

## Diabetic Cardiomyopathy and Heart Failure

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### Introduction

The global prevalence of diabetes, especially type 2 diabetes mellitus (T2DM), has been on a concerning upward trend over the years.<sup>1</sup> The most recent estimates published in the International Diabetes Federation *Diabetes Atlas* account for more than 450 million adults with diabetes worldwide, with 693 million persons estimated to have T2DM by the year 2045.<sup>2</sup> This diabetes pandemic will impose a significant burden on society, both in terms of substantial costs to the healthcare system and poor health outcomes for T2DM patients.<sup>2</sup>

The Framingham Heart Study demonstrated the epidemiological linkage between diabetes and increased risk of heart failure (HF).<sup>3</sup> It is well established that diabetes not only increases the risk of HF, but also increases its incidence by approximately 2.5-fold regardless of age or other comorbidities.<sup>1</sup> Diabetic patients now represent up to one-third of participants in HF clinical trials, with diabetes being an independent predictor of poor outcome<sup>4,5</sup> and a leading driver of the worldwide HF epidemic.<sup>6</sup>

Diabetic cardiomyopathy can be defined by the development of structural and functional abnormalities in the myocardium in the absence of other cardiac risk factors, such as coronary artery disease, hypertension, or significant valve disease, in individuals with diabetes.<sup>7</sup> The term diabetic cardiomyopathy was first used by Rubler in 1972 to describe a small cohort of 4 patients. The author demonstrated that there was no evidence of coronary artery disease on postmortem examination of the 4 study patients with diabetic glomerulosclerosis and HF.<sup>7</sup> Myocardial hypertrophy and fibrosis were observed in these patients, suggesting a role of altered metabolism in these findings. Rubler's findings meet the contemporary European Society of Cardiology definition of cardiomyopathy.<sup>8</sup> Further supporting this work, Regan<sup>9</sup> in 1977 performed postmortem examinations in 11 patients with uncomplicated diabetes and found that 9 did not have coronary artery disease and most had died of HF. Multiple specimens from the left ventricle (LV) and interventricular septum revealed increased levels of triglycerides and cholesterol compared to controls. Therefore, the presence of

a diffuse extravascular abnormality has been suggested as the basis for diabetic cardiomyopathy.<sup>9</sup>

### Clinical features of diabetes-associated cardiomyopathy

Studies show that the prevalence of HF in patients with diabetes ranges from 19% to 26%, and this association was independent of obesity, hypertension, dyslipidemia, and coronary artery involvement.<sup>3</sup> One study showed that the incidence of HF was higher in diabetics (39%) compared to non-diabetics (23%), with a relative risk of 1.3 for developing HF after 43 months of observation.<sup>10</sup> Additional data from population-based observational studies such as the Cardiovascular Health Study (CHS),<sup>11</sup> the Strong Heart Study (SHS),<sup>12</sup> and the Multi-Ethnic Study of Atherosclerosis (MESA)<sup>13</sup> demonstrated differences in LV wall mass and thickness and increased rates of diastolic and systolic dysfunction in diabetic patients compared to non-diabetic subjects. In patients with T2DM, every 1% increase in glycated hemoglobin levels was associated with an 8% increase in the risk of HF, independent of other risk factors such as obesity, smoking, hypertension, dyslipidemia, and coronary artery disease, suggesting that gradual increases in blood glucose are a powerful promoter of HF in diabetes.<sup>14</sup>

Hyperglycemia and systemic insulin resistance are the core clinical abnormalities of diabetes, and both are involved in the pathogenesis of diabetic cardiomyopathy.<sup>15</sup> In its early stages, diabetic cardiomyopathy is usually asymptomatic. One of the first manifestations is LV hypertrophy and/or decreased LV compliance, characterized by impaired early diastolic filling, increased atrial filling, and prolonged isovolumic relaxation time. LV enlargement and symptomatic HF follow the development of systolic dysfunction.<sup>15</sup> Cardiomyocyte stiffness and hypertrophy, as well as myocardial fibrosis, contribute to this abnormality (Figure 1). The CHS found that, in a cohort of 5,201 men and women, ventricular septal and left posterior myocardial wall thicknesses were greater in diabetic than in non-diabetic subjects, and that this finding was associated with impaired systolic and/or diastolic function.<sup>11</sup>

The clinical course of diabetic cardiomyopathy can be divided into two stages. The first stage is clinically asymptomatic and characterized by increased fibrosis and stiffness; there is a reduction in early diastolic filling, remodeling of atrial volumes, and an increase in LV end-diastolic pressure.<sup>16</sup> Underlying pathological factors include hyperglycemia, systemic and cardiac insulin resistance, increased levels of free fatty acids (FFA), systemic and local inflammation, and oxidative stress (Figure 1). Reduced activity of the calcium ( $\text{Ca}_2^+$ ) pump, manifested by inefficient sequestration of  $\text{Ca}_2^+$  by the sarcoplasmic reticulum, is considered to play an important role in the development of cardiac diastolic dysfunction in these patients.<sup>17</sup>

### Keywords

Diabetes Mellitus; Cardiomyopathies; Heart Failure

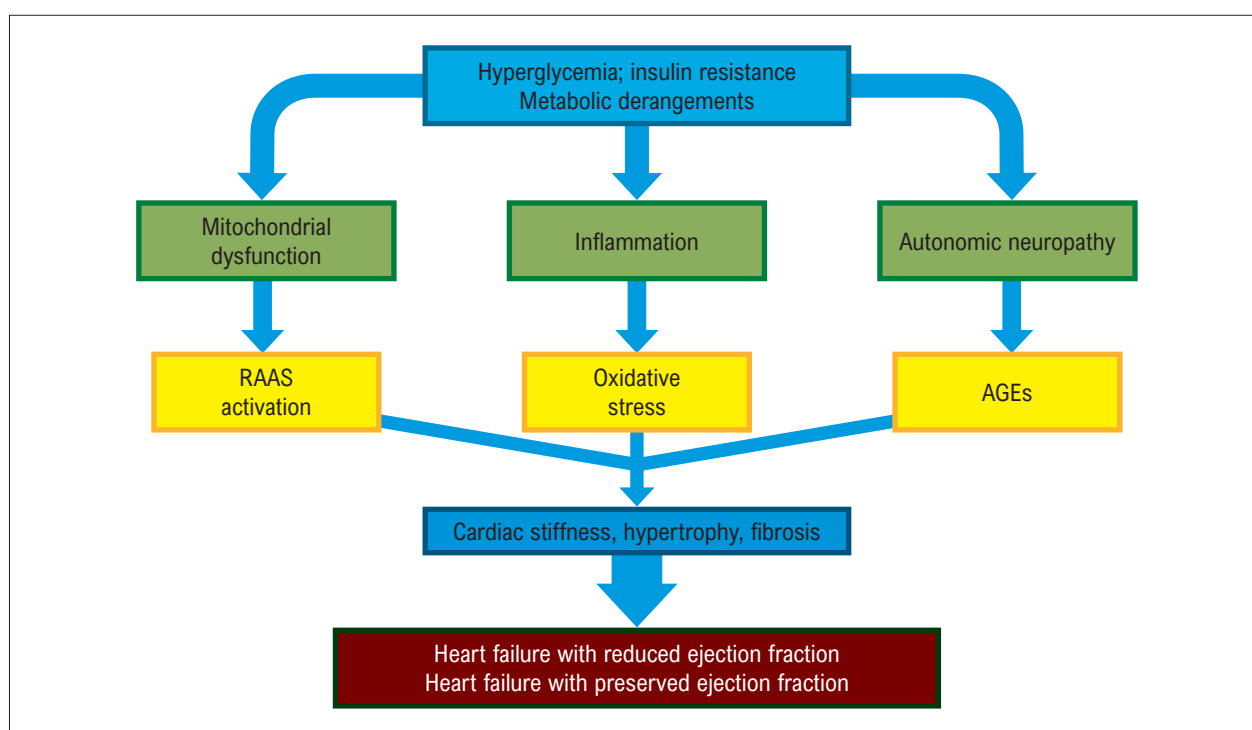
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**Figure 1** – Pathophysiological mechanisms of diabetic cardiomyopathy. Hyperglycemia, insulin resistance, and metabolic derangements within the cardiomyocyte induce insulin resistance and metabolic disorders that increase mitochondrial dysfunction, inflammation, autonomic neuropathy, oxidative stress, renin-angiotensin-aldosterone system (RAAS) activation, and advanced glycation end-products (AGE) production, leading to cardiomyocyte death as well as microvascular dysfunction. These pathophysiological abnormalities promote cardiac stiffness, hypertrophy, and fibrosis, resulting in cardiac diastolic dysfunction, systolic dysfunction, and heart failure. Adapted from Jia et al.<sup>14</sup>

The second stage of diabetic cardiomyopathy is characterized by LV hypertrophy, cardiac remodeling, worsening of diastolic dysfunction, and consequent emergence of clinical manifestations of HF with preserved ejection fraction (HFpEF). As diabetic cardiomyopathy progresses, diastolic dysfunction and reduced cardiac compliance may coexist with systolic dysfunction, leading to the reduced ejection fraction (HFrEF) phenotype.<sup>15</sup>

#### The pathophysiology of diabetes-associated cardiomyopathy

Abnormalities such as fibrosis, hypertrophy, and worsening of coronary microvascular perfusion have been evaluated in the setting of diabetes-associated cardiomyopathy. These are now known to be characteristics of the diabetic heart, both in clinical and experimental settings. Changes ranging from indices of cardiac remodeling to impairment of coronary microvascular perfusion have been recorded. These morphological defects may contribute to the functional deficiencies identified in the diabetic human heart.

Other mechanisms for the development of diabetes-induced cardiomyopathy (Figure 2) include such well-established mediators as inflammation, oxidative stress, metabolic derangements, insulin signaling, gene regulation, stress, neurohumoral activation, and cardiac cell death.<sup>18,19</sup>

The endothelium is the largest organ in the human body and is responsible for maintaining normal vessel function. It acts by regulating the release of secretory factors in response

to mechanical stimuli. The main role of the endothelium is to ensure adequate blood flow, which depends on the proper balance between vasodilators and vasoconstrictors. Vasodilators include prostacyclin  $I_2$  ( $PGI_2$ ) and nitric oxide (NO), while vasoconstrictors, including endothelin-1 (ET1) and thromboxane A2 ( $TXA_2$ ), act as a counterbalance to excessive vasodilation and maintain vascular tone. Insulin resistance and diabetes are known to be associated with endothelial dysfunction, which is also found in conditions such as obesity, physical inactivity, and smoking. These findings suggest that the complex pathophysiology of endothelial dysfunction involves multiple mechanisms and plays a role in several diseases, including in the development of diabetic cardiomyopathy.<sup>20</sup>

Impaired NO signaling is closely related to tissue damage in diabetes mellitus, characterized by dysregulation of NO generation and NO bioavailability.<sup>21</sup> Studies<sup>22</sup> have found cardiac abnormalities in diabetic rats and suggested a key role of NO in the pathophysiology of diabetic cardiomyopathy. In addition, inhibition of NO synthesis (NOS) has been found to reduce levels of NO, nitrotyrosine, and reactive oxygen species (ROS), suggesting endothelial NOS uncoupling in diabetic hearts.<sup>23</sup> ROS-induced tetrahydrobiopterin oxidation and increased asymmetric dimethylarginine (ADMA) content contribute to endothelial NOS uncoupling in T2DM.<sup>23,24</sup>

NOS is catalyzed by L-arginine and nicotinamide adenine dinucleotide phosphate (NADPH) in the presence of oxygen. However, in diabetic vessels, NOS is affected. Some studies

have suggested that the cause of NO inactivation and, therefore, NO deficiency is the increase in free radicals per se rather than downregulation of endothelial NOS activity or expression.<sup>25,26</sup>

Abnormal metabolism and mitochondrial dysfunction are associated with the metabolic derangements seen in diabetic cardiomyopathy. Hyperglycemia has been reported to cause oxidative damage to mitochondrial DNA in endothelial cells by increasing mitochondrial ROS.<sup>27</sup>

Inflammation is a major mechanism underlying diabetic cardiomyopathy. To address factors that cause damage, endothelial cells are activated and produce interleukins, chemokines, interferons, monocyte chemoattractant protein-1 (MCP-1), and other pro-inflammatory factors.<sup>28</sup> Monocytes and neutrophils are recruited to the activated endothelium after the release of these mediators, and initiate inflammation. Elevated pro-inflammatory factors stimulate endothelial cells to secrete even more pro-inflammatory factors, which in turn induce secretion of various acute-phase reactants and modulate chronic inflammation.<sup>20</sup>

Furthermore, inflammatory levels rise when endothelial cells are exposed to hyperinsulinemic serum. Mitochondrial dysfunction induces endothelial dysfunction and promotes inflammation through excess production of ROS.<sup>29,30</sup> The inflammatory state triggered by endothelial activation may thus be a consequence of an imbalance between excess ROS and insufficient antioxidants, resulting in oxidative stress and cell damage.<sup>20</sup>

Vascular endothelial cells are prone to damage from hyperglycemia due to their characteristics and location. Damaged endothelial cells cause increased vessel permeability, barrier dysfunction, and impaired vasodilation.<sup>31</sup> Hemodynamic studies suggest that the endothelium-dependent vasodilator response is altered in diabetes.<sup>32,33</sup> In diabetic cardiomyopathy, excessive release of various vasoconstrictors by endothelial cells is observed, interfering with the coronary vascular structure and ensuring normal blood flow. The balance between vasoconstrictors and vasodilators is lost in this scenario.<sup>20</sup>

In diabetic cardiomyopathy, levels of vasodilators such as NO and PGI<sub>2</sub> are elevated, as are those of vasoconstrictors such as ET1 and TXA<sub>2</sub>. ET1 is upregulated in T2DM target organs, including the heart and kidneys.<sup>34</sup> ET1 is predominantly expressed in cardiac endothelial cells compared to cardiomyocytes in normal adult cardiac tissue, highlighting the important role of endothelial cells in diabetic cardiomyopathy.<sup>35</sup> Furthermore, increased endothelin production in the diabetic heart can lead to vessel hypertrophy and increased myocardial fibrosis, both of which are characteristic of diabetic cardiomyopathy.<sup>26</sup>

The first evidence of diabetes-associated cardiac fibrosis in the human heart was largely derived from postmortem or biopsy specimens.<sup>36</sup> Increased deposition of type I and III interstitial collagen is evident in diabetic compared to non-diabetic human myocardial biopsies.<sup>36</sup> Recent approaches using cardiac magnetic resonance (CMR) T1 mapping and late gadolinium enhancement (LGE) imaging have proven useful in the noninvasive detection of cardiac fibrosis in

humans.<sup>37,38</sup> These modalities reveal that diabetes is associated with increased cardiac fibrosis, even in the absence of prior ischemic injury,<sup>5,39,40</sup> although some authors suggest that fibrosis may arise later in the course of the disease, even after deficits in cardiac function are already manifest.<sup>4</sup>

T2DM leads to LV diastolic dysfunction, restrictive LV remodeling, and HFpEF, due to induction of a pro-inflammatory state followed by deterioration of endothelial function in the coronary microvasculature. In patients with HFpEF, coronary microvascular endothelial inflammation and cardiomyocytes exposed to altered paracrine endothelial signaling contribute mainly to concentric LV remodeling.<sup>41</sup>

Another stage of diabetic cardiomyopathy is characterized by LV hypertrophy, cardiac remodeling, worsening of cardiac diastolic dysfunction and consequent emergence of HFpEF.<sup>15</sup> As diabetic cardiomyopathy progresses, diastolic dysfunction and reduced cardiac compliance may coexist, with systolic dysfunction leading to reduced ejection fraction, LV enlargement, and reduced ejection time as a consequence of reduced LV compliance. In this setting, abnormalities in the expression of contractile and regulatory proteins account for mechanical defects in cardiac contraction.<sup>15</sup>

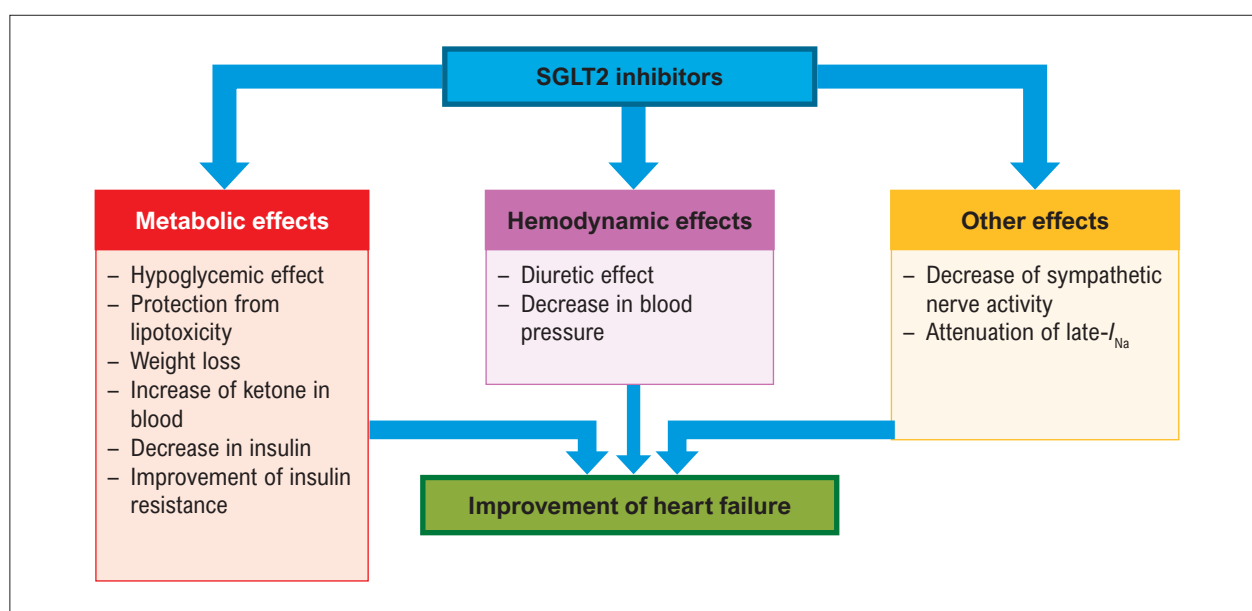
The association between decreased NO bioavailability in the coronary microcirculation and worsening diastolic function is complex, involving multiple pathways. Protein kinase G-dependent hypophosphorylation is responsible for delayed active relaxation and reduced passive distensibility of the LV. Depressed coronary flow reserve (CFR) is also a major contributor to diastolic dysfunction.<sup>20</sup>

### Diagnosis of diabetes-associated cardiomyopathy

Cardiac dysfunction is often clinically silent in diabetes and often goes undetected until its advanced stages. Even among asymptomatic, normotensive patients with well-controlled diabetes, approximately 50% will have some degree of cardiac dysfunction. It is widely accepted that one of the hallmarks of the diabetic heart is LV diastolic dysfunction – indeed, it is one of the first signs of diabetic cardiomyopathy, often detectable before clinically significant LV systolic dysfunction occurs.<sup>14,42</sup>

Until recently, the presence of isolated diastolic dysfunction as an indicator of diabetic cardiomyopathy was disputed, as patients in the early stages of diabetes were not routinely subjected to careful assessment of diastolic function. Cardiac complications of diabetes were usually only investigated after overt symptoms of HF became evident. With the advent of more sensitive imaging techniques and the more frequent recognition of HF in people affected by diabetes, this approach may change. Whether in a clinical or preclinical/laboratory setting, CMR is widely considered the gold-standard modality for assessment of cardiac function.<sup>5</sup>

However, although diabetes is associated with altered LV diastolic function parameters on CMR, this technique is not always readily available, with access particularly limited in some regional and/or low-income settings. Advances in echocardiography in recent years, both in clinical and experimental settings, now allow for relatively high-resolution, detailed, noninvasive serial assessment of cardiac function without the time-consuming nature or availability



**Figure 2** – Protective mechanisms of SGLT2 inhibitors in heart failure. There are several mechanisms by which sodium-glucose cotransporter 2 (SGLT2) inhibitors prevent and improve heart failure. These include metabolic effects, hemodynamic effects, and additional mechanisms involving decreased activity of the sympathetic system and of the late sodium current. Late- $I_{Na}$ , late component of cardiac sodium channel current. Adapted from Nakamura et al.<sup>19</sup>

and access restrictions usually imposed by CMR; as such, echocardiography is now the imaging approach of choice for most routine clinical and preclinical cardiac and interventional research studies.<sup>43</sup>

Early changes in LV diastolic function that are considered characteristic of diabetes-induced cardiomyopathy include changes in LV filling and relaxation, often in the absence of changes in LV systolic function.<sup>5,44</sup> As described in detail in the most recent guidelines published by the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging, a wide range of Doppler-based signals can be used for the assessment of various parameters of diastolic function. These parameters include those determined at end-diastole (which correlate with LV end-diastolic pressure), which are obtained by measuring the velocity of blood flow through the mitral valve (via Doppler) or the analogous velocity of movement of adjacent myocardial tissue (tissue Doppler imaging).<sup>1</sup>

Echocardiographic examination produces two main phases of movement: an initial phase, referred to as E (Doppler flow) and e' (tissue Doppler), and a later atrial phase, referred to as A on Doppler and a' on tissue Doppler.<sup>45</sup> Mitral peak A velocity and tissue Doppler-derived mitral annular a' velocity, as well as measurements obtained earlier in diastole, such as the mitral E/A ratio, E-wave deceleration time, and the E/e' ratio, are common echocardiographic parameters. Among these examples, E/e' is one of the most reproducible and reliable parameters.<sup>43</sup> Isovolumic relaxation time (IVRT) has also been widely used to assess diastolic function, but is highly dependent on heart rate and afterload.<sup>43</sup> Additional approaches include evaluation of atrial strain. Atrial cardiomyopathy is one of the aspects of diabetes-related cardiomyopathy. Dogdus et al. described impaired atrial

functions (both reservoir and contractile) in obese diabetic patients.<sup>46</sup> They also note that the presence of interatrial block in these patients is an early disease marker at the preclinical stage of HF. Dysfunction in the diabetic heart progresses from subclinical cardiac abnormalities, such as LV fibrosis, to diastolic dysfunction and, ultimately, systolic dysfunction with reduced ejection fraction. Several noninvasive techniques, including echocardiography, computed tomography, and CMR, can be used to detect changes in cardiac structure and function (particularly fibrosis).<sup>47</sup> In addition, elevated levels of atrial natriuretic peptide, B-type natriuretic peptide (BNP), and N-acetylglucosamine (O-GlcNAc), among other laboratory parameters, may also serve as markers of diabetic cardiomyopathy and HF.<sup>15</sup>

#### Heart failure with preserved ejection fraction and the diabetic heart

The HFpEF phenotype is more prevalent than the HFrEF phenotype, secondary to the increased overall prevalence of diabetes, obesity, and hypertension in an aging population.<sup>48-50</sup> HFpEF represents a spectrum of various etiologies, including hypertension, obesity, and aging, in addition to other risk factors and comorbidities. Women (particularly older women) and people with diabetes are overrepresented in the HFpEF population compared to the HFrEF population.<sup>49,51,52</sup>

However, one should not make the mistake of considering HFpEF as a single phenotype; this disorder is particularly heterogeneous, with at least three distinct groups identified.<sup>51</sup> These include the obesity-cardiometabolic phenotype, which has classically been associated with HFpEF – patients with high body mass index and marked diastolic dysfunction, commonly with concomitant diabetes and/or hypertension. Other subgroups include the natriuretic peptide deficiency



syndrome – obese patients with low BNP who are often also hypertensive – and, finally, the cardiorenal phenotype, with right ventricular failure.<sup>53,54</sup> Of these three groups, event-free survival is highest for those in the natriuretic peptide deficiency group and worst in the cardiorenal syndrome group.<sup>49</sup> Overlap and intersection between these groups of phenotypes also appears evident.<sup>48</sup>

The growing emergence and awareness of HFpEF within the field of HF research may lead some to consider diabetic cardiomyopathy simply as the manifestation of HFpEF when it coexists with diabetes, as both share several features in common. In fact, however, diabetic patients may have HFpEF or HFrEF.<sup>55,56</sup> If these diabetic patients also have microvascular complications, then an HFpEF phenotype rather than an HFrEF phenotype is more prevalent, and the prognosis is worse.<sup>55</sup> Postmortem features of human myocardium in HFpEF include clear evidence of increases in both cardiac mass and fibrosis, with reduced microvascular density.<sup>57</sup> These findings are also detectable on echocardiography.<sup>48</sup> It is likely that a large component of the increased cardiac mass is attributable to fibrosis rather than hypertrophy per se, as clinically significant hypertrophy may be evident in only approximately 50% of patients with HFpEF.<sup>57</sup> In addition to cardiac fibrosis and microvascular dysfunction, inflammation and cardiac stiffness are also evident.<sup>51</sup> Unlike what is seen in HFpEF cohorts,<sup>58</sup> diabetic cardiomyopathy seems to have no gender predilection.<sup>59</sup> Thus, although diabetic cardiomyopathy is a more complex condition than merely a manifestation of HFpEF coexisting with diabetes, it is clear that the HFpEF phenotype is enriched in diabetes.

### Treatment of diabetes-associated cardiomyopathy

HF treatment is similar for patients with and without diabetes. However, antidiabetic drugs have different effects in patients with HF, and clinicians must prioritize drugs that are safe in this setting and reduce HF-related events.<sup>60</sup>

Poor glycemic control unquestionably contributes to the increased risk of HF in patients with diabetes, with HF risk correlating with glycated hemoglobin (HbA1c) levels.<sup>61</sup> Prior to the current era, intensive glucose-lowering therapies largely failed to reduce the risk of incident HF and could even exacerbate the risk of HF – e.g., thiazolidinediones, sulfonylureas, certain dipeptidyl peptidase-4 (DPP-4) inhibitors, and, potentially, insulin and glucagon (GLP-1) agonists.<sup>62,63</sup> Although the GLP-1 agonist dulaglutide was shown to be safe and tolerable in patients with T2DM in the REWIND trial, with evidence of sustained glucose lowering (reduction in HbA1c of 0.61 percentage points over 5 months) compared with placebo over a 5-year follow-up, no differences were observed in the cumulative incidence of cardiovascular outcomes.<sup>64</sup>

However, the advent of sodium-glucose cotransporter-2 inhibitors (SGLT2i) (Figure 2) led to a major change in treatment of these patients.<sup>65,66</sup> The EMPA-REG OUTCOME trial<sup>67</sup> provided the first evidence that SGLT2i provided robust cardioprotection as well as effective glucose-lowering therapy. The risk of HF hospitalization and cardiovascular mortality was reduced by 35%–50% with empagliflozin compared to

placebo in T2DM patients.<sup>66</sup> Similar findings regarding benefits in HFrEF hospitalization and cardiovascular mortality rates were subsequently observed in clinical trials of canagliflozin<sup>68-70</sup> (CANVAS, CREDENCE, CVD-REAL) and dapagliflozin<sup>71,72</sup> (DECLARE-TIMI 58) in T2DM. Reduction in HF hospitalization thus emerged as a class effect.<sup>73</sup> Furthermore, SGLT2i therapy appears equally beneficial in T2DM patients with HFpEF or HFrEF.<sup>63</sup>

The mechanisms that contribute to SGLT2i cardioprotection, particularly with regard to their benefit in HF in the context of diabetes, remain unclear, with myriad putative mechanisms reported in the literature.<sup>74</sup> Whether beneficial effects on cardiac remodeling and/or dysfunction are evident in the diabetic heart at this time remains to be established. Although it has been suggested that the benefits of SGLT2i simply reflect mechanisms such as increased glycosuria, natriuresis, and BP reduction,<sup>75</sup> a consensus on their mechanism of cardioprotective action has not yet been reached. SGLT2 is not detected in the heart,<sup>76,77</sup> therefore, the cardioprotective effects are probably extracardiac in nature; furthermore, it is likely that more than one mechanism is implicated. Although increased glycosuria and natriuresis are likely to provide renoprotection, they are probably not sufficient to fully explain the cardiac benefit, particularly in the presence of HF.<sup>76,77</sup>

Despite this lack of consensus on the mechanism responsible, this benefit of SGLT2i has been accepted as certain and with great enthusiasm. Indeed, clinical trials are underway for SGLT2i in HF even in the absence of diabetes, and evidence is already emerging that SGLT2i are effective in non-diabetic patients with HF.<sup>78</sup> The DAPA-HF phase 3 trial, for instance, in which over 4700 HF patients with LVEF <40% were randomized to receive dapagliflozin or placebo in addition to standard care, revealed a markedly reduced risk of HF worsening or cardiovascular death in diabetics and non-diabetics alike.<sup>79</sup>

### Conclusion

The core features of diabetic cardiomyopathy include cardiac stiffness, fibrosis, and ventricular hypertrophy with diastolic dysfunction and progression to systolic dysfunction and HF. Endothelial dysfunction has been considered a crucial link in the development of diabetic cardiomyopathy. Importantly, hyperglycemia and systemic insulin resistance are independently associated with the development and progression of cardiac dysfunction and HF in diabetes. SGLT2i therapy is currently one of the most effective treatments for diabetes-associated cardiomyopathy. Effective treatment of myocardial lipotoxicity, however, remains elusive.

### Author Contributions

Conception and design of the research, Writing of the manuscript; Critical revision of the manuscript for important intellectual content: Jorge AJL, Carvalho MRM.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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