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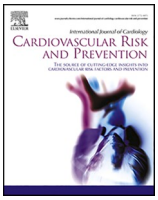

Diabetic cardiomyopathy: pathophysiology, imaging assessment and therapeutical strategies

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ABSTRACT

Diabetes mellitus (DM) is one of the most prevalent cardiovascular risk factors in the general population, being associated with high morbidity and socioeconomic burden. Diabetic cardiomyopathy (DCM) is a non-negligible complication of DM, whose pathophysiological fundaments are the altered cardiac metabolism, the hyperglycemia-triggered formation of advanced glycation end-products (AGEs) and the inflammatory milieu which are typical in diabetic patients. These metabolic abnormalities lead to cardiomyocytes apoptosis, interstitial fibrosis and mechanical cardiac dysfunction, which can be identified with non-invasive imaging techniques, like echocardiography and cardiac magnetic resonance. This review aims to: 1) describe the major imaging features of DCM; 2) highlight how early identification of DCM-related anatomical and functional remodeling might allow patients' therapy optimization and prognosis improvement.

1. Introduction

Diabetic cardiomyopathy (DCM) is a peculiar cardiovascular complication characterized by the presence of myocardial dysfunction in individuals with diabetes mellitus (DM) in the absence of other cardiac diseases, such as coronary artery disease, valvular heart disease or high stage arterial hypertension (AH) [1]. DCM is typically associated to a long-standing DM condition, representing a major cause of heart failure (HF) [2]. Early recognition of DCM is crucial for management, and prevention of adverse outcomes.

The prevalence of DM has been steadily increasing worldwide, and its association with cardiovascular diseases (CVD) is well established. DM affects more than 10 % of the adult population globally [3]. This high prevalence contributes to a substantial burden of DCM. The risk of developing DCM is significantly higher in individuals with long-standing DM, poor glycemic control, and concomitant cardiovascular risk factors. In fact, DCM has been observed in up to 30 % of diabetic patients and its prevalence increases with the duration of DM, affecting around 12–22 % of patients after 10 years of disease duration [4].

2. Pathophysiology

The pathophysiology of DCM involves multiple interrelated mechanisms, including metabolic derangements, oxidative stress, inflammation, and fibrosis. Impaired insulin signaling plays a crucial role in the development of DCM. Insulin resistance, a hallmark of type 2 diabetes, leads to inadequate glucose uptake by cardiomyocytes, resulting in energy deprivation and metabolic disturbances [5].

Alterations in cardiac metabolism, such as increased fatty acid utilization and reduced glucose oxidation, contribute to the development of myocardial lipotoxicity. Excessive accumulation of lipids within the cardiomyocytes leads to mitochondrial dysfunction, increased reactive oxygen species (ROS) production, and impaired contractile function [6]. These metabolic abnormalities are implicated in the development of

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diabetic cardiac dysfunction, which progresses to DCM over time.

Chronic hyperglycemia also has a central role in the pathogenesis of DCM. Elevated glucose levels contribute to the formation of advanced glycation end-products (AGEs), which promote oxidative stress and inflammation. AGEs interact with their receptors (RAGE) on cardiomyocytes and cardiac fibroblasts, triggering intracellular signaling pathways that promote fibrosis, hypertrophy, and apoptosis [7].

Inflammation and immune dysregulation are important contributors to the development and progression of DCM. The release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), is increased in diabetic patients [8]. These cytokines activate intracellular pathways involved in fibrosis, hypertrophy, and myocardial dysfunction. Additionally, infiltrating immune cells, such as macrophages and T lymphocytes, perpetuate the inflammatory response and contribute to myocardial damage [9].

Cardiac fibrosis, characterized by excessive deposition of extracellular matrix proteins, is a key pathological feature of DCM. Increased production of profibrotic factors, such as transforming growth factor-beta (TGF-β), promotes the activation of cardiac fibroblasts and subsequent collagen synthesis [10]. Cardiac fibrosis disrupts normal myocardial architecture, leading to impaired diastolic and systolic function [11].

3. Imaging in diabetic cardiomyopathy

A definitive diagnosis of DCM would require invasive hemodynamic assessment and myocardial biopsy. Nevertheless, non-invasive imaging techniques, such as echocardiography and cardiovascular magnetic resonance (CMR), represent the most appropriate, feasible and risk/benefit-weighted approach to detect functional and structural alterations in diabetic patients.

3.1. Echocardiography

Echocardiography is the cornerstone technique for the bedside evaluation of DM patients, thanks to its wide availability and low costs. It allows the early identification of morpho-functional alterations and is the most widely used technique to monitor disease progression. Beyond traditional parameters such as ejection fraction and trans-mitral Doppler flow, technologies such as tissue Doppler imaging (TDI) and speckle tracking echocardiography (STE) have gained ground in myocardial systolic and diastolic functional assessment.

3.1.1. LV hypertrophy

The first feature of DCM described by autoptic studies was left ventricular (LV) hypertrophy (LVH), with histopathological evidence of myocardial fibrosis and myocytes hypertrophy (Fig. 1) [12]. DM is associated with concentric adverse remodeling and some degree of LVH may be present even in the prediabetic stage. Impaired glucose tolerance (IGT) correlates with relative wall thickness and LV mass/height ratio [13]. The increase in LV myocardial mass impacts prognosis and, interestingly, seems to be partly reversible if adequate blood glucose control is achieved [14].

3.1.2. LV diastolic dysfunction

Diastolic dysfunction is observed in 35 % of DM patients without overt heart disease. It encompasses lower E/A, lower mitral annular early diastolic velocity, greater E/e' (Fig. 2) and larger left atrial (LA) volume [15,16]. The use of 2D and 3D STE, measuring peak strain rate at early diastole (SRE) and E/SRE, confirmed the high prevalence of diastolic dysfunction in DCM and its worsening over time [17,18].

Since many conditions such as age, obesity and AH often coexist and concur to cause diastolic dysfunction, the independent contribution of DM is difficult to ascertain. However, T2DM patients without clinical HF show signs of diastolic dysfunction when compared to obese, non-diabetic, age, sex, weight and systolic blood pressure-matched controls [19]. Moreover, LV filling pattern assessed by E/A ratio may be early altered even in presence of normal LV mass [20] and in patients with Type 1 DM (T1DM) without significant comorbidities [21].

Diastolic dysfunction holds prognostic value in DCM. A large study including 1760 diabetic patients detected diastolic dysfunction using TDI (E/e' ratio >15) in 23 % of the population and showed an increased risk of HF and death independently of AH, coronary artery disease (CAD) and other echocardiographic parameters [22]. DM patients with variations in LV EDV/BSA and E/e', even in normal range, showed worse clinical phenotype including longer DM duration, lower eGFR, higher pulse pressure, increased prevalence of AH and retinopathy [23].

Leung et al. reported possible improvement in diastolic function assessed by septal e' after optimization of treatment and reduction of HBA1c [24].

3.1.3. LV systolic dysfunction

DM is a highly prevalent comorbidity in patients with HF with reduced and intermediate ejection fraction, regardless of the presence of CAD and other determinants of LV dysfunction. Data from the Framingham population showed a 2- to 5-fold excess risk for developing HF in individuals with DM, and the highest risk of 5- to 8-fold was among younger patients [25]. Furthermore, patients with DM and HF have high mortality as compared to diabetic patients without HF.

There are conflicting results on whether systolic impairment precedes or follows diastolic dysfunction. A study on rat models supports the hypothesis of DCM as a progression from diastolic to systolic dysfunction, culminating in overt HF [26]. At the same time, it has been observed that in 20–30 % of patients with DM, abnormal systolic strain was detected before diastolic dysfunction [27]. Both reduced LV longitudinal systolic deformation [28] and altered diastolic function [29] are precociously observed in pre-diabetic patients. Myocardial performance index, which reflects both diastolic and systolic functions, is also altered during the pre-diabetic stage [30].

Young individuals affected by DM without associated arterial hypertension or obesity are more often diagnosed with subclinical systolic dysfunction, LV hypertrophy and worse outcomes, as compared to

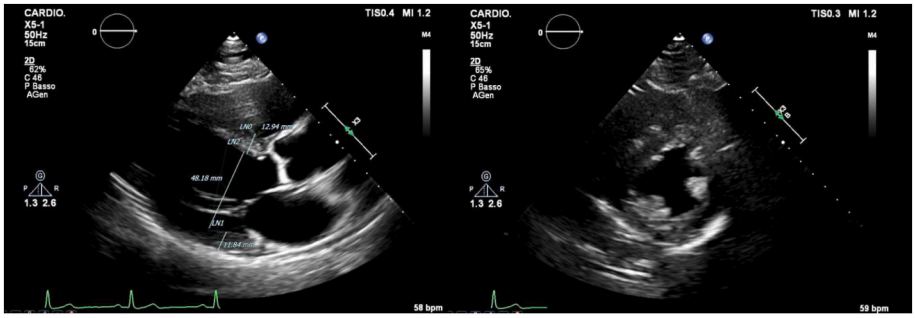

Fig. 1. Left ventricle concentric hypertrophy assessed with the parasternal long-axis (Panel A) and short-axis (Panel B) B-mode echocardiographic views.

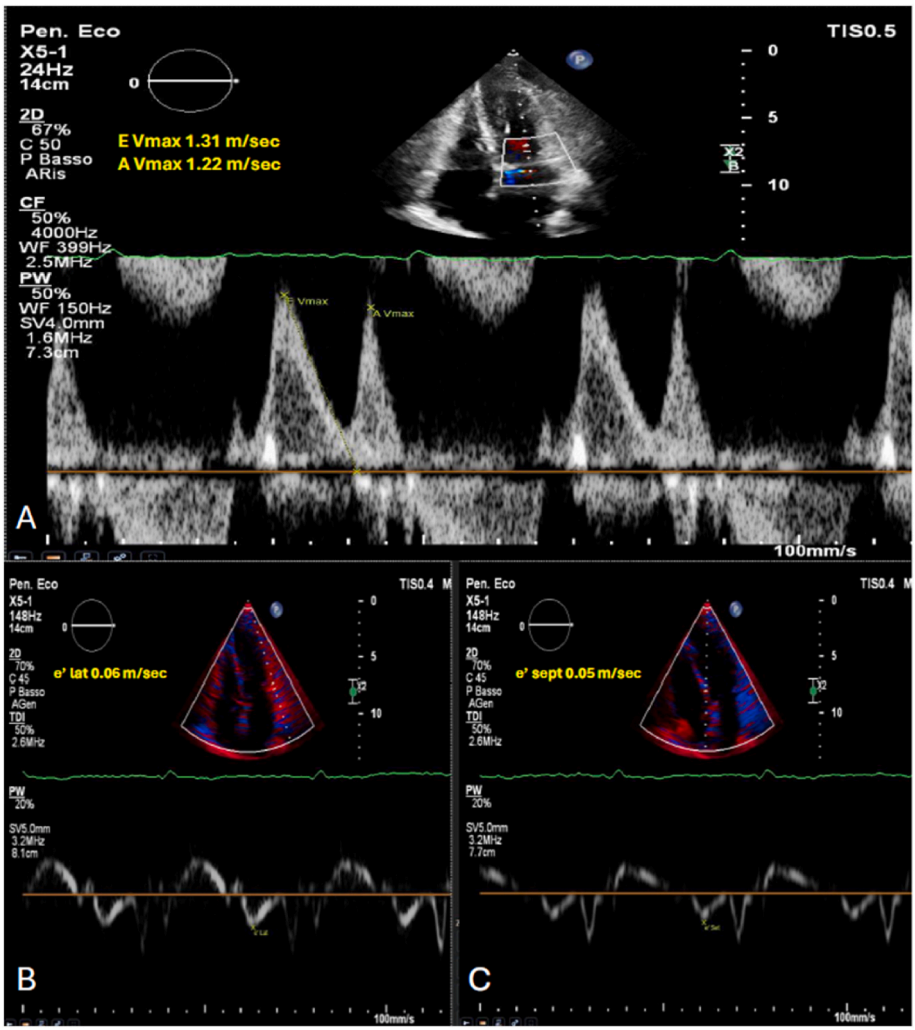

Fig. 2. Grade II diastolic dysfunction assessed using mitral inflow E and A velocities (with the PWD, Panel A), lateral e' and septal e' velocities (with TDI, Panels B and C). *LN0 = Line number 0 corresponding to the interventricular septum thickness; LN1 = Line number 1 corresponding to the posterior wall thickness; LN2 = Line number 2 corresponding to the left ventricular end-diastolic diameter.*

elderly, obese women with AH, which often display diastolic dysfunction and have better outcomes [31].

In T1DM subclinical myocardial dysfunction with deteriorating GLS at follow-up was observed by 2D and 3D-STE, independently of any other cardiovascular risk factors; no similar changes were detected in global circumferential (GCS) and radial (GRS) strain [31]. GLS is also independently associated with NT-proBNP, cardiovascular events, hospital mortality, all-cause death and hospitalization in diabetic subjects [24]. Leung et al. reported possible improvement in GLS after optimization of treatment and reduction of HBA1c [24].

3.1.4. RV systolic and diastolic dysfunction

In T1DM, in absence of confounders such as CAD and AH, RV diastolic impairment seems to precede RV systolic dysfunction [23]. Patients with T1DM showed impaired RV diastolic function, with higher tricuspid A-wave velocities and lower E/A values [23]. RV diastolic dysfunction in rat models with T2DM is similar to that in patients with RV dilation, with decreased peak early tricuspid filling velocity and peak early tricuspid filling velocity/peak tricuspid atrial filling velocity [32]. TDI directly measures tissue velocities and provides increased sensitivity to early changes in RV diastolic function, besides being independent of ventricular loading and respiratory variations. TDI revealed RV dysfunction in T1DM and T2DM compared to controls when conventional E/A ratio failed to detect such difference [33].

Impairment of RV systolic function in patients with T2DM includes lower RV long-axis fractional shortening, reduced systolic excursion of tricuspid annulus, reduced pulmonary valve peak and mean velocities and impaired systolic strain [33]. RV strain has also been correlated with levels of HBA1c [34]. RV 3D echocardiography data in DM patients are limited. A study comparing 3D- and 2-D echocardiography showed that RV and right atrial strain were decreased in patients with pre-diabetes and DM as compared to controls [34]. The early and deteriorating impact of diabetes on RV systolic and diastolic function develops independently from LV diastolic dysfunction, pulmonary hypertension and CAD [35].

3.1.5. CPET and stress echocardiography

Cardiopulmonary exercise testing (CPET) is useful for the identification of the mechanisms underlying exercise intolerance. Ryckeghem et al. showed that in T2DM impaired exercise capacity is primarily attributed to peripheral limitations in oxygen extraction, rather than to the reduction in classic parameters of systolic and diastolic dysfunction (cardiac output, LV EF and E/E') [36]. Besides that, they also observed that longitudinal strain, as a marker of subclinical LV dysfunction, increased less during exercise in T2DM patients with impaired capacity.

Both systolic and diastolic functional reserves are reduced in DCM and pharmacological/exercise stress echocardiography may be useful to unveil the presence of effort induced ventricular dysfunction and the

potential coexistence of inducible ischemia. The assessment of GLS during dobutamine stress echocardiography may identify early subclinical LV functional changes in asymptomatic T2DM patients [37]. Dual-imaging dipyridamole stress echocardiography (conventional wall motion analysis and Doppler-derived coronary flow velocity reserve of the left anterior descending artery) was reported to be abnormal in 23 % of asymptomatic patients with DM, representing a strong and independent predictor of MACEs [38]. The addition of TDI analysis to exercise stress echocardiography may increase the ability to unmask diastolic dysfunction in asymptomatic patients with a history of T2DM and normal rest echocardiography [80].

3.1.6. Atrial morpho-functional alterations

Several studies exploring LA volumes demonstrate LA enlargement in DCM. The CARDIA study showed that after a 20-year follow-up both unindexed and indexed left atrial (LA) diameters were increased in patients affected by DM [39]. Poulsen et al. report that increased LA volume index (≥32 ml/m2) is an independent and incremental predictor of cardiovascular morbidity and mortality in T2DM patients with no history of CVD [40].

As concerns atrial function, a progressive deterioration of LA and right atrial (RA) reservoir and conduit functions was observed across normal subjects, pre-diabetics and DM patients, while the contraction phase increased in pre-DM and DM. LA passive emptying fraction, LA longitudinal strain during systole, RA passive and active emptying fractions are independently associated with HbA1c [41].

A significant prolongation of inter- and intra-atrial conduction time, with reduction of LA passive emptying volume, was found in patients with impaired fasting glucose as compared with control subjects, suggesting early LA electrical remodeling [42].

In asymptomatic patients with AH and DM, peak LA longitudinal strain and global atrial-ventricular strain are better predictors of subclinical myocardial dysfunction compared to GLS [43].

4. Cardiovascular magnetic resonance

CMR is endowed with a large field-of-view, operator-independency and good spatial and temporal resolution; it lacks interferences with extra cardiac structures and permits the acquisition of functional and anatomical images in any desirable plane. It is the gold standard technique for the evaluation of biventricular volumes, mass and function, and is superior to other imaging modalities in identifying myocardial infarction. The utmost advantage of CMR over echocardiography is the ability to perform tissue characterization, with 1) visualization and quantification of myocardial fibrosis by late gadolinium enhancement (LGE), T1 mapping and extracellular volume (ECV) estimation, 2) identification of myocardial edema by T2 weighted imaging and T2 mapping (Figs. 3 and 4).

4.1. LV function

As well as echocardiography, CMR is able to explore LV mechanics and deformation using myocardial tagging and the more recent feature-tracking post-processing semi-automated tools.

Dating back to thirty years ago, a study using MRI-tagging showed that peak longitudinal and circumferential strain and strain rates were reduced in T2DM, while peak torsion was significantly increased, as a potential compensatory mechanism to preserve EF [44]. These results were later disproved by two recent studies showing that LV multidirectional strain was similar between T2DM patients and controls,

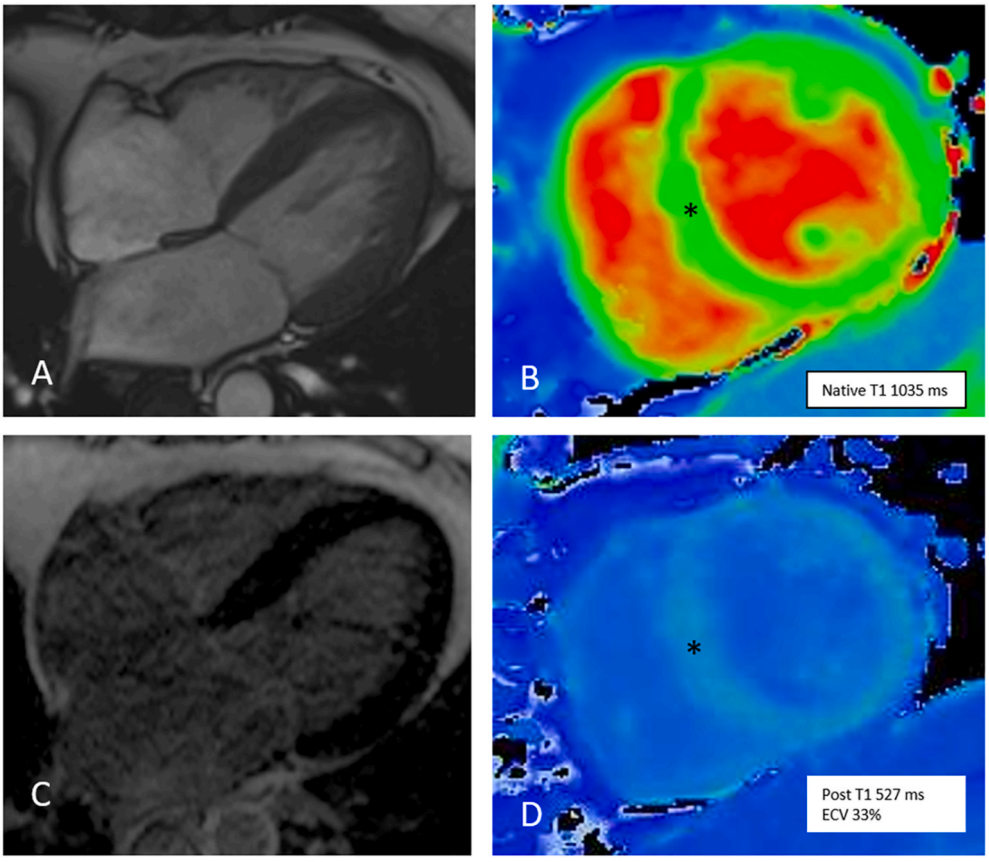

Fig. 3. Diabetic cardiomyopathy associated with biatrial enlargement (Panel A), left ventricular hypertrophy and large amount of epicardial fat (Panel B), intramyocardial LGE in the interventricular septum (Panels D and E), pre- and post-contrast MOLLI sequences showing elevated myocardial native T1 (Panel C) and increased ECV (Panel F). *MOLLI - Modified Look-Locker inversion recovery.*

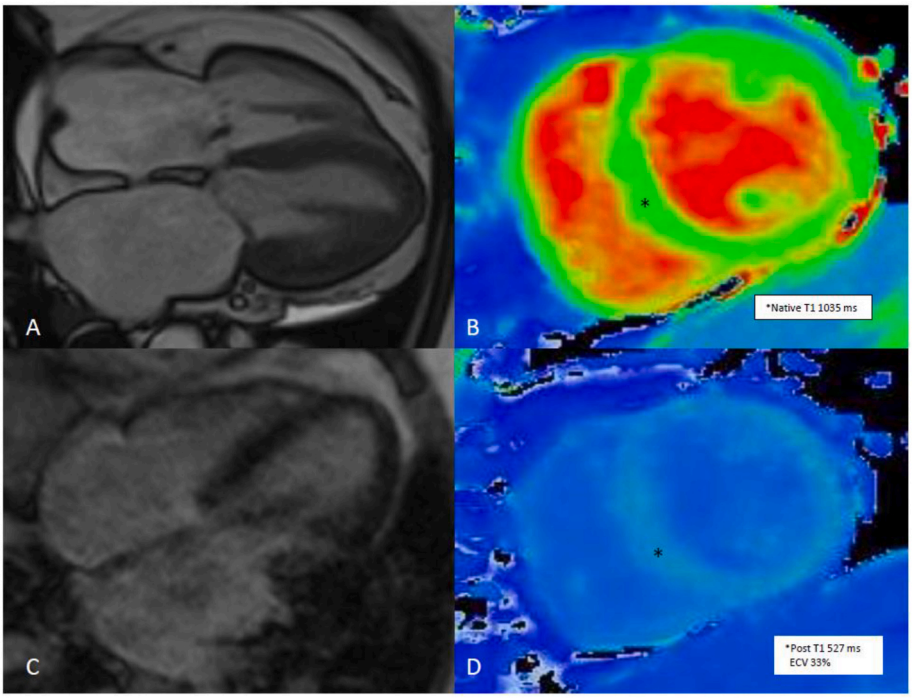

Fig. 4. Diabetic cardiomyopathy associated with left atrial enlargement (Panel A) and interstitial fibrosis as illustrated by elevated native T1 (Panel B) and increased ECV (Panel D) in pre and post-contrast ShMOLLI sequences, in the absence of LGE (Panel C). *ShMOLLI - shortened Modified Look-Locker inversion recovery.*

although the former group had increased LV mass and ECV [45,46]. Similarly, in T1DM no significant alteration of LV multidirectional strain was observed, while torsion and ECV were increased as compared to controls [47]. These results enhance the early onset and role of interstitial fibrosis in DCM pathogenesis. In long-standing T2DM a reduction in CMR-derived GLS and diastolic strain rates were observed [48].

Results on LV mechanics deriving from echocardiography and CMR are in part conflicting, possibly due to technical (differences between and within imaging methods, different vendors) and clinical issues (DM type, DM duration and patients' comorbidities).

4.1.1. Tissue characterization

LGE has long been considered the cornerstone of CMR for the identification of myocardial fibrosis. In DM patients, the presence of infarct-pattern LGE may recognize silent myocardial infarction and is associated with worse cardiovascular outcome [49].

LGE sensitivity for diffuse, interstitial, non-confluent fibrosis is suboptimal if compared to the most recent parametric mapping techniques: T1 mapping provides a quantitative measure of myocardial T1 relaxation time and can be performed without contrast (native T1) or post-gadolinium administration, allowing calculation of myocardial ECV.

Interstitial fibrosis is an early sign of DCM and, interestingly, it seems to be partly reversible with timely initiation of treatment.

In DCM multiple studies showed increased myocardium native T1, T2 and ECV, with a significant correlation between ECV-HBA1c [45,46] and ECV-DM duration [50].

Global post-contrast T1 is lower in DM patients, indicating a higher fibrotic burden, and is independently associated with reduced longitudinal systolic (GLS) and diastolic function (septal E') by echocardiography [51]. Post-contrast T1 is also related to impaired exercise capacity, independently of AH and metabolic disturbances [52].

A recent metanalysis by Salvador et al. including 32 studies, reports that DM is associated with a higher degree of myocardial fibrosis assessed by histology and ECV, and worse glycemic control is associated with higher myocardial fibrosis degrees [53].

To date, there are few prognostic data on T1 mapping and ECV in DCM but the early identification of DM patients at risk for HF is crucial and CMR mapping technique and STE may permit to identify who could benefit from anti-remodeling therapies. More recently, in a population of 442 DM and pre-DM patients with preserved EF and without obstructive CAD, Khan et al. showed that ECV is an independent predictor of mortality and could play an additive role in DM-related outcomes [54].Obesity and T2DM are associated with enlarged epicardial adipose tissue, which may contribute to myocardial inflammation and fibrosis, as well as exert mechanical stress on the pericardium. Epicardial adipose tissue detected by CMR has been associated with reduced systolic strain and increased arterial stiffness [55].

In IGT patients with preserved EF (1H) magnetic resonance spectroscopy (MRS) showed increased myocardial triglyceride content, indicating early lipid over storage in the spectrum of DM [56]. Cardiac steatosis is associated with decreased systolic strain, concentric LV remodeling and impaired myocardial energetics [57]. (31P) MRS detected a decrease in myocardial energetics, which also correlated with reduced perfusion and oxygenation, coronary microvascular impairment and diastolic dysfunction [58].

4.1.2. Left atrial morpho-functional abnormalities

Studies comparing 3DE and CMR-derived LA volumes showed higher accuracy than 2DE-based

analysis, even if 3DE measurements still underestimate real LA volumes. The reproducibility of.

CMR-derived LA volumes is significantly higher, due to better image quality.

Graca et al. showed that CMR-derived LA volumes are similar between DM patients and controls, while CMR successfully detects subtle LA dysfunction (reduced LA reservoir and conduit functions) in asymptomatic DM patients. DM is independently associated with reduced LA reservoir function [59]. Data deriving from the MESA study showed that LA minimum volume and LA emptying fraction are predictive of cardiovascular disease in a DM multi-ethnic population [60].

4.1.3. Stress CMR

Stress perfusion CMR provides independent prognostic utility and

risk reclassification in non-invasive assessment of DM patients with suspected inducible myocardial ischemia. Even in absence of obstructive CAD and AH, impaired myocardial perfusion at rest and during adenosine-stress were both observed in DCM [61]. Microvascular dysfunction is the main mechanism deemed responsible for reduced coronary flow reserve (CFR) and CFR reduction holds strong prognostic relevance [38,62].

Table 1 shows the main advantages and limitation of echocardiography and CMR in the assessment of DCM.

5. Therapy

Diabetic cardiomyopathy (DCM) is a complex metabolic condition [63] that requires a comprehensive therapeutic approach to effectively manage cardiac dysfunction and reduce cardiovascular events [64,65]. Several medications have shown potential in ameliorating DCM outcomes, including metformin, SGLT2 inhibitors (SGLT2i), GLP1 receptor agonists (GLP1ra), and DPP4 inhibitors (DPP4i).

Metformin, a commonly used oral hypoglycemic agent, has been found to have beneficial effects on DCM. It activates the PK2/PKR pathway, which plays a role in cellular stress response and inflammation, thereby reducing oxidative stress, inflammation, and fibrosis in the diabetic heart [66]. Metformin also improves myocardial energy metabolism by promoting glucose utilization and inhibiting excessive fatty acid oxidation, which helps prevent myocardial lipotoxicity and dysfcuntion [67].

SGLT2i (i.e. empagliflozin or dapagliflozin) demonstrated remarkable cardioprotective effects [68], reducing the rate of cardiovascular events in high-risk patients with DM and optimizing clinical outcomes in subjects affected by heart failure (HF) irrespective of LVEF (reduced or preserved) and diabetic condition [69–72]. The multifaceted effects of SGLT2i, including glucose lowering, natriuretic effects, and attenuation of oxidative stress, inflammation, and fibrosis in the heart, contribute to improved heart function assessed through cardiac imaging techniques [73–75]. Particularly, therapy with empagliflozin has been associated with reduction in left ventricular mass and improvement in diastolic function detected with echocardiography, decreased myocardial fibrosis, improved LVEF, reduced left ventricular end-diastolic volume (LVEDV) evaluated with cardiac MRI [75]. Furthermore, SGLT2i enhance myocardial glucose utilization, leading to better cardiac glucose metabolism assessed by PET [75]: such imaging findings underly the potential of SGLT2i in improving heart function and metabolic processes in DCM.

GLP1ra (i.e. liraglutide), offer significant cardiovascular benefits, reducing the risk of major adverse cardiovascular events (MACE) and cardiovascular mortality in patients with DMT2: these effects depend on GLP1a ability to enhance myocardial glucose uptake, improve endothelial function, and reduce cardiomyocyte apoptosis [76]. As a result, GLP1ra contributes to preserved cardiac contractility and relaxation, leading to improved heart function and enhanced cardiac contractility [76]. In fact, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial, patients treated with liraglutide exhibited a reduction in the incidence of heart failure hospitalizations and presented improved LVEF and reduced left ventricular end-systolic volume (LVESV) at the transthoracic echocardiography. Moreover, in the same trial, cardiac MRI documented a decrease in myocardial fibrosis and improved myocardial deformation parameters (strain and strain rate) in patients receiving GLP1a therapy [76].

Both the direct effects of DPP4i on cardiac imaging outcomes and their pleiotropic effects on cardiovascular health warrant further investigation. By elevating GLP1 levels and modulating other signaling pathways, DPP4i may improve cardiac function and imaging parameters in DCM, but. Future studies are essential to fully elucidate DPP4i impact on cardiac performance [65].

In addition to these conventional therapies, novel strategies such as gene therapy and non-coding RNA regulation hold great promise in DCM management. Targeting the mitochondrial heat shock protein 70 (mtHsp70) nuclear locus through gene therapy has demonstrated significant success in mitigating mitochondrial proteome disruption, inflammation, and fibrosis in the diabetic heart [77]. This approach addresses the root causes of mitochondrial dysfunction and oxidative stress, leading to improved heart mechanics. Additionally, non-coding RNA, such as miR-146a, has emerged as a potential therapeutic target in DCM, as it mediates inflammatory changes and fibrotic damage in the heart [78]. Modulating non-coding RNA expression could lead to the regulation of key molecular pathways involved in diabetic organ injury, offering opportunities for the optimization of cardiac function.

Table 1
Advantages and limitations of echocardiography and CMR in the assessment of DCM. *CPET - Cardiopulmonary Exercise Testing; DCM - Diabetic Cardiomyopathy; ECV - Extracellular Volume; EF - Fractional Ejection; GLP1ra - Glucagon-Like Peptide-1 Receptor Agonist; LGE - Late Gadolinium Enhancement; LA - Left Atrium; LV - Left Ventricle; RA - Right Atrium; RV - Right Ventricle; SGLT2i - Sodium-Glucose Cotransporter-2 Inhibitors; STE - Speckle Tracking Echocardiography; TDI - Tissue Doppler Imaging.*

	Ecocardiography	CMR
Advantages	• No radiation exposure • Wide availability and low costs • Rapid LV myocardial mass and volumes estimation (2D \3D) • Diastolic dysfunction assessment (mitral inflow, TDI, STE) • LV and RV systolic function assessment (EF 2D/3D, TDI, STE) • LA volume and LA\RA function assessment • Presence and severity of valvular heart disease • Possible advanced evaluation with CPET or stress echocardiography • Assessment of mass reduction during SGLT2i therapy	• No radiation exposure • Poor operator-dependency • Good spatial and temporal resolution • Gold standard for the evaluation of biventricular volumes, mass and function • Quantification of ECV and myocardial fibrosis by T1-mapping and LGE • Identification of myocardial edema by T2 weighted imaging and T2-mapping. • Possible advanced evaluation with stress CMR • Assessment of fibrosis progression/regression during SGLT2i and GLP1ra therapy
Limitations	• Operator dependency • Influenced by good image quality and geometrical assumptions • Lack of standardization of GLS cut-off • Limited data for RV 3D echocardiography • Underestimation of real LA volumes and limited data for atrial STE in DCM	• Possible contraindications • Less available and high costs • Long time for image acquisition • Cardiac and respiratory motion related artifacts • Data analysis and interpretation • Few prognostic data of ECV in DCM

6. Conclusion

DCM is a specific form of cardiac dysfunction that occurs in the setting of diabetes, independent of other known cardiac diseases. It is associated with significant morbidity and mortality in diabetic patients. The epidemiology of DCM is characterized by high prevalence in subjects with long-standing diabetes and poor glycemic control. The pathophysiology of DCM involves multiple mechanisms, including metabolic impairment, oxidative stress, inflammation, and fibrosis. Several imaging techniques can be adopted in the clinical practice to identify abnormalities on tissue characterization, cardiac mechanics and stress response which are typical of DCM. Antidiabetic drugs like, SGLT2i, GLP1a and DPP4i have shown beneficial effects on DCM by modulating various pathways involved in DCM physiopathology and their utilization improve patients' clinical outcomes [79]. Novel pioneering therapeutical strategies, like gene therapy and non-coding RNA, ameliorate cardiac metabolism and seem to be promising in hindering DCM-related

cardiac dysfunction. A better understanding of DCM might be crucial to avoid misdiagnosis and aim patients to an early tailored, optimized management.

CRediT authorship contribution statement

Vincenzo Rizza: Writing – review & editing, Writing – original draft, Conceptualization. **Lara Tondi:** Writing – review & editing, Writing – original draft, Data curation. **Angelo Maria Patti:** Writing – review & editing, Supervision. **Damiano Cecchi:** Writing – review & editing, Writing – original draft, Supervision. **Massimo Lombardi:** Supervision. **Francesco Perone:** Supervision. **Marco Ambrosetti:** Supervision. **Manfredi Rizzo:** Supervision. **Domenico Cianflone:** Supervision. **Francesco Maranta:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

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