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REVIEW

*Clinical update*

# Clinical diabetic cardiomyopathy: a two-faced disease with restrictive and dilated phenotypes

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Diabetes mellitus-related cardiomyopathy (DMCMP) was originally described as a dilated phenotype with eccentric left ventricular (LV) remodelling and systolic LV dysfunction. Recently however, clinical studies on DMCMP mainly describe a restrictive phenotype with concentric LV remodelling and diastolic LV dysfunction. Both phenotypes are not successive stages of DMCMP but evolve independently to respectively heart failure with preserved left ventricular ejection fraction (HFPEF) or reduced left ventricular ejection fraction (HFREF). Phenotype-specific pathophysiological mechanisms were recently proposed for LV remodelling and dysfunction in HFPEF and HFREF consisting of coronary microvascular endothelial dysfunction in HFPEF and cardiomyocyte cell death in HFREF. A similar preferential involvement of endothelial or cardiomyocyte cell compartments explains DMCMP development into distinct restrictive/HFPEF or dilated/HFREF phenotypes. Diabetes mellitus (DM)-related metabolic derangements such as hyperglycaemia, lipotoxicity, and hyperinsulinaemia favour development of DMCMP with restrictive/HFPEF phenotype, which is more prevalent in obese type 2 DM patients. In contrast, autoimmunity predisposes to a dilated/HFREF phenotype, which manifests itself more in autoimmune-prone type 1 DM patients. Finally, coronary microvascular rarefaction and advanced glycation end-products deposition are relevant to both phenotypes. Diagnosis of DMCMP requires impaired glucose metabolism and exclusion of coronary, valvular, hypertensive, or congenital heart disease and of viral, toxic, familial, or infiltrative cardiomyopathy. In addition, diagnosis of DMCMP with restrictive/HFPEF phenotype requires normal systolic LV function and diastolic LV dysfunction, whereas diagnosis of DMCMP with dilated/HFREF phenotype requires systolic LV dysfunction. Treatment of DMCMP with restrictive/HFPEF phenotype is limited to diuretics and lifestyle modification, whereas DMCMP with dilated/HFREF phenotype is treated in accordance to HF guidelines.

**Keywords** Diabetic cardiomyopathy • Diabetes mellitus • Heart failure • Left ventricular Remodelling • Diastolic dysfunction

## Introduction

### Clinical presentation of two phenotypes

The concept of diabetes mellitus (DM) directly causing myocardial dysfunction dates back from 1954, when Lundbæk observed myocardial dysfunction to be a common DM-related complication present in two-thirds of elderly DM patients.[1] He subsequently became the first to suggest the diagnosis of a specific Diabetes mellitus-related cardiomyopathy (DMCMP).[2] Almost 20 years later, Rubler *et al.* provided further evidence that cardiomyopathic dysfunction could indeed directly result from DM and not merely indirectly from concomitant coronary artery disease.[3] This landmark study reported on post-mortem findings of four patients with diabetes related nephropathy and heart failure (HF) unrelated to valvular, congenital or hypertensive heart disease, alcoholism or significant epicardial coronary artery atherosclerosis. The study proposed that they suffered from a novel DMCMP caused by myocardial microangiopathy or disturbed myocardial metabolism. The use of the term cardiomyopathy to indicate this condition corresponds to the currently used definition of cardiomyopathy:[4] 'A cardiomyopathy is defined as a heart muscle disease in which the myocardium is structurally and functionally abnormal in the absence of coronary artery disease as well as hypertensive, valvular, or congenital heart disorders'. In the patients described by Rubler *et al.*, DM had lasted for 5–20 years and the patients presented clinically with cardiomegaly, pulmonary congestion, and gallop sounds. On pathological examination, there was myocardial hypertrophy, fibrosis, and microvascular wall thickening because of accumulation of acid mucopolysaccharides. Based on presentation and pathological findings, the clinical phenotype of this DMCMP corresponded with a dilated cardiomyopathy similar to dilated

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cardiomyopathy induced by toxic agents or viral myocarditis. When becoming symptomatic, DMCMP patients with a dilated phenotype present as heart failure with reduced ejection fraction (HFREF).

Recently, however, most clinical reports on DMCMP present a phenotype which differs from a dilated cardiomyopathy.[5,6] The typical patient suffering of DMCMP is now described as an elderly woman suffering from obesity and type 2 DM (T2DM) with a small left ventricular (LV) cavity, normal LV ejection fraction, thick LV walls, elevated LV filling pressures, and a large left atrium. This description fits a restrictive but not a dilated cardiomyopathy. The current shift in appreciation of DMCMP from a dilated to a restrictive phenotype is matched by a rising awareness that many HF patients present with a normal-sized left ventricle and a normal left ventricular ejection fraction (LVEF).[7–9] These patients are currently labelled as suffering from heart failure with preserved left ventricular ejection fraction (HFPEF).[10] When becoming symptomatic, DMCMP patients with a restrictive phenotype present as HFPEF.

## Successive stages or distinct phenotypes?

Diabetes mellitus-related cardiomyopathy with restrictive/HFPEF phenotype has been described in two reviews[11,12] and in both reports it is considered to be a precursor stage of DMCMP with dilated/HFREF phenotype. In an HFPEF patient population, the incidence of HFPEF progressing to HFREF is however limited and related to intervening myocardial infarctions or very old age (>80 years) but not to DM.[13] Normal cardiac remodelling over the adult life course is characterized by decreasing LV dimensions and increasing fractional shortening. Diabetes mellitus attenuates but does not reverse this LV remodelling pattern.[14] Furthermore, in arterial hypertension, another condition frequently associated with HFPEF, the progression from an asymptomatic stage to HFPEF is characterized by LV shrinkage but not LV dilatation.[15] Based on the foregoing arguments, an evolution from DMCMP with restrictive/HFPEF phenotype to DMCMP with dilated/HFREF phenotype seems unlikely and DMCMP therefore evolves as two distinct phenotypes.

Such an evolution implies existence of phenotype-specific mechanisms that drive the cardiac remodelling process into a restrictive or a dilated DMCMP phenotype. Recently, phenotype-specific mechanisms have been proposed for LV remodelling in HFPEF and HFREF. In HFPEF concentric LV remodelling results from coronary microvascular endothelial inflammation with cardiomyocytes only exposed to altered paracrine endothelial signalling, whereas in HFREF eccentric LV remodelling results from cardiomyocyte cell death because of ischaemia, viral infection, or toxic agents.[16] A similar selective involvement of endothelial or cardiomyocyte cell compartments could explain DMCMP development into distinct restrictive/HFPEF or dilated/HFREF phenotypes.

## Clinical implications of two phenotypes

The distinction between dilated and restrictive phenotypes of DMCMP is of therapeutic importance because when symptomatic, a dilated phenotype will present as HFREF, whereas a restrictive phenotype will present as HFPEF. For numerous HF drugs, the outcome of large trials differed in HFREF and HFPEF being positive in HFREF and neutral in HFPEF.[17] The therapeutic strategy therefore differs in both DMCMP phenotypes with angiotensin-converting enzyme inhibitors, β-blockers, angiotensin II receptor blockers, and mineralocorticoid-receptor antagonists clearly indicated for DMCMP with dilated/HFREF phenotype and of uncertain value for DMCMP with restrictive/HFPEF phenotype.

# Epidemiology

The existence of a dilated/HFREF phenotype of DMCMP was confirmed in the United States by nation-wide hospital discharge data showing an independent association between DM and non-ischaemic dilated cardiomyopathy whereby DM significantly increases the odds for dilated cardiomyopathy (odds ratio: 1.75; 95% CI: 1.71–1.79).[18] Diabetes mellitus-related cardiomyopathy patients with a dilated/HFREF phenotype were also shown to have worse haemodynamic features than other dilated cardiomyopathy patients evident from a lower LVEF and a higher myocardial stiffness modulus.[19] Specific epidemiological and clinical features of the restrictive/HFPEF phenotype of DMCMP were recently reported in an RELAX ancillary study.[20] Apart from a worse clinical presentation with more frequent hospitalizations and less exercise capacity, they had more LV hypertrophy and higher LV stiffness. These two haemodynamic features had previously also been reported in an invasive study on DMCMP patients with restrictive/HFPEF phenotype and attributed to microvascular advanced glycation end-products (AGEs) deposition and stiff cardiomyocytes.[19]

Mortality and hospitalization rates are particularly high in HF patients suffering of DM[21–25] and as demonstrated by Mc Donald *et al.*, DM is associated with a greater risk of death or HF hospitalization in both HFPEF and HFREF.[26] The latter study is especially relevant to the presence of two DMCMP phenotypes as it demonstrated the additional risk to differ between dilated/HFREF and restrictive/HFPEF phenotypes with the largest DM-related additional risk counterintuitively observed in the restrictive/HFPEF phenotype. At present, it remains unclear if the DM-related excess mortality and hospitalizations relate to larger ischaemic myocardial dysfunction or to direct DM-related myocardial dysfunction.

The relation between DM and HF is bidirectional: the outcome of HF patients is worse in the presence of DM and DM patients are at higher risk for HF.[27] Not only the presence of DM but also the extent of glycaemic control is associated with HF risk.[28] For each 1% increase in glycosylated haemoglobin ($HbA_{1C}$), there is a 8% risk increment for HF. Because of the close epidemiological interrelation between HF and DM, HF can no longer be ignored as a cardiovascular outcome measure for new glucose-lowering drugs.[29]

# Pathophysiology

Myocardial structure and function differ between DMCMP with restrictive/HFPEF phenotype and DMCMP with dilated/HFREF phenotype.[19,30] In DMCMP with restrictive/HFPEF phenotype, the left ventricle is normal sized, hypertrophied, and stiff. At the ultrastructural level, cardiomyocytes are also hypertrophied with normal sarcomeric structure and high resting tension (*Figure 1*). Myocardial collagen volume fraction is moderately raised with collagen deposition in-between cardiomyocytes (i.e. reactive fibrosis) (*Figure 1*). In DMCMP with dilated/HFREF phenotype, the left ventricle is enlarged. At the ultrastructural level, cardiomyocytes appear damaged with loss of sarcomeres (*Figure 1*). Myocardial collagen

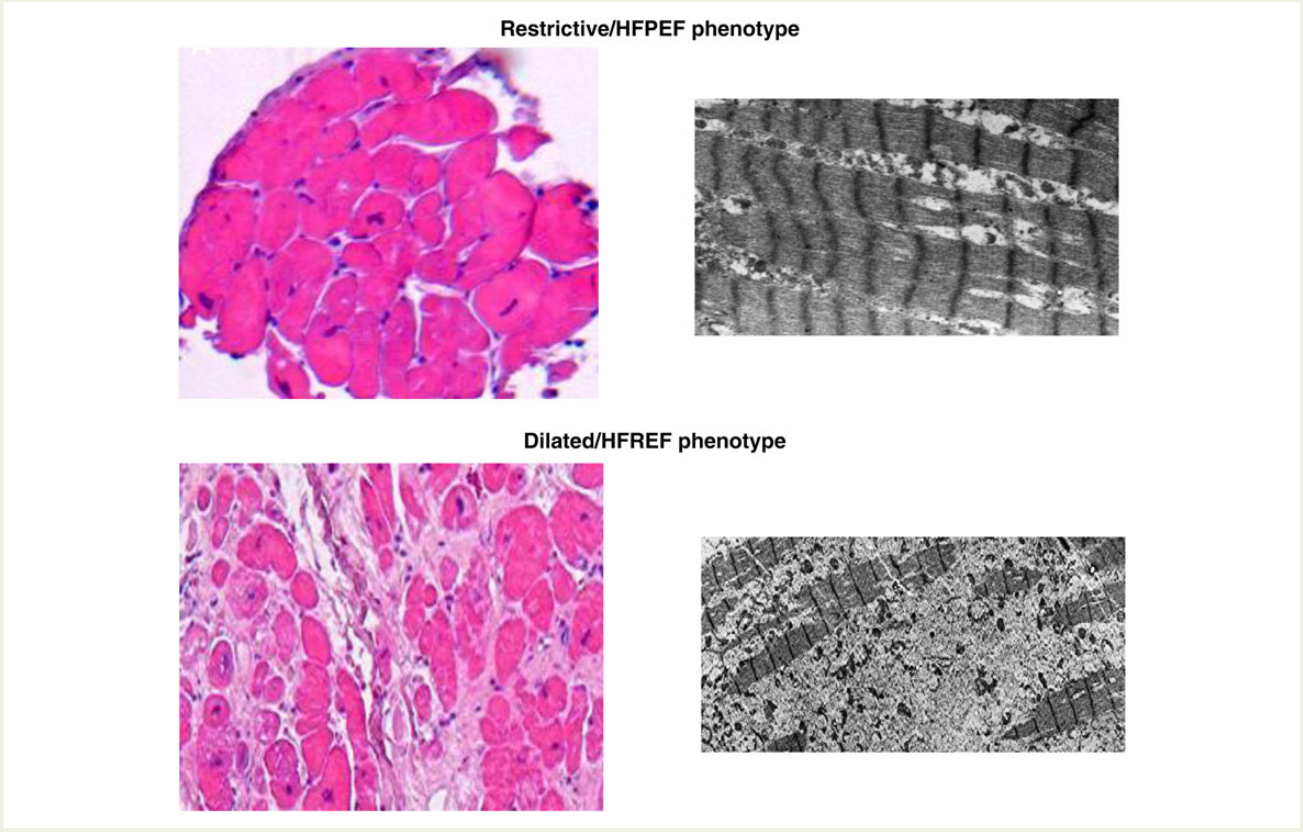


**Figure 1** Myocardial structure in restrictive/ heart failure with preserved ejection fraction (HFPEF) and dilated/ heart failure with reduced ejection fraction (HFREF) phenotypes. In the restrictive/ heart failure with preserved ejection fraction phenotype cardiomyocytes are hypertrophied, collagen is laid down in-between cardiomyocytes (reactive fibrosis) (left-hand panel) and sarcomeric structure is preserved (right hand panel). In the dilated/ heart failure with reduced ejection fraction phenotype, cardiomyocytes are small and damaged, collagen is laid down over larger areas (replacement fibrosis) (left-hand panel) and sarcomeres have disappeared (right hand panel). Reproduced with permission from Van Heerebeek *et al.*[19,30]

volume fraction is high with collagen laid down not only in-between cardiomyocytes but also over larger areas indicative of replacement fibrosis following cardiomyocyte cell death (*Figure 1*). In both phenotypes, there is coronary microvascular rarefaction and coronary microvascular deposition of AGEs[19] (*Figure 2*).

Numerous mechanisms have been identified that contribute to myocardial remodelling and dysfunction in DMCMP. These mechanisms include hyperglycaemia, lipotoxicity, microvascular AGEs deposition, microvascular rarefaction, autoimmunity, and insulin resistance/ hyperinsulinaemia. They appear to be of variable relevance for the two DMCMP phenotypes: hyperglycaemia, lipotoxicity, and insulin resistance are more important for DMCMP with restrictive/HFPEF phenotype, autoimmunity is especially relevant for DMCMP with dilated/HFREF phenotype and AGEs deposition and microvascular rarefaction seem to contribute to both phenotypes (*Figures 3* and *4*).

## Hyperglycaemia

Exposure of endothelial cells to hyperglycaemia induces mitochondrial fission and mitochondrial generation of superoxide.[31–34] Increased mitochondrial superoxide production is associated with impaired activation of endothelial nitric oxide (NO) synthase and reduced cGMP production.[33] This lowers protein kinase G (PKG) activity in adjacent cardiomyocytes[35] and reduces cardiomyocyte distensibility because of hypophosphorylation of the giant cytoskeletal protein titin that functions as a bidirectional spring controlling early diastolic recoil and late diastolic myocardial distensibility.[36,37] A reduced cardiomyocyte distensibility can contribute to the high LV diastolic stiffness observed in DMCMP with restrictive/HFPEF phenotype. Proof of concept for the relevance of this mechanism was provided by *in vitro* experiments, in which PKG administration to cardiomyocytes isolated from DMCMP patients with restrictive/ HFPEF phenotype corrected the high cardiomyocyte resting tension.[19] Similar results were also obtained in cardiomyocytes isolated from patients suffering from both aortic stenosis and DM.[38] Apart from altering paracrine endothelial signalling, hyperglycaemia can also directly affect the cardiomyocytes. Contractile dysfunction of right atrial myocardial strips of DM patients was associated with mitochondrial network fragmentation and oxidative stress.[39] The clinical relevance of this contractile dysfunction is however uncertain as all patients had normal LVEF at the time of perioperative procurement of the right atrial strip. Finally, hyperglycaemia raises PKC activity in fibroblasts, which augments collagen production and deposition.[19,38,40]

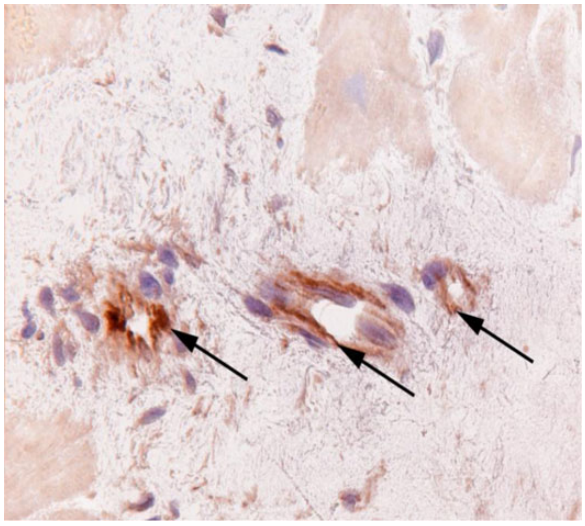

**Figure 2** Microvascular advanced glycation end-products deposition in diabetes mellitus-related cardiomyopathy. AGEs, advanced glycation end-products. Reproduced with permission from van Heerebeek *et al.*[19]

## Lipotoxicity

The enhanced cardiac free fatty acid uptake in DM patients exceeds the free fatty acid oxidation capacity. This leads to myocardial triglyceride accumulation and can eventually induce cell death. This process is referred to as *lipotoxicity* and has been reported in numerous DM animal models.[41–45] In DM, the contribution of fatty acids to cardiac energy production is larger than normal because of decreased insulin-mediated glucose uptake and because excess fatty acids inhibit glucose utilization.[46] Increased use of free fatty acids was observed clinically in DM patients using positron emission tomography. In these patients, the altered use of substrate was associated with increased cardiac oxygen consumption and LV diastolic dysfunction.[47,48] Excess fatty acid uptake into cardiomyocytes can eventually induce mitochondrial dysfunction, trigger cardiomyocyte cell death, and lead to DMCMP with dilated/HFREF phenotype.[49] Such a lipotoxicity-induced evolution to DMCMP with dilated/HFREF phenotype is however not clinically substantiated because DM patients have preserved LVEF despite appearance of cardiac steatosis on proton-MR spectroscopy.[50,51] Excess myocardial fatty acid uptake can also affect endothelial cells of the coronary microvasculature through generation of toxic lipid intermediates such as diacylglycerol and ceramide.[52,53] Presence of ceramide disrupts endothelial NO synthase signalling and reduces NO bioavailability. This effect

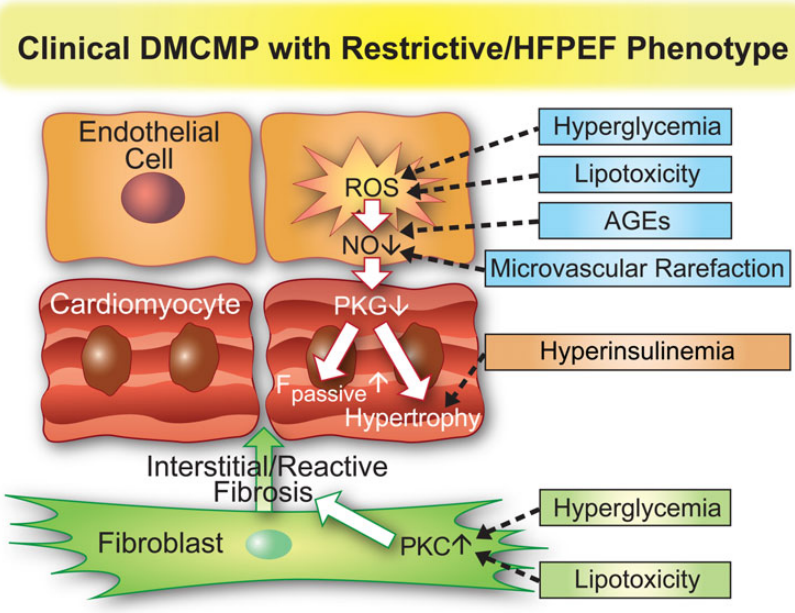


**Figure 3** DM-related pathophysiological mechanisms in diabetes mellitus-related cardiomyopathy with restrictive/ heart failure with preserved ejection fraction phenotype. In diabetes mellitus-related cardiomyopathy with restrictive/ heart failure with preserved ejection fraction phenotype coronary microvascular endothelial dysfunction drives left ventricular remodelling and dysfunction through lowering of myocardial NO bioavailability and PKG activity. This releases the brake on myocardial hypertrophy, stiffens cardiomyocytes (i.e. raised passive force ($F_{passive}$)) and causes reactive interstitial fibrosis. Coronary microvascular endothelial dysfunction results from hyperglycaemia, lipotoxicity, and advanced glycation end-products deposition. Microvascular rarefaction also contributes to low NO bioavailability and hyperinsulinaemia to cardiomyocyte hypertrophy. Hyperglycaemia and lipotoxicity raise PKC in fibroblasts and augment interstitial collagen deposition. DM, diabetes mellitus; DMCMP: diabetic cardiomyopathy; HFPEF, heart failure with preserved ejection fraction; ROS: reactive oxygen species; NO, nitric oxide; PKG, protein kinase G; $F_{passive}$: cardiomyocyte resting tension; AGEs, advanced glycation end-products; PKC, protein kinase C.

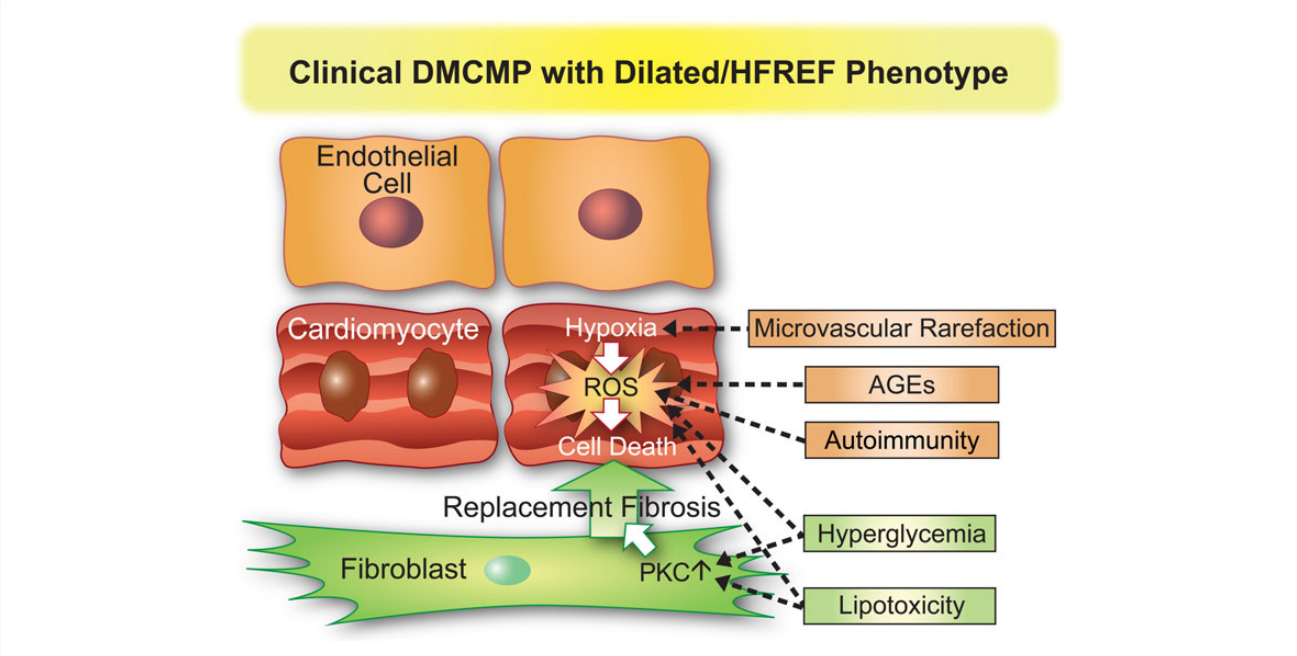


**Figure 4** DM-related pathophysiological mechanisms in diabetes mellitus-related cardiomyopathy with dilated/ heart failure with reduced ejection fraction phenotype. In diabetes mellitus-related cardiomyopathy with dilated/ heart failure with reduced ejection fraction phenotype cardiomyocyte cell death drives left ventricular remodelling and dysfunction. Cardiomyocyte cell death results from oxidative stress within the cardiomyocyte compartment because of tissue hypoxia induced by microvascular rarefaction, presence of autoimmunity-related inflammatory cells, advanced glycation end-products deposition and possibly hyperglycaemia and lipotoxicity. Because of cardiomyocyte cell death there is extensive replacement fibrosis, which is reinforced by high PKC in fibroblasts because of hyperglycaemia and lipotoxicity. DM, diabetes mellitus; DMCMP, diabetic cardiomyopathy; HFREF, heart failure with reduced ejection fraction; ROS, reactive oxygen species; AGEs, advanced glycation end-products; PKC, protein kinase C.

is relevant to the development of DMCMP with restrictive/HFPEF phenotype. Diabetes mellitus-related cardiomyopathy with restrictive/HFPEF phenotype was indeed observed in the aforementioned DM patients with cardiac steatosis, in whom high myocardial triglyceride content related to diastolic LV dysfunction.[51]

## Microvascular advanced glycation end-products deposition

In both DMCMP phenotypes, there is abundant myocardial microvascular AGEs deposition (*Figure 2*).[19] Light microscopic immunohistochemical visualization of the AGE *N*-$^{\varepsilon}$(carboxymethyl)lysine (CML) shows its deposition in the endothelial and smooth muscle cells of the myocardial microvasculature.[19,38] Vascular deposition of AGEs triggers vascular inflammation and quenches endothelially produced NO.[54–56] This lowers myocardial NO bioavailability and predisposes to concentric LV remodelling and high diastolic LV stiffness as observed in DMCMP with restrictive/HFPEF phenotype. Electron microscopic immunohistochemical visualization of the AGE CML reveals that AGEs are also deposited in the myocardial interstitium in between cardiomyocytes.[57] Interstitial AGEs deposition triggers reactive oxygen species production in cardiomyocytes by NADPH oxidase,[58] which could lead to activation of cell death pathways and eccentric LV remodelling with systolic LV dysfunction as observed in DMCMP with dilated/HFREF phenotype. The extent of AGEs deposition is relevant to the therapeutic use of AGE cross-link breakers such as alagebrium hydrochloride, which yielded favourable results in a limited phase II trial[59] but failed in a large outcome trial.[60]

## Microvascular rarefaction

Apart from vascular AGEs deposition, DM impairs myocardial perfusion through microvascular rarefaction with a reduction in coronary flow reserve.[61] Microvascular rarefaction implies a reduced capillary surface area relative to cardiomyocyte surface area and results mainly from cardiomyocyte hypertrophy.[19] Microvascular rarefaction lowers NO bioavailability for adjacent cardiomyocytes and can therefore contribute to DMCMP with restrictive/HFPEF phenotype. Microvascular rarefaction could eventually also lead to tissue hypoxia with production of reactive oxygen species, cell death, and DMCMP with dilated/HFREF phenotype.

## Autoimmunity

Cardiac myosin autoantibody signatures were identified that were shared between type 1 DM (T1DM) patients after myocardial infarction and non-diabetic patients with myocarditis. These findings suggested a post-MI autoimmune syndrome in T1DM patients.[62] Patients with DM were recently also shown to have cardiac release of troponin T, which was related to clinical outcome.[63] Such a continuous release of troponin T could trigger an autoimmune response, especially in autoimmune-prone T1DM patients and predispose them to DMCMP with dilated/HFREF phenotype.

## Insulin resistance/hyperinsulinaemia

Insulin resistance/hyperinsulinaemia is another important metabolic disturbance especially in obese T2DM patients. Insulin resistance induces a cluster of metabolic or signalling derangements especially relevant to DMCMP with restrictive/HFPEF phenotype.[64–66] The underlying obesity causes a systemic pro-inflammatory state with high circulating levels of pro-inflammatory cytokines,[67] which induce endothelial production of reactive oxygen species and reduce NO bioavailability for neighbouring cardiomyocytes.[16] Insulin resistance impairs myocardial glucose utilization and leads to less efficient high-energy phosphate production through increased expression of myocardial uncoupling proteins with production of heat rather than adenosine triphosphate (ATP).[68,69] As a result, a low phosphocreatine/adenosine triphosphate (PCr/ATP) ratio has been observed in obese, T2DM, and HFPEF patients.[70–72] In all these conditions, it was related to diastolic LV dysfunction at rest or during exercise. Insulin resistance also affects a number of signalling pathways, which are involved in cardiomyocyte hypertrophy, such as PI3K/Akt signalling.[73] Hyperinsulinaemia could therefore account for the pronounced cardiomyocyte hypertrophy observed in DMCMP with restrictive/HFPEF phenotype.[19] Via PI3K/Akt signalling, insulin also directly reduces cardiomyocyte distensibility as it enhances expression of the stiff N2B titin isoform.[74]

*Table 1* summarizes the relevance of DM-related pathophysiological mechanisms for both DMCMP phenotypes. Metabolic abnormalities such as hyperglycaemia, lipotoxicity, and insulin resistance/hyperinsulinaemia favour the development of DMCMP with restrictive/HFPEF phenotype. In contrast, autoimmunity, which usually manifests itself in autoimmune-prone T1DM patients, predisposes to a myocarditis-like DMCMP with dilated/HFREF phenotype. Limited myocardial perfusion because of AGEs deposition and microvascular rarefaction could be relevant for both DMCMP phenotypes because of reduced endothelial NO production, which favours development of DMCMP with restrictive/HFPEF phenotype and because of tissue hypoxia, which induces cardiomyocyte cell death and DMCMP with dilated/HFREF phenotype. Other pathophysiological mechanisms could be relevant for subsets of DM patients such as DM patients suffering from autonomic neuropathy. In these patients, sympathetic denervation causes impaired β-adrenergic signalling which reduces myocardial contractile strength, relaxation kinetics, and diastolic distensibility.[75,76]

**Table 1 Relative importance of DM-related pathophysiological mechanisms for development of diabetes mellitus-related cardiomyopathy with restrictive/ heart failure with preserved left ventricular ejection fraction or dilated/ heart failure with reduced ejection fraction phenotypes**

| | DMCMP with restrictive/HFPEF phenotype | DMCMP with dilated/HFREF phenotype |
|---|---|---|
| Hyperglycaemia | +++ | + |
| Lipotoxicity | +++ | + |
| AGEs deposition | +++ | +++ |
| Microvascular rarefaction | +++ | +++ |
| Autoimmunity | − | +++ |
| Insulin resistance/ Hyperinsulinaemia | +++ | − |

DM, diabetes mellitus; DMCMP, diabetic cardiomyopathy; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; AGEs, advanced glycation end-products.

# Diagnosis of diabetes mellitus-related cardiomyopathy with restrictive/heart failure with preserved left ventricular ejection fraction phenotype

Diabetes mellitus-related cardiomyopathy patients with restrictive/HFPEF phenotype are usually obese and suffer of T2DM. Patients will present with complaints of dyspnoea and/or pedal oedema. Physical examination will reveal an S4 gallop sound and signs of left- and right-sided congestion such as bibasilar rales, distended neck veins, and increased liver span.

The diagnosis of DMCMP with restrictive/HFPEF phenotype requires exclusion of coronary artery, valvular, congenital, infiltrative, or hypertensive heart disease[4] (*Table 2* and *Figure 5*). Presence of significant coronary artery, valvular, or congenital heart disease can easily be excluded using coronary angiography and Doppler echocardiographic imaging. Endomyocardial biopsy is indicated when there is concern about infiltrative heart disease. In accordance to published guidelines, HF associated with unexplained restrictive cardiomyopathy is considered a class IIa indication for endomyocardial biopsy procurement.[77] The relative importance of arterial hypertension and DM for a restrictive/HFPEF phenotype of LV remodelling is often difficult to establish as it is unclear if the observed concentric LV remodelling and diastolic LV dysfunction are caused by the systolic LV overload of arterial hypertension or by the metabolic disturbances of DM. Some recent evidence favours diastolic LV dysfunction to be maintained more by metabolic disturbances than by systolic overload. In the MONICA registry left atrial size, a reliable measure of chronic diastolic LV dysfunction, strongly related to body mass index and weakly to ageing but failed to relate to arterial hypertension.[78] Similarly, a Japanese study identified body mass index but not arterial hypertension as a significant predictor of HFPEF development in DM.[79] Finally, a recent epidemiological survey in Olmsted County revealed ageing-related changes in diastolic LV stiffness to be related to gain in body weight and unrelated to blood pressure.[80]

After exclusion of concomitant coronary, valvular, congenital, infiltrative, or hypertensive heart disease, the diagnosis of DMCMP with restrictive/HFPEF phenotype requires evidence of normal systolic LV function, of diastolic LV dysfunction, and of impaired glucose metabolism. Evidence of normal systolic LV function and of diastolic LV dysfunction can be obtained as outlined in the recent recommendations for the diagnosis of HFPEF established by the HF and echocardiography associations of the ESC.[9] Evidence of normal systolic LV function has to consist not only of a normal LVEF (≥50%) but also of a normal LV end-diastolic volume index (≤97 mL/m$^2$). Evidence of diastolic LV dysfunction can be obtained

**Table 2 Comparison between diabetes mellitus-related cardiomyopathy with restrictive/ heart failure with preserved left ventricular ejection fraction and dilated/ heart failure with reduced ejection fraction phenotypes**

| | DMCMP with restrictive/HFPEF phenotype | DMCMP with dilated/HFREF phenotype |
|---|---|---|
| Pathophysiology | | |
| *Myocardial structure* | | |
| | Cardiomyocyte hypertrophy | Cardiomyocyte apoptosis |
| | Reactive interstitial fibrosis | Cardiomyocyte necrosis |
| | Microvascular AGEs | Reactive interstitial fibrosis |
| | Microvascular rarefaction | Replacement fibrosis |
| | | Microvascular AGEs |
| | | Microvascular rarefaction |
| *Myocardial function* | | |
| | Cardiomyocyte stiffness ↑↑ | Cardiomyocyte stiffness ↑ |
| | | Cardiomyocyte shortening ↓ |
| *Mechanisms* | | |
| | Endothelial dysfunction caused by hyperglycaemia, lipotoxicity, and AGEs | Cardiomyocyte cell death caused by autoimmunity and AGEs |
| | Microvascular dysfunction leading to low NO bioavailability | Microvascular dysfunction leading to cardiomyocyte hypoxia |
| | Cardiomyocyte hypertrophy because of hyperinsulinaemia | |
| Diagnosis | | |
| | DM (mainly T2DM, obese) | DM (mainly longstanding T1DM) |
| | Dyspnoea and signs of congestion, S4 Gallop | Dyspnoea and signs of congestion, S3 Gallop |
| | No coronary, valvular, or congenital cardiac disease | No coronary, valvular, or congenital cardiac disease |
| | No arterial hypertension | No arterial hypertension |
| | No infiltrative heart disease in endomyocardial biopsy | No inflammation or virus in endomyocardial biopsy |
| | LVEF $\geq$50% | LVEF $<$50% |
| | LVEDVI $\leq$97 mL/m$^2$ | LVEDVI $>$97 mL/m$^2$ |
| | Diastolic LV dysfunction | |
| Treatment | | |
| | Diuretics | ACEIs, ARBs, $\beta$-blockers, mineralocorticoid-receptor antagonists, ivabradine |
| | | Resynchronization |

DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; DMCMP, diabetic cardiomyopathy; HFPEF, heart failure with preserved ejection fraction; HFREF, heart failure with reduced ejection fraction; AGEs, advanced glycation end-products; NO, nitric oxide; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

invasively or non-invasively with Doppler echocardiography and biomarkers. Only when $E/E'$ (ratio of early transmitral velocity to TDI mitral annular early diastolic velocity) exceeds 15, does Doppler echocardiography provide direct evidence of diastolic LV dysfunction. When $8 < E/E' < 15$, secondary evidence of diastolic LV dysfunction is required. This can be derived from mitral flow velocity Doppler, combined mitral and pulmonary vein flow velocity Doppler, left atrial size, LV hypertrophy and presence of atrial fibrillation or elevated natriuretic peptides. Natriuretic peptides do not provide stand-alone evidence of diastolic LV dysfunction because of their poor positive predictive value for HFPEF. Patients with HFPEF indeed have lower plasma natriuretic peptide levels than patients with HFREF.[81] Levels are especially low in HFPEF patients presenting in an outpatient clinic with complaints of limited exercise tolerance.[82] The limited value of natriuretic peptides for the diagnosis of HFPEF was confirmed in the large HFPEF registry of the diastolic congestive heart failure study[83] which observed a sensitivity of 65% for the diagnosis of HFPEF when using the recommended N-terminal-pro brain natriuretic peptide cut-off value of 220 pg/mL.[9] Even lower sensitivities (27 and 38%) were recently reported in a critical comparison of diagnostic HFPEF algorithms.[84] This comparative analysis of HFPEF algorithms confirmed the diagnostic accuracy of the recommendations for the diagnosis of diastolic LV dysfunction established by the HF and echocardiography associations of the ESC[9] as sensitivity and specificity of this algorithm were the highest, equalling, respectively, 76 and 85%.

The diagnosis of DMCMP with restrictive/HFPEF phenotype requires evidence of impaired glucose metabolism. It should be noted that insulin resistance usually precedes manifest hyperglycaemia by years if not decades. Accordingly, a substantial proportion of patients is in a state of latent impairment of glucose metabolism without manifest hyperglycaemia.[85,86]

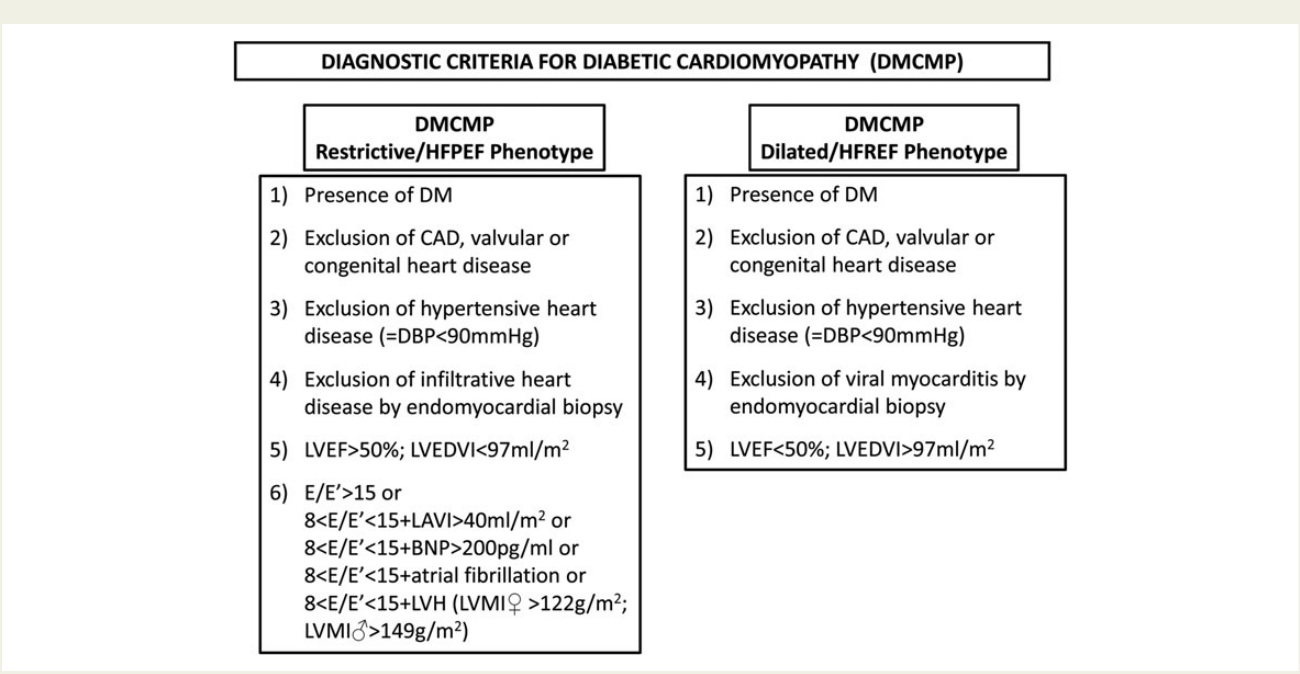


**Figure 5** Diagnostic criteria fordiabetes mellitus-related cardiomyopathy. DM, diabetes mellitus; DMCMP, diabetic cardiomyopathy; HFPEF, heart failure with preserved ejection fraction; HFREF: heart failure with reduced ejection fraction; CAD, coronary artery disease; DBP, diastolic blood pressure. *E/E'*, ratio of early transmitral velocity to TDI mitral annular early diastolic velocity; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; BNP, brain natriuretic peptide; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index.

The future diagnosis of DMCMP with restrictive/HFPEF phenotype will probably rely more heavily on use of biomarkers[87] and on cardiac magnetic resonance imaging. A series of recent studies indeed demonstrated HFPEF to be associated with high plasma levels of biomarkers of inflammation and of collagen turnover.[88–90] Cardiac magnetic resonance is useful for the diagnosis of DMCMP with restrictive/HFPEF phenotype as it allows for accurate assessment of left atrial volume and LV mass and of interstitial fibrosis using T1 mapping technique.

# Treatment of diabetes mellitus-related cardiomyopathy with restrictive/heart failure with preserved left ventricular ejection fraction phenotype

## HF treatment

In contrast to HFREF, large outcome trials in HFPEF using angiotensin-converting enzyme inhibitors (ACEis), angiotensin II receptor blockers (ARBs), and mineralocorticoid-receptor antagonists yielded neutral results for endpoints such as overall mortality, cardiac mortality, or need for hospitalizations.[91–93] Because of absence of prognostic benefit of ACEis, ARBs, or spironolactone, current HF guidelines limit treatment recommendations for HFPEF to control of arterial hypertension and use of diuretics.[94] Use of β-blockers in HFPEF is also questionable. A recent study, that assessed β-blocker use in HFPEF, actually demonstrated worse outcome in terms of symptoms or need for hospitalizations especially in women.[95] The neutral outcome of the large HFPEF treatment trials has been related to unsatisfactory HFPEF patient recruitment criteria,[17] but it may also relate to different mechanisms driving LV remodelling in HFPEF and HFREF. Concentric LV remodelling in HFPEF was recently proposed to be driven by coronary microvascular endothelial inflammation because of comorbidities in contrast to eccentric LV remodelling in HFREF, which is driven by cardiomyocyte death because of ischaemia, viral infection, or toxicity.[16] This new paradigm emphasizes the importance of metabolic comorbidities like obesity and DM, which constantly fuel the LV remodelling process in HFPEF through a systemic pro-inflammatory state. Against such a relentless pro-inflammatory background, inefficacy in HFPEF of neurohumoral blockade is no surprise because in HFREF viral persistence or failure to discontinue toxic agents also greatly reduces the benefit of neurohumoral blockade.

## Lifestyle modification

Over the last decennium numerous investigators attempted to correct diastolic LV dysfunction of DMCMP with restrictive/HFPEF phenotype through manipulation of myocardial metabolism. In these patients, myocardial glucose uptake is replaced by uptake of non-esterified fatty acids and this substrate switch is associated with diastolic LV dysfunction.[48,96] Prolonged caloric restriction in obese T2DM patients decreased myocardial triglyceride content and improved diastolic LV dysfunction.[97] Following an exercise training programme, obese patients with normal LVEF (>50%) lowered

cardiac lipid content and raised LVEF by 2%[98] but T2DM patients with normal LVEF failed to decrease cardiac lipid content despite a similar 5% improvement in LVEF.[99] These data on the effects of lifestyle modification indicate coupling between myocardial metabolism and function to vary in accordance to extent of metabolic compromise (e.g. obesity vs. DM) and support the notion of myocardial metabolic inflexibility in DM.[100] Metabolic inflexibility was also obvious from the use of acipimox, which inhibits lipolysis and drastically lowers serum free fatty acid concentrations. Acipimox deteriorated cardiac efficiency consistent with inability to use glucose as alternative metabolic substrate.[101] In an intention to treat analysis participation in a regular exercise programme failed to alter progression of diastolic LV dysfunction in DMCMP patients with restrictive/HFPEF phenotype but in the subset of patients that finished the 3 year programme it prevented progression of diastolic LV dysfunction.[102] The positive outcome of exercise training in DMCMP with restrictive/HFPEF phenotype is in line with beneficial effects of similar exercise training programmes in the overall HFPEF population.[103,104]

## Glucose-lowering medications

### Metformin and sulfonylureas

Metformin exerts its favourable action through reduced hepatic glucose production and activation of adenosine monophosphate activated protein kinase (AMPK). Because of activation of AMPK, metformin could induce regression of myocardial hypertrophy. Several randomized trials however failed to clinically substantiate this effect. Because of concerns of induction of lactic acidosis, metformin was considered contraindicated in HF. Recently, these concerns appeared unjustified and metformin is considered safe in patients with both DM and HF.[105] Treatment with metformine also restores endothelium-dependent vasodilation through increased NO bioavailability. In a comparative analysis with pioglitazone, metformin however failed to improve LV stiffness in T2DM despite increased NO bioavailability.[106] Sulfonylureas bind to ATP-sensitive potassium channels, which are involved in the myocardial response to ischaemia. As they can potentially interfere with adaptive responses to ischaemia, their use in DMCMP is not recommended.

### Thiazolidinediones

Pioglitazone has been shown to improve diastolic LV stiffness in men with uncomplicated T2DM, in whom inducible ischaemia was excluded.[106] This improvement was accompanied by a higher glucose but unchanged fatty acid uptake, oxidation, or esterification and therefore probably resulted from mechanistic pathways directly affecting diastolic LV dysfunction. In this respect, a substudy of this trial demonstrated significant associations between diastolic LV dysfunction and adiponectin or osteoprotegerin, a soluble member of the TNF receptor superfamily.[107] Whether the pioglitazone-induced improvement of diastolic LV dysfunction translates into prognostic or symptomatic benefit for DMCMP with restrictive/HFPEF phenotype remains doubtful because of reports of aggravated oedema with thiazolidinediones.[108]

### Insulin

Use of the intense insulin therapy also failed to provide evidence that diastolic LV dysfunction in DMCMP with restrictive/HFPEF phenotype can be corrected by manipulation of myocardial metabolism. Despite a promising pilot study,[109] the DADD trial which compared the effects on diastolic LV dysfunction of intense insulin and oral glucose-lowering therapy had a neutral outcome.[110] This neutral outcome could be explained by the relatively good glycaemic control prior to the intervention and by the opposite evolution of BMI in both study groups with weight gain in the intense insulin and weight loss in the control group. The latter suggests a harmful effect on obesity to eventually override a beneficial effect on hyperglycaemia.

### Dipeptidyl peptidase 4 inhibitors and GLP-1 agonists

Use of dipeptidyl peptidase 4 (DPP4) inhibitors has recently been linked to an increased incidence of HF hospitalizations without raising the incidence of myocardial infarctions or strokes.[111–113] The HF phenotype (HFPEF or HFREF) responsible for this increased incidence of HF hospitalizations remains unclear but in the absence of an increased incidence of myocardial infarctions, an HFPEF phenotype seems likely. A higher incidence of HF in DM patients treated with either thiazolidinediones or DPP4 inhibitors raises suspicion that it is not a class-specific side-effect but more generally linked to forced entry of glucose into metabolically inflexible cardiomyocytes. A forced entry of glucose stimulates glycolysis and leads to intracellular acidosis when glucose oxidation fails to rise proportionally. This mechanism has previously also been invoked to explain the neutral outcome of glucose-insulin-potassium regimens.[114] As intracellular acidosis reduces distensibility of titin,[115] it could adversely affect diastolic LV dysfunction in DMCMP with restrictive/HFPEF phenotype. Despite favourable reports of glucagon like peptide-1 agonists on myocardial function in animal studies, a meta-analysis failed to reveal a significant effect on natriuretic peptide levels in HF.[116]

### Sodium glucose transporter 2 inhibitors

Sodium glucose transporter 2 inhibitors lower blood glucose through increased renal glucose elimination.[117] Because their mode of action is insulin independent, they promote weight loss and avoid deleterious effects of hyperinsulinaemia on diastolic LV function. Eventual beneficial effects on DMCMP with restrictive/HFPEF phenotype still need to be evaluated.

# Diagnosis of diabetes mellitus-related cardiomyopathy with dilated/heart failure with reduced ejection fraction phenotype

Diabetes mellitus-related cardiomyopathy patients with dilated/HFREF phenotype usually have longstanding T1DM. Patients will present with complaints of dyspnoea and/or pedal oedema. Physical examination will reveal a displaced apical impulse, an S3 gallop sound and signs of left- and right-sided congestion.

Diagnosis of DMCMP with dilated/HFREF phenotype is based on: (i) exclusion of coronary, valvular, congenital, or hypertensive heart disease; (ii) evidence of eccentric LV remodelling with LV cavity dilatation and depressed LVEF; (iii) exclusion of dilated familial cardiomyopathy or dilated cardiomyopathy induced by toxic agents or

myocarditis; and (iv) the presence of impaired glucose metabolism evident from fasting or post-load hyperglycaemia (*Table 2* and *Figure 5*). Significant coronary, valvular, or congenital heart disease should be excluded by coronary angiography, Doppler echocardiographic or MRI imaging. The same imaging techniques will also provide evidence of eccentric LV remodelling (i.e. low LV mass/volume ratio), depressed LVEF (<50%), and LV cavity dilatation (LVEDVI >97 mL/m$^2$). For the diagnosis of dilated familial cardiomyopathy, a gene defect specifically affecting cardiac muscle proteins should be identified because familial occurrence of T1DM could also be responsible for hereditary DMCMP with dilated/HFREF phenotype. Diabetes mellitus-related cardiomyopathy with dilated/HFREF phenotype can be difficult to distinguish from dilated cardiomyopathy following viral myocarditis. Under these circumstances endomyocardial biopsy is useful. Presence of an inflammatory infiltrate makes cardiomyopathy following viral myocarditis more likely, although diabetes sometimes presents with autoimmune features[62] and extensive AGEs deposition can trigger an inflammatory response.[54,55] Viral presence should be confirmed in the biopsy using electronmicroscopy or polymerase chain reaction.[118] Electronmicroscopy can also reveal nuclear blebs characteristic of familial laminopathies. Although endomyocardial biopsy can provide evidence for exclusion of ongoing myocarditis, it currently does not provide positive arguments for the diagnosis of DMCMP with dilated/HFREF phenotype. In this respect, immunohistochemical quantification of myocardial microvascular AGEs deposition[19,38] could provide a diagnostic inroad because of the association of DMCMP with dilated/HFREF phenotype with other manifestations of microangiopathy such as glomerulosclerosis or retinopathy.[3] Cardiac magnetic resonance is also helpful for the diagnosis of DMCMP with dilated/HFREF phenotype as it allows for accurate assessment of LV volumes, LVEF, LV mass, and replacement fibrosis using late gadolinium enhancement.

# Treatment of diabetes mellitus-related cardiomyopathy with dilated/heart failure with reduced ejection fraction phenotype

## HF treatment

Treatment of DMCMP with dilated/HFREF phenotype should be conducted in accordance to current guidelines[94] and includes a combination of ACEis, ARBs, β-blockers, aldosterone antagonists, ivabradine, and resynchronization therapy. Although these treatment modalities have not been formally tested in DMCMP with dilated/HFREF phenotype, most of them have been assessed in subgroups of HFREF patients with DM, in whom positive outcome persisted.[119,120]

## Glucose-lowering medications

The use of insulin in advanced HF with HFREF phenotype is associated with an increased mortality risk.[121] It remains however unclear if this higher risk relates to use of insulin or to longer duration of DM. Numerous experimental studies observed beneficial effects of metformin in ischaemic myocardium. Clinical outcome studies however failed to confirm these observations.[122] Sitagliptin was also reported to improve function of ischaemic myocardium[123] but in view of the recently reported increase in HF with use of DPP-4 inhibitors,[111,112] this action apparently has limited clinical relevance.

# Clinical perspective

Diabetes mellitus-related cardiomyopathy was initially identified as a cardiomyopathy with a dilated/HFREF phenotype. Currently it manifests itself mainly as a cardiomyopathy with a restrictive/HFPEF phenotype. The existence of two distinct DMCMP phenotypes could be related to unequal contributions of DM-linked pathophysiological mechanisms, which result in coronary microvascular endothelial dysfunction in DMCMP with restrictive/HFPEF phenotype and in cardiomyocyte cell death in DMCMP with dilated/HFREF phenotype. Future research into pathophysiological mechanisms responsible for DMCMP should be phenotype specific and focus on signalling between endothelium and cardiomyocytes in DMCMP with restrictive/HFPEF phenotype and on autoimmunity directed against cardiomyocytes in DMCMP with dilated/HFREF phenotype. Diagnostic algorithms and therapeutic strategies also differ in both phenotypes. Guidelines-based HF therapy is applicable to DMCMP with dilated/HFREF phenotype in contrast to DMCMP with restrictive/HFPEF phenotype which seems to benefit more from lifestyle modification. Future large outcome trials for treatment of DMCMP should use phenotype-specific patient cohorts and address pathophysiological mechanisms relevant for each phenotype.

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