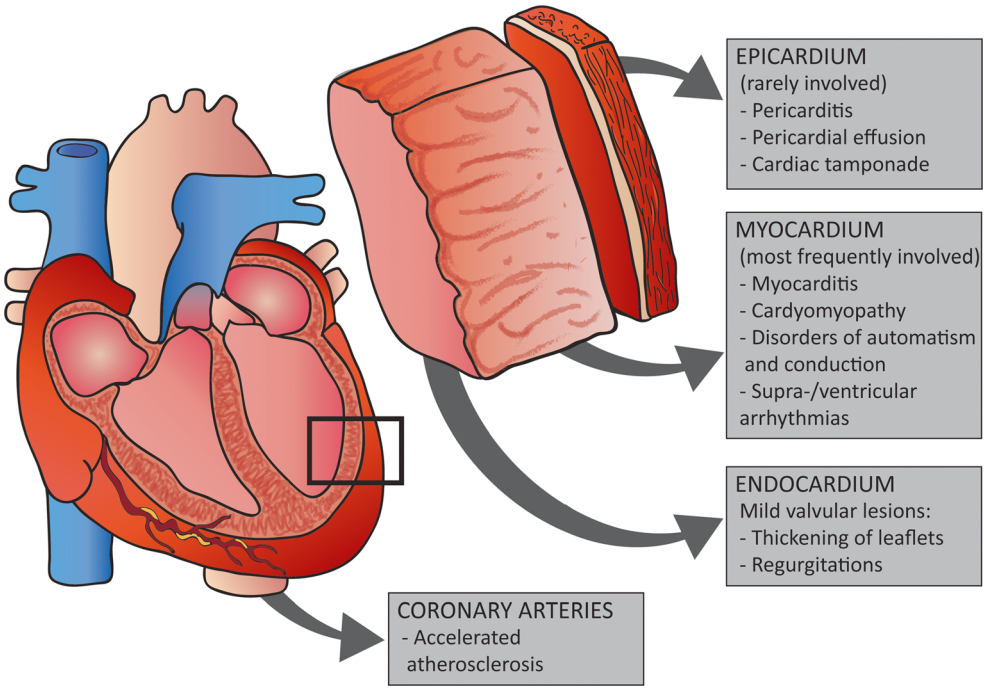

Fig. 2 The most common manifestations of cardiac involvement in patients with idiopathic inflammatory myopathies divided according to the affected layer of the heart wall

methods in 2.6–15.38% of patients [17, 27–30]; left atrium enlargement was seen in 7.69–15% cases [18, 29, 30]. Right ventricular hypertrophy or enlargement affected up to 4% of patients [18, 28], while right atrium enlargement occurred in 7.69% cases [30]. Besides, 58.5% of patients with IIM presented early myocardial enhancement on T1-weight imaging that correlated with right ventricular hypertrophy [23].

Disorders of automatism and conduction

According to literature, the prevalence of first-degree atrioventricular block ranges from 2.2 to 15% of patients [18, 24, 27, 28, 31], and in a single study, second-degree atrioventricular block occurred in 4% of patients [18], while complete block in 2.2% [31]. It is probable that conductive disorders in patients with IIM are predominantly caused by disturbances in ventricular conduction, as the frequency of right bundle branch block ranged from 0.9 to 9.52% (in children population even up to 21.43%) [18, 28, 31–34]. Left bundle branch block (LBBB) was observed less frequently as in 0.9–2.6% of patients [27, 28, 35], since if we consider studies that mention Hiss bundle branch blocks in general the prevalence can range from 0.9 to 10% [27, 28, 31, 32, 35]. Left anterior hemiblock (LAH) was described in 4–13% of examined patients, but that observations were based on single studies with limited study groups [18, 27]. Non-specific intraventricular conduction delay (IVCD) was noted in 1.3–15% of patients [18, 27]. Non-specific ST-T or T-wave changes were the most frequently observed pathologies in ECG. Prevalence of those abnormalities ranged from 12.5 to even 63.63% of cases and in numerous studies was highlighted as the predominant ECG manifestation [18, 28–33]. Sinus bradycardia and sinus tachycardia, which could possibly indicate disturbances of automatism, were noted respectively in 7.69–9% (bradycardia) and 23.07% (tachycardia) of patients with IIM, yet studies on that topic are limited [29, 30]. Cases of pacemaker implantation in the course of IIM were reported [36, 37].

Fibrosis could lead to both conduction disturbances and supraventricular or ventricular arrhythmias [13]. Besides, observations from the authors' clinical practice indicate that it may hinder invasive treatment such as ablation. Myocardial fibrosis was detected in 1 out of 4 autopsies with fibrosis affecting the conductive system in approximately 20% of cases [21, 22]. Extensive inflammatory-induced fibrosis was also reported in a case of a man, in whom the post-mortem study revealed the coexistence of atherosclerotic foci with fibrosis of all of the heart chambers and intraventricular septum [37].

Arrhythmia

Supraventricular arrhythmia Atrial fibrillation (AF), which is itself an independent risk factor of cardiovascular and cerebrovascular events such as ischaemic stroke, occurred in 0.9–4.76% of patients with IIM [24, 27, 28, 34, 38]. According to Baek et al., out of all autoimmune rheumatic diseases, patients with IIM were most frequently affected by AF as it was observed in 3.5% of 343 patients [38]. Ectopic atrial rhythm was observed in 1.8–4.76% cases of IIM, and sinus arrhythmia was reported in 2.7% of ECGs [28, 30]. Supraventricular extrasystoles affected 0.9% of patients from a single study [33], while the frequency of supraventricular tachycardia varied from 0.9 to 12% of myositis patients [18, 28, 35].

Ventricular arrhythmia Prevalence of premature ventricular complexes and ventricular extrasystoles vary significantly depending on the study and was observed from 1.3 to even 69% of patients [18, 27, 28, 34, 35]. A single observation of nonsustained ventricular tachycardia was stated in 1 out of 22 patients with myositis [18]. Such discrepancies in ranges of frequency may origin in unequal and often limited study groups. Further investigations on large study groups are required to reliably assess those abnormalities.

Heart rate variability Heart rate variability (HRV) based on ECG Holter monitoring, which indicates the influence of the autonomic nervous system on heart rate, was found to be decreased in patients with juvenile dermatomyositis. Those observations could imply impaired autonomic control in IIM patients [39]. Studies on HRV in the adult population are required.

Clinical manifestations of myocardial involvement

Symptomatic cardiac involvement in the course of myositis occurs less frequently than its subclinical manifestation [40]. According to literature, in patients with IIM, who have symptomatic course of cardiac involvement, it usually manifests as congestive heart failure (CHF). The prevalence of CHF was assessed as 3–45% in older studies; review of 26 publications estimated the frequency of this disorder as even up to 77% of IIM patients [14, 17, 19]. Original publications evaluating the prevalence of congestive heart failure are summarized in Table 2. In a study conducted on 76 IIM patients, the prevalence of non-specific symptoms, which may possibly reflect cardiac involvement, was surprisingly high. Even 57% of IIM patients complained of dyspnoea and 34% reported palpitations [24]. Cases of patients with IIM suffering from orthopnoea, chest pain, ischaemic pain, peripheral oedema, dry cough, dizziness and syncope were also reported [13, 14, 18]. Recently, a single small study ($n = 26$) reported symptomatic myocardial involvement in 62% of patients [18]. The main limitation that prevents from stating define conclusions is that many of the original publications refer to less advanced diagnostic or therapeutic tools and therefore could be perceived as outdated. Moreover, the groups of patients gathered for these studies are of limited size and frequently comprise of individuals at different stages of the disease or with concomitant diseases other than IIM. State-of-the-art imaging technologies should be employed to carry out more accurate epidemiological studies.

Endocardium and pericardium

Valvular disease

Valvular lesions in patients with IIM are usually mild and do not require surgical treatment. Thickening of valvular leaflets was observed in 23.07–46.7% of patients [30, 41]. The prevalence of mitral prolapse varied significantly from 8 to 65% [18, 34]. Cases of valvular regurgitations were also described [30].

Pericardium

Pericarditis, pericardial effusion and tamponade are rarely reported in patients with IIM and seem to be less prevalent compared with other connective tissue diseases [42]. Nevertheless, cases of patients with severe pericardial involvement were reported even as the first manifestation of IIM [43, 44].

Increased risk of cardiovascular events

Accelerated atherosclerosis and myocardial infarction

The risk of developing coronary artery disease in PM/DM patients has been described as at least 3-fold higher than in the general population, and it remained increased even after 10 years post the first hospitalization for IIM [45]. Data from the Healthcare Cost and Utilization Project Nationwide

Table 2 Prevalence of congestive heart failure in patients with idiopathic inflammatory myopathies

Author	Patients (*n*, diagnosis)	Congestive heart failure *n* (%)	Year of publication	Ref. number
Bohan et al.	153 PM/DM*	5 (3.27%)	1977	[31]
Oka et al.	16 PM*	4 (25%)	1978	[36]
Denbow et al.	20 PM*	9 (45%)	1979	[22]
Haupt and Hutchins	16 PM/DM*	7 (44%)	1982	[21]
Hochberg et al.	76 PM/DM*	18 (24%)	1986	[32]
Baek et al.	343 IIM*	8 (2.3%)	2017	[38]

PM polymyositis, *DM* dermatomyositis, *IIM* idiopathic inflammatory myopathies, *n* number of patients

*Diagnosis included IIM or IIM with other concomitant autoimmune diseases or IIM with neoplasm

Inpatient Sample for the period of 1993–2007 stated that 20% out of 50,322 hospitalizations of DM patients were associated with concomitant atherosclerotic disease; thus, the prevalence of atherosclerosis seems to be comparable to the general population [46]. However, the coexistence of DM and cardiovascular disease with atherosclerotic compounds significantly worsened the prognosis both for DM and for cardiovascular diseases [46]. In this study, odds ratio of death was twice as high for patients with DM and concomitant cardiovascular disease when compared with control groups suffering only from cardiovascular disease or only from DM [46]. In PM/DM patients, similarly to the general population, lipid disorders and hypertension were strongly associated with the occurrence of vascular incidents [47]. Frequency of myocardial infarction was evaluated in two retrospective analyses of 607 and 774 patients with IIM and was stated as 13.8–22.52/1000 persons/year (in the control group respectively 5.50/1000 persons/year) [47, 48]. The risk of myocardial infarction is the highest within the first year after the diagnosis of PM but remains elevated during the following 5 years after the diagnosis [48]. In a single study, the risk of myocardial infarction was higher than in the general population for both women and men with PM/DM older than 65 years old, but for a group of younger PM/DM patients that risk was elevated only in women [47]. During the 2-year follow-up of 907 patients with DM, 1.5% of them manifested with myocardial infarction, while it was reported only in 0.4% of the control group [49]. In a single study, mortality caused by myocardial infarction was 16 times higher than expected, with an increased risk of death observed especially among female PM patients (32 times higher than in the general population); however, some of the patients had other concomitant diseases apart from PM what could contribute to the results. Furthermore, as the study was performed a long time ago, the mortality caused by myocardial infarction could be associated more with low availability of effective methods of treatment rather than the diagnosis of PM itself [50].

Coronary arteriopathy and vasculopathy

Non-ischaemic lesions in coronary arteries such as vasculitis, media proliferation, vessel walls sclerosis and calcification were detected in 31% of the post-mortem examinations of patients with IIM or IIM with concomitant diseases [21]. In some cases, features of previous myocardial infarction and narrowed lumen of coronary arteries were detected [22, 36]. An extraordinary case of a patient affected with DM, Raynaud syndrome and concomitant Prizmetal's angina was reported [51]. Abnormalities of microcirculation lead to recurrent ischaemia and decreased perfusion of the cardiac muscle, which manifests in CMR imaging as diffuse fibrosis [10]. Patients with PM/DM are also at greater risk of venous thromboembolism (both deep vein thrombosis and pulmonary embolism), especially within the first year after the diagnosis [52, 53].

Cerebrovascular events

The incidence rate of ischaemic stroke within the first year after the diagnosis of PM/DM was estimated to be at least twice as high as in the general population [54, 55]. However, in another study, no differences were observed as for the prevalence of ischaemic stroke among patients with IIM and the general population [48]. The risk of cerebrovascular haemorrhagic stroke seems to be comparable to the risk observed in the general population [55].

Comorbidities related to increased cardiovascular risk

Patients with IIM frequently suffer from comorbidities that are considered as independent risk factors of cardiovascular incidents. The higher incidence of hypertension (28.7–71% of patients), hyper- or dyslipidaemia (12.8–48%) and diabetes (13–37% of patients) was reported in IIM compared with control groups [24, 28, 35, 38, 56]. In a study based on Taiwanese National Health Insurance database diabetes, hypertension, hyperlipidaemia, coronary heart disease, chronic rheumatic heart disease and other heart diseases were more frequently observed in DM patients than in the control population [49]. Interestingly, in the majority of PM patients, hypertension and ischaemic heart disease were diagnosed earlier than myopathy, which indicates that the observed comorbidities are not only the consequence of glucocorticosteroid intake [56].

Pulmonary hypertension

In the course of DM, pulmonary hypertension was firstly reported in 1956, but since that time, prevalence of this abnormality in patients with IIM was rarely assessed [57, 58]. Pulmonary arterial hypertension was found to be less prevalent in individuals with IIM than in patients with systemic sclerosis, systemic lupus erythematosus, mixed connective tissue disease and rheumatoid arthritis but more frequent than in patients with undifferentiated connective tissue disorder or Sjogren syndrome [59]. It was diagnosed in 16.39% of 67 patients with PM and a frequent coexistence of pulmonary hypertension, interstitial lung disease and pericardial effusion was observed [60]. In patients with concomitant symptoms of scleroderma, pulmonary hypertension is also usually accompanied by interstitial lung disease [57]. Pulmonary hypertension significantly worsens the prognosis for patients with IIM; several fatal cases were described [58, 61]. According to literature, the frequency of pulmonary hypertension might depend on the type of detected autoantibodies, as it occurred, in 8% of anti-aminoacyl tRNA synthetase (anti-ARS)-positive

patients while in particular even 29% of IIM patients with anti-PL7 antibodies [57]. Researchers found that isolated arterial pulmonary hypertension, not associated with interstitial lung disease, could be more common in anti-SSA-positive DM patients with cutaneous lesions or dysfunction in small peripheral vessels [62].

Diagnosis of cardiac involvement

Electrocardiography and imaging techniques

Tables 3 and 4 present the most common abnormalities observed in ECG and echocardiography based on original publications. However, the majority of studies assessing echocardiographic or ECG lesions are either old or performed on limited study groups; therefore, further studies with the use of contemporary protocols and on large study groups are required in order to form reliable conclusions. So far, to the best of our knowledge, no correlations were found between the presence of ECG abnormalities and disease activity, CK levels, clinical symptoms or patients' age [27]. Noteworthy, there is a growing role of novel techniques such as cardiac magnetic resonance imaging, scintigraphy of cardiac muscle or speckle-tracking echocardiography [10, 20, 63]. It can be assumed that the use of such new technologies will contribute to a more accurate evaluation of cardiac involvement and will increase the number of subclinical diagnoses. With the use of scintigraphy-based techniques, abnormal marker uptake was observed in up to 57% of the examined patients [20].

Biochemical markers

Markers of myocardial damage Elevated levels of muscle enzymes, released into serum due to myocyte damage such as creatine kinase, lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase, are one of the hallmarks of myositis and therefore were included in the 2017 EULAR/ACR (European League Against Rheumatism/American College of Rheumatology) classification criteria for adult and juvenile IIM [64]. Cardiac troponin I (cTnI) derive only from myocardium, while cardiac troponin T (cTnT) may originate from regenerating skeletal muscle and therefore falsely suggest cardiac involvement in patients with isolated myopathy [65–67]. Similarly, expression of muscle-brain isoform of creatine kinase (CK-MB), usually associated with cardiac damage, is now believed to increase in regenerating skeletal muscles [67]. When assessing the usefulness of individual parameters for cardiac prediction, it should be noted that cardiac involvement was confirmed in 23% of patients with abnormal total creatine kinase (CK), 21% of patients with abnormal cTnT, but even 62% of patients with abnormal cTnI [68]. Elevated levels of cTnT were found in 41–78% of patients with IIM, while in the same group of patients only 2–2.5% presented increased cTnI [65, 66]. In another study, abnormal levels of CK in total were detected in 61% of cases, cTnT in 83% and cTnI in 44% of patients [68]. Cases of patients without cardiac involvement and increased cTnT were reported [66]. Researchers suggest that increased cTnT in patients without cardiac involvement may be associated with a severe course of myositis [69]. Yet even though cTnT is less specific, it is advised to start the assessment with this enzyme and in case of elevated concentration measure also cTnI [66]. A close correlation was stated between levels of CK/CK-MB and cTnT but not between CK and cTnI [66, 67]. However, such correlation was not confirmed in another study, in which both concentration and kinetics of CK and cTnT were not related [69]. Such inconsistent data can be explained by the fact that in patients with muscle inflammation or degeneration it is not easy to form reliable conclusions as cardiac and muscular lesions may interfere and alter the final levels of cardiac muscle-associated enzymes. Besides, those markers lack sensitivity and specificity, as high troponins can be observed in various conditions leading to damage of cardiomyocytes including ischaemia, heart failure, pulmonary embolism or even non-cardiac conditions such as for instance subarachnoid haemorrhage, renal failure or side effects of pharmacotherapy [65, 66]. It requires further examinations, whether those enzymes could serve as a marker of cardiac involvement or rather indicator of muscular regeneration.

Markers of cardiac failure Brain natriuretic peptide (BNP) or N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were so far rarely evaluated in patients with myositis, and only a few studies based on limited study groups displayed elevated levels of those markers in patients with IIM and dysfunctional heart [65]. Researchers stated also that both BNP and CK serum levels were significantly higher in cases of PM complicated by congestive heart failure as compared with isolated PM. In this study, higher BNP concentrations were observed in patients with reduced left ventricular ejection fraction as compared with patients with preserved ejection fraction. A decrease in elevated levels of BNP after therapy was more noticeable in patients with concomitant PM and heart failure as compared with isolated PM [70].

Predictive factors of cardiovascular involvement

Correlation between the presence of anti-Ro antibodies and myocardial involvement was investigated by Behan et al. On a group of 55 PM patients, cardiac involvement was reported in 60% of patients, yet 69% of those with cardiac complications were anti-Ro positive. The presence of this type of antibodies seems to be associated with conductive disturbances, as in that study 80% of patients with complete heart block were anti-Ro

Table 3 Abnormalities in electrocardiography in patients with IIM

Author	Study group *n*, diagnosis	Abnormalities *n* (%)	Type of abnormality	Year of publication	Ref. number
Devere and Bradley	95 PM*	35 (37%)	Non-specific changes of T wave, left ventricular hypertrophy and LBBB, right ventricle hypertrophy and RBBB, atrial ectopic extrasystolia, atrial fibrillation, AV I block, intraventricular conduction abnormalities—no data for prevalence of each abnormality available	1975	[50]
Bohan et al.	153 PM/DM*	3–31 (2.2–23.1%)	Changes of ST-T segment (23.1%), arrhythmia (6%, no precise data available), changes of Q wave (6%), Hiss bundle branch blocks (5%), complete heart block (2.2%), PR elongation (2.2%)	1977	[31]
Oka et al.	16 PM*	11 (68.75%)	Rhythm disorder (50%), conduction disorders (18.5%)—no precise data available	1978	[36]
Gottdiener et al.	21 PM	11 (52%)	Atrial fibrillation (4.76%), ectopic atrial rhythm (4.76%), ventricular premature complexes (19.05%), left axis deviation or left atrial abnormalities (19.05%), RBBB (9.52%)	1978	[34]
Stern et al.	77 PM*	25 (32.5%)	LAH (13%), RBBB (9.1%), LBBB (2.6%), left ventricular hypertrophy (2.6%), poor R wave (2.6%), IVCD (1.3%), Frequent PVCs (1.3%), Atrial fibrillation (1.3%), AV I grade block in follow-up (1.3%)	1984	[27]
Hochberg et al.	76 PM/DM* (56 definite, 20 probable diagnosis)	Up to 25 (33%)	Changes of ST-T segment (33%), Hiss bundle branch blocks (10%)—no date on types of abnormality available	1986	[32]
Hebert et al.	11 PM*	9 (81.81%)	Non-specific changes of ST-T segment (63.63%), right atrium enlargement (9%), left atrium enlargement and history of myocardial infarction (9%), left ventricle enlargement (9%), RBBB (9%), sinus bradycardia (9%)	1990	[29]
Byrnes et al.	13 IIM*	11 (84.61%)	Non-specific changes of ST-T segment (61.54%), left ventricular hypertrophy (15.38%), myocardial infarction pattern (15.38%), sinus tachycardia (23.07%), poor precordial R wave progression (7.69%), left atrial enlargement (7.69%), right atrial enlargement (7.69%), sinus bradycardia (7.69%), pacemaker (7.69%)	1991	[30]
Taylor et al.	26 PM*	22 (85%)	Non-specific changes of ST-T segment and changes in T-wave morphology (58%), non-specific intraventricular conduction abnormalities (15%), AV I degree block (15%), RBBB (4%), LAFB (4%), enlargement of left ventricle (15%), enlargement of left atrium (15%), enlargement of right ventricle (4%), enlargement of right atrium (4%), premature ventricular contractions (69%), poor R-wave progression (12%), low voltage (4%), paroxysmal supraventricular tachycardia (12%), nonsustained ventricular tachycardia (4%), AV II degree block (4%)	1993	[18]
Na et al.	48 DM* adults	11 (22.9%)	RBBB (6.25%), changes of ST-T segment (12.5%), tachyarrhythmia (4.17%)	2009	[33]
	16 DM* children (ECG done in 14)	6 (37.5%)	RBBB (21.43%), changes of ST-T segment (21.43%)		
Deveza et al.	112 (78 DM, 34 PM)*	37 (33%)	Ventricular extrasystoles (2.7%), sinus arrhythmia (2.7%), atrial fibrillation (0.9%), atrial ectopic rhythm (1.8%), AV I block (2.7%), supraventricular tachyarrhythmia (0.9%), SV extrasystole (0.9%), LV hypertrophy (10.7%), RV hypertrophy (0%), LA hypertrophy (4.5%), RA hypertrophy (0%), ASDBB (4.5%), RBBB (0.9%), LBBB (0.9%), diffuse ventricular repolarization changes (12.5%)	2016	[28]
Zhong et al.	60 PM/DM	No data	Paroxysmal supraventricular tachycardia (1.6%), ventricular extrasystole (1.6%), complete LBBB (1.6%), higher heart rates and longer mean QTc intervals compared with controls ($P = 0.012$ and $P = 0.001$), similar PR intervals and QRS duration	2017	[35]
Baek et al.	343 IIM*	12 (3.5%)	Atrial fibrillation (3.5 to >16.7% paroxysomal, 83.3% non-paroxysomal)	2016	[38]
Diederichsen et al.	76 PM/DM	14 (18%)	AV I degree block (5%), QRS > 120 msec (4%), prolonged QTc (5%), atrial fibrillation (1%), supraventricular tachycardia in 48 h (47%), ventricular tachycardia in 48 h (1%)	2016	[24]

DM dermatomyositis, *PM* polymyositis, *IIM* idiopathic inflammatory myopathies, *n* number of patients, *RBBB* right bundle branch block, *AV* atrioventricular, *LAH* left anterior hemiblock, *LBBB* left bundle branch block, *IVCD* intraventricular conduction delay, *PVCs* premature ventricular contractions, *LAFB* left anterior fascicular block, *LA* left atrium, *RA* right atrium, *ASDBB* anterosuperior divisional branch block

*Diagnosis included IIM or IIM with other concomitant autoimmune diseases or IIM with neoplasm

Table 4 Abnormalities in echocardiography in patients with IIM

Author	Study group	Abnormalities *n* (%)	Type of abnormality	Year of publication	Ref. number
Gottdiener et al.	21 PM (ECHO in 17)	11 (65%)	Mitral valve prolapse (65%), slight pericardial effusion (4.76%), significant increase in cardiac output without enlargement of left ventricle, hypertrophy of left ventricle walls or left atrium enlargement	1978	[34]
Hebert et al.	11 PM*	7 (63.63%)	Suspected pulmonary hypertension in 63.63%	1990	[29]
Byrnes et al.	13 IIM*	9 (69.23%)	Pulmonary hypertension (69.23%), thickening of valvular leaflets (23.07%), pleural effusion (15.38%), tricuspid regurgitation (7.69%), left ventricular hypertrophy (15.38%), left atrial enlargement (7.69%), left ventricle enlargement (7.69%)	1991	[30]
Taylor et al.	26 PM*	11 (42%)	Small pericardial effusion (12%), left atrial enlargement (12%), dilated left ventricle (8%), left ventricle systolic hypokinesia (12%), right ventricle hypertrophy (4%), mitral valve prolapse (8%), moderate tricuspid regurgitation (4%), mild mitral regurgitation (8%)	1993	[18]
Wang et al.	51 DM	39 (76.5%)	E/Em elevation (76.5%) significant differences between DM and controls: E/Em, A, E/A ratio, Em, Em/Am ratio, deceleration time	2004	[25]
Plazak et al.	15 PM/DM	7 (46.7%)	Thickening of the mitral/aortic valvular leaflets (46.7%), pulmonary wedge pressure higher in study group vs control group (13.2 ± 2, 5 vs 9.2 ± 3.7 mmHg)	2011	[41]
Diederichsen et al.	76 PM/DM	9 (12%)	Systolic dysfunction-LVEF < 50% (8%), diastolic dysfunction (e′ < =10 cm/s (63%), abnormal E/e′ (7%), cor pulmonale (5%), LVDD (12%)	2016	[24]
Zhong et al.	60 PM/DM	28 (47%) to 35 (58%)	Abnormal LVGLS (47%), abnormal RVLS (58%), LV E/e′ ratio (as a marker of LVDD) significantly higher in IIM patients compared with control group, LVDD (7%)	2017	[35]
Guerra et al.	28 IIM	12–21 (42.9–75%)	E/A ratios: mild LVDD (75%), mild RVDD (60.7%, insignificant when compared with control group), impaired LVGLS (57.1%), impaired RVGLS (42.9%)	2017	[63]

DM dermatomyositis, *PM* polymyositis, *IIM* idiopathic inflammatory myopathies, *n* number of patients, *ECHO* echocardiography, *E* mitral peak of early diastolic velocity, *Em* mitral annular early diastolic velocity, *A* late diastolic flow velocity, *Am* late diastolic velocity, *LVEF* left ventricle ejection fraction, *LVDD* left ventricle diastolic dysfunction, *e′* early diastolic tissue velocity, *E/e′* early diastolic transmitral flow/early diastolic tissue velocity, *LVGLS* left ventricular global longitudinal strain, *RVLS* right ventricular longitudinal strain, *RVDD* right ventricle diastolic dysfunction, *RVGLS* right ventricular global longitudinal strain

*Diagnosis included IIM or IIM with other concomitant autoimmune diseases or IIM with neoplasm

positive. Moreover, anti-Ro antibodies were detected in 75% of patients with first-degree AV block and in 1 out of 3 cases of LBBB or RBBB. On the contrary, 30% of anti-Ro-positive patients presented no features of cardiac involvement [71]. Anti-SRP antibodies are also suggested to be associated with cardiac complications as in a study based on 12 anti-SRP-positive PM patients 25% of them presented arrhythmia and 1 out of 12 patients manifested with cardiomyopathy [13]. In a study based on 23 anti-SRP-positive PM patients, dyspnoea at exercise, peripheral oedema and chest pain were reported respectively by 34%, 17% and 8% of patients; however, no statistically significant differences were found between study group and control group (consisting of anti-SRP-negative PM patients) [72]. Recently, anti-mitochondrial antibodies (AMA) were described in patients with myositis, and AMA-positive phenotype is now suggested to be associated with cardiac involvement [73, 74]. Maeda et al. estimated prevalence of AMA in a group of 212 myositis patients as 11.3% [73]. Their study revealed that cardiac involvement is significantly more prevalent if anti-mitochondrial antibodies are present (33% in AMA positive group vs 9% in AMA negative group) and that patients with primary biliary cirrhosis are more prone to cardiac complications. However, as some of the patients included in this study were diagnosed also with overlapping autoimmune diseases or malignancies, the results could be related not only to myositis. Besides, as compared with AMA-negative patients, AMA-positive group had a longer disease duration, and at the time of diagnosis, features of muscular atrophy were more common if AMA were present [73]. Myocarditis, arrhythmia and cardiomyopathy affected 71% out of 7 AMA-positive patients with myositis (3 out of 7 patients had concomitant disorders such as primary biliary cirrhosis, autoimmune hepatitis, psoriasis or Hashimoto's thyroiditis) in another study [74]. A case of a patient with atrial

flutter, intraventricular conduction disturbances and positive late gadolinium enhancement in CMR was also described as AMA-positive myositis [75].

Treatment of patients with IIM and cardiovascular involvement

Since there are no randomized controlled trials comparing the effectiveness of different medications in IIM, current treatment is based on experts' opinion and cases rather than guidelines. Glucocorticosteroids are considered as first-line therapy, leading to a reduction in musculoskeletal symptoms in 60% of patients, but at the same time bringing plenty of side effects like among others hypertension (due to persistent fluid retention), diabetes and dyslipidaemia that contributes to increased cardiovascular risk [9]. In many patients, monotherapy with glucocorticosteroids is not sufficient and immunosuppressants are added [9]. While IBM is progressive and resistant to immunosuppressive treatment, PM and DM respond at least partially to glucocorticosteriods and immunosuppressive agents [9]. However, to the best of our knowledge, there were no studies comparing the influence of glucocorticosteroids or other treatment options on cardiac symptoms. Researchers remain inconsistent whether cardiac disorders improve after treatment [14, 27]. In a single study, steroid therapy led to an improvement of cardiac disorders but only in 2 paediatric patients with PM (at first examination ECG abnormalities were detected in 4 out of 13 children), in contrary in adult patients such therapy did not prevent progression (at first examination ECG abnormalities were detected in 21 adult patients out of 64) [27]. On the other hand, in a case report of a patient with DM and Raynaud syndrome, cardiac symptoms such as palpitations, vertigo and exertional dyspnoea, as well as ECG abnormalities such as multifocal atrial tachycardia, premature ventricular excitations and Mobitz block, withdrew after treatment with rituximab and glucocorticoids [76]. Study based on CMR examination performed in 4 patients (including 2 patients with PM, 1 patient with DM, 1 patient with systemic sclerosis-polymyositis overlap syndrome) showed in each patient areas of early and delayed enhancement which significantly reduced after treatment as well as hypokinesis of the myocardium, which normalized after 6 months of therapy with glucocorticosteroids and immunosuppressant [20]. Another study demonstrated an inverse correlation between the incidence of vascular events and the use of azathioprine [47]. Due to limited study groups, further studies are required, especially in a form of randomized controlled trials.

Cardiovascular involvement as a cause of death

Numerous studies list myocardial involvement as an unfavourable prognostic factor [36, 47, 48, 77, 78]. A poorer 8-year survival was observed in patients with cardiac lesions in the course of PM/DM when compared with patients without myocardial involvement [77]. In the course of IIM, cardiovascular diseases are the third most common cause of death [17, 27, 31, 40, 77–82], after pulmonary diseases and neoplasms [36, 77, 78, 82]. Depending on the study, cardiac or vascular lesions accounted for from 6.12% to even 55% of deaths in myositis patients [40, 78–83]. Noteworthy, in prospective studies, congestive heart failure occurred in 5.6% of myositis patients but this percentage accounted for over 1/5 of deaths

Table 5 Causes of death in patients with IIM

Author	Study group	Deaths *n* (%)	Causes of mortality	Year of publication	Ref. number
Bohan et al.	153 PM/DM*	21 (13.7%)	Neoplasm (23.8%), sepsis (19%), cardiovascular (9.5%), cerebrovascular (9.5%), muscle weakness (9.5%), gastrointestinal perforation (4.8%)	1977	[31]
Maugars et al.	69 PM/DM*	30 (42.48%)	Cardiovascular (26.67%)	1996	[81]
Sultan et al.	46 IIM*	6 (13%)	Cardiovascular (50%)	2002	[83]
Dankó et al.	162 IIM*	20 (12.35%)	Cardiovascular (55%), pulmonary (55%), gastrointestinal (5%), neoplasm (5%). Overlapping syndrome ($n = 3$): cardiovascular (100%)	2004	[78]
Marie	160 PM/DM	27 (16.88%)	Cardiovascular (22%), pulmonary (22%), infectious (15%), neoplasm (11%)	2012	[77]
Marie	197 DM	53 (26.9%)	Interstitial lung disease (37.7%), neoplasm (28.3%), congestive heart failure (7.5%)	2012	[77]
Danieli et al.	91 (43 PM, 48 DM)*	22 (24.18%)	Cardiovascular (13.64%)	2014	[79]
Xiao et al.	676 IIM	49 (7.2%)	Infectious (69.39%), neoplasm (8.16%), viral hepatitis (6.12%), myocardial infarction (4%), interstitial lung disease (4%), arrhythmia, pneumothorax, ventilation disorders, pulmonary hypertension, gastrointestinal bleeding, liver failure, renal failure (each 2%)	2016	[82]

PM polymyositis, *DM* dermatomyositis, *IBM* inclusion body myositis, *n* number of patients

*Diagnosis included IIM or IIM with other concomitant autoimmune diseases or IIM with neoplasm

due to cardiac involvement [13, 14]. Other causes of deaths related to cardiovascular lesions included cardiac arrest, myocardial infarction, arrhythmia, complete heart block, obstructive cardiomyopathy and myocardial necrosis [14, 17, 27, 83]. Nonetheless, other factors such as male sex, interstitial lung disease, arthritis and age of above 65 years at diagnosis are associated with increased risk of fatal outcome [78–80]. Non-cardiac causes of death in PM/DM patients include respiratory diseases, neoplasm, infections and sepsis as well as gastrointestinal complications [31, 77, 78]. Interestingly, pulmonary complications usually occurred within the first 12 months after the diagnosis, while majority of deaths due to cardiovascular involvement were reported after 5 years of disease duration [78]. Main causes of death in IIM patients with the prevalence of fatal myocardial involvement are presented in Table 5.

Conclusions

Myocardial involvement in patients with idiopathic inflammatory myopathies occurs frequently and significantly worsens the prognosis. Connective tissue diseases including idiopathic inflammatory myopathies should be considered in the differential diagnosis if a patient presents cardiac ailments and concomitant non-specific musculoskeletal or cutaneous symptoms. Cardiovascular disorders remain one of the major causes of death in PM/DM patients with significantly elevated risk of myocardial infarction, coronary artery disease and thromboembolism. Implementing effective methods of treatment can improve the prognosis. Due to the high frequency of subclinical disturbances, cardiovascular assessment in individuals with IIM seems to be necessary and justified, even in asymptomatic patients. Widely available, non-invasive tests assessing morphology and function of the cardiovascular system, such as ECG or echocardiography, as well as novel methods such as CMR allow to detect abnormalities at an early stage and thus prevent further progression. Correlation between myocardial involvement and the type of autoantibodies requires further studies, as detailed research in this area might enable to identify a group of patients that could benefit from special cardiovascular alertness. Another area requiring a more detailed analysis is the impact of different ways of treatment on the progression of cardiovascular lesions, which could help to implement effective methods of therapy for patients with myopathy and myocardial involvement.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval and consent to participate This article does not contain any studies with human participants or animals performed by any of the authors.

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