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REVIEW IN TRANSLATIONAL CARDIOVASCULAR MEDICINE

The role of hyperglycaemia in the development of diabetic cardiomyopathy

Le rôle de l'hyperglycémie dans le développement de la cardiomyopathie diabétique

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Summary Diabetes mellitus is a metabolic disorder with a chronic hyperglycaemic state. Cardiovascular diseases are the primary cause of mortality in patients with diabetes. Increasing evidence supports the existence of diabetic cardiomyopathy, a cardiac dysfunction with impaired cardiac contraction and relaxation, independent of coronary and/or valvular complications. Diabetic cardiomyopathy can lead to heart failure. Several preclinical and clinical studies have aimed to decipher the underlying mechanisms of diabetic cardiomyopathy. Among all the co-factors, hyperglycaemia seems to play an important role in this pathology.

Abbreviations: AGE, advanced glycated end-product; ATP, adenosine triphosphate; CaMKII, calmodulin kinase II; CI, confidence interval; DM, diabetes mellitus; DPP4, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide-1; GRK2, β-adrenergic receptor kinase; HbA1c, glycated haemoglobin; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; MACE3, three-point major adverse cardiovascular events; O-GlcNAc, O-linked-N-acetylglucosamine; O-GlcNAcylation, O-linked-N-acetylglucosaminylation; ROS, reactive oxygen species; SERCA, sarco/endoplasmic reticulum Ca^{2+} adenosine triphosphatase; SGLT2, sodium/glucose co-transporter 2.

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Hyperglycaemia has been shown to alter cardiac metabolism and function through several deleterious mechanisms, such as oxidative stress, inflammation, accumulation of advanced glycated end-products and upregulation of the hexosamine biosynthesis pathway. These mechanisms are responsible for the activation of hypertrophic pathways, epigenetic modifications, mitochondrial dysfunction, cell apoptosis, fibrosis and calcium mishandling, leading to cardiac stiffness, as well as contractile and relaxation dysfunction. This review aims to describe the hyperglycaemic-induced alterations that participate in diabetic cardiomyopathy, and their correlation with the severity of the disease and patient mortality, and to provide an overview of cardiac outcomes of glucose-lowering therapy.

MOTS CLÉS
Diabète ;
Glucose ;
Cardiomyopathie

Résumé Le diabète est une maladie métabolique avec une hyperglycémie chronique. Chez les patients diabétiques, les maladies cardiovasculaires représentent la principale cause de mortalité. De nombreux travaux soutiennent l'existence d'une cardiomyopathie diabétique, qui se définie par une dysfonction cardiaque, incluant une altération de la contraction et de la relaxation, qui est indépendante des complications coronaires et/ou valvulaires. La cardiomyopathie diabétique peut conduire à l'insuffisance cardiaque. De nombreuses études précliniques et cliniques ont tenté de décrypter les mécanismes sous-jacents de la cardiomyopathie diabétique. Parmi les éléments impliqués, l'hyperglycémie semble jouer un rôle important dans cette pathologie. En effet, l'hyperglycémie altère le métabolisme et la fonction cardiaque en activant plusieurs mécanismes délétères, tels que le stress oxydatif, l'inflammation, l'accumulation de produits de glycation et l'activation de la voie de biosynthèse des hexosamines. Ces mécanismes sont responsables de l'activation des voies hypertrophiques, des modifications épigénétiques, du dysfonctionnement mitochondrial, de l'apoptose cellulaire, de la fibrose et de l'altération de la signalisation calcique conduisant à une chute de la contraction et de la relaxation cardiaque. Cette revue vise à décrire les altérations induites par l'hyperglycémie, qui participent au développement de la cardiomyopathie diabétique, ainsi que la corrélation avec la gravité de la maladie et la mortalité des patients. Dans cette revue, nous abordons également l'effet bénéfique des traitements hypoglycémiants sur la fonction cardiovasculaire.

Background

Diabetes mellitus (DM) is ranked as the seventh leading cause of death and is responsible for a considerable health burden worldwide [1], with cardiovascular complications being the main cause of death. The Framingham study has shown that heart failure (HF) is the major contributor to morbi-mortality, with a risk that is doubled in patients with DM compared with in those without DM [2]. In 1972, in patients with DM, Rubler et al. [3] reported HF with left ventricular hypertrophy, but no coronary artery disease or other aetiologies, introducing for the first time the concept of diabetic cardiomyopathy, which was also described subsequently by Regan et al. [4]. The Strong Heart Study [5,6] and others [7—9] have shown that patients with DM are at 1.5-fold higher risk of HF, after adjustment for multiple co-factors, including age, sex, obesity, fat distribution, atrial fibrillation, cholesterol concentration and glycated haemoglobin (HbA1c). Since then, diabetic cardiomyopathy has been defined as a contractile and relaxation dysfunction that leads to HF, independent of coronary and/or valvular complications, hypertension, congenital cardiomyopathy or other known HF aetiologies, the underlying mechanism of which remains unclear.

Clinical studies have highlighted a correlation between glycaemia and HF prevalence in DM [10—12]. Irbarren et al. [12] showed that a 1% increase in HbA1c was associated with an 8% rise in HF hospitalization in DM, after excluding the factors cited earlier (Fig. 1). As DM is a multifactorial disease, the respective contribution of hyperglycaemia, insulin resistance and obesity to cardiac dysfunction is not clear. Interestingly, Montaigne et al. [13] found that ex vivo contractile dysfunction was associated with mitochondrial dysfunction, and was related to HbA1c level, regardless of insulin resistance or obesity, supporting the idea that hyperglycaemia is a key component of diabetic cardiac dysfunction. Similarly, preclinical studies have recently shown that hyperglycaemia alters Ca^{2+} signalling, advanced glycated end-products (AGEs) and upregulation of the hexosamine biosynthesis pathway, leading to cell apoptosis, structural modifications and contractile dysfunction.

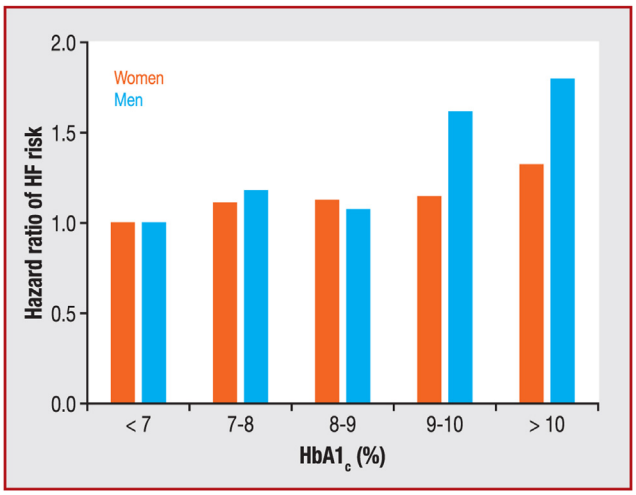

Figure 1. Relationship between glycated haemoglobin (HbA1c) level and risk of heart failure (HF) hospitalization in patients with diabetes mellitus, after adjustment for race/ethnicity, education level, cigarette smoking, alcohol consumption, hypertension, obesity, angiotensin-converting enzyme inhibitors, beta-blockers, diabetes type, diabetes duration and interim myocardial infarction. Adapted from Irbarren et al. [12].

More recently, *O*-linked-N-acetylglucosaminylation (O-GlcNAcylation), a post-translational modification of proteins, has emerged as a key player in DM and HF [14]. O-GlcNAcylation modifies protein activity by the addition of a N-acetylglucosamine to serine and threonine residues. Like phosphorylation, O-GlcNAcylation is a dynamic and rapid modification. However, in contrast to phosphorylation, O-GlcNAcylation is regulated by two different enzymes (versus hundreds for phosphorylation): *O*-linked-N-acetylglucosamine (O-GlcNAc) transferase (OGT) and O-GlcNAcase (OGA), which respectively add or remove the N-acetylglucosamine. Contrary to the N- and O-glycosylation process (which is restricted to the endoplasmic reticulum, the Golgi apparatus or secreted extracellular proteins), O-GlcNAcylation affects nuclear, cytosolic and mitochondrial proteins. In the heart, increased O-GlcNAc levels have been shown to reduce rodent myocardial infarct size [15] and ischaemia/reperfusion injury damage [16]. However, in HF, O-GlcNAcylation is increased, showing that equilibrium in O-GlcNAc homeostasis is key for normal cardiomyocyte function [17]. In patients with DM and in animal models [18], O-GlcNAcylation is upregulated and participates in diabetic cardiomyopathy. Once O-GlcNAcylation is inhibited, cardiac function is improved in DM [19,20]. Additionally, in DM, proteins undergo modification through AGE formation, involving the non-enzymatic addition of a sugar moiety (fructose or glucose) to a protein, leading to cell damage, such as oxidative stress, inflammation, alteration of Ca^{2+} signalling and cardiac stiffness [21].

This review is a translational overview of hyperglycaemia-mediated dysregulation of cardiomyocyte function and the impact on the cardiac function, with an overview of the effect of glucose-lowering drug therapy on cardiac outcomes.

Clinical evidence for the role of hyperglycaemia in the development of diabetic cardiomyopathy

Recently, two forms of HF have been described in DM: HF with reduced ejection fraction (HFrEF; defined as an ejection fraction < 40%); and HF with preserved ejection fraction (HFpEF; defined as an ejection fraction > 50%). Among patients with HFpEF, the prevalence of DM is 45%; however, little is known about the characteristics and outcomes of this population.

Epidemiological studies support a strong association between DM and HF, with a 2.4-fold increase in men with DM versus a 5-fold increase in women with DM [22], with higher hospitalization for HF (hazard ratio [HR] 1.45, 95% confidence interval [CI] 1.34—1.57) [23]. This relationship between DM and HF is bidirectional, with patients with HF having a 4-fold higher prevalence of type 2 DM than those without, rising to 40% in hospitalized patients with HF [24], and worsened HF prognosis, with a 1-year mortality rate of 30% (~1.5-fold higher in DM versus non-DM) [25]. In the CHARM trial (Candesartan in HF: Assessment of Reduction in Mortality and Morbidity), a median follow-up of 37.7 months showed, in DM, an HR of 2.0 (95% CI 1.70—2.36) in HFpEF and an HR of 1.60 (95% CI 1.44—1.77) in HFrEF [26], with an increased risk of mortality or hospitalization for HF — an observation also made in the I-PRESERVE trial [27]. The mortality risk rises to 10-fold higher with age (> 65 years) [28]. Finally, in the EVEREST trial, including patients with HFrEF, patients with DM had higher rates of postdischarge cardiovascular mortality and HF hospitalization than those without DM (HR 1.17, 95% CI 1.04—1.31) [29]. DM unfavourably affects left ventricular remodelling in patients with left ventricular pressure or volume overload [30—32], and increases the risk of arrhythmia, notably atrial fibrillation, by up to 40% [33,34]. Although a population-based control study reported a correlation between HbA1c level and HF [35], the relationship between HbA1c level and atrial fibrillation prevalence is unclear.

High glucose: epidemiologic data on HbA1c levels and mortality

Controversies concerning the link between glycaemic control, HbA1c (< 7.0%) and cardiovascular outcome have arisen from observational studies and randomized trials [36,37]. In the UKPDS study, despite an early loss of glycaemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up [36]. However, the Diabetes Control and Complications trial (DCCT), including patients with type 1 DM, reported that intensive glucose treatment had a beneficial effect on cardiovascular events [38]. Finally, in a recent observational study, HbA1c ≥ 7% was a strong predictor for all outcomes (death, acute myocardial infarction, stroke and hospitalization for HF), especially atherothrombotic events [23]. Conversely, follow-up in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [39], the Action in Diabetes and Vascular disease (ADVANCE) trial [40] and the Veterans Affairs Diabetes trial (VADT) [41] showed no

evidence of cardiovascular benefit from intensive compared with standard glycaemic control.

Evolution of diabetic cardiomyopathy

Consensus definition

Nowadays, diabetic cardiomyopathy is recognized in international guidelines [42,43] as a specific and direct aetiology of HF in the absence of coronary artery disease, long-standing hypertension, valvular complications or any other aetiology of HF. Diabetic cardiomyopathy relies on a diagnosis of exclusion based on the presence of symptomatic cardiomyopathy and a long history of DM, with many exclusion criteria. However, because of frequent associated comorbidities, diagnosing diabetic cardiomyopathy is challenging.

Early phenotype of diabetic cardiomyopathy

American Heart Association guidelines [44] classically classify preclinical stages of HF as stage A in patients with HF risk factors, and stage B in asymptomatic patients with structural and/or functional abnormalities, whereas stages C and D refer to symptomatic HF. In asymptomatic patients with DM, an early phenotype of diabetic cardiomyopathy (stage B HF) is observed in one quarter to one third of patients. This phenotype may include left ventricular concentric remodelling or hypertrophy [6,45], left ventricular diastolic dysfunction [46,47] and mildly decreased global longitudinal strain [48—50]. Alteration of global longitudinal strain is a sensitive marker of systolic dysfunction in patients with normal ejection fraction (HFpEF) and can be the first alteration seen in the early form of diabetic cardiomyopathy [46]. Alteration of global longitudinal strain is associated with left ventricular remodelling [51] and a poorer prognosis, as assessed by all-cause mortality after a 10-year follow-up [52]. HFpEF is very common and is reported in around 40—50% of patients [46,53,54]. Diastolic dysfunction is also associated with a poorer prognosis, with an increased risk of overt HF [55]. Interestingly, when testing the exercise capacity in patients declared asymptomatic, an increased number of components of the early phenotype of stage B HF (left ventricular concentric remodelling/hypertrophy, diastolic dysfunction and altered strain) is associated with decreased exercise capacity, as assessed by peak oxygen uptake (VO_2), compared with healthy subjects [56].

Obesity and hypertension are frequent comorbidities of type 2 DM, in addition to age and sex, which may also influence cardiac phenotype. The specific contribution of all these potential causative factors is unclear, as is their synergistic contribution to cardiac dysfunction in patients with type 2 DM. Cluster analysis is an exploratory technique (without prespecified hypothesis) that provides tools to identify unknown subgroups, to classify individuals with similar characteristics into the same group (or cluster), and individuals with distinct characteristics into different clusters. Using cluster analysis in a large set of asymptomatic patients with DM, three clusters were recently identified in this population: a first cluster with preserved systolic and diastolic function (mainly men), associated with a favourable prognosis; a second cluster with obesity, hypertension and diastolic dysfunction (mostly women); and a third cluster with left ventricular hypertrophy and systolic dysfunction as assessed by strain (mainly men). The latter two clusters had similar prognoses, which were less favourable than that of the first cluster, with an increased risk of cardiovascular mortality and hospitalization [57]. Despite these data, current evidence is not strong enough to support systematic screening for stage B HF phenotype in asymptomatic patients with DM [58].

Diabetic cardiomyopathy in type 1 DM

As type 1 DM is a rare disease, finding evidence of a specific diabetic cardiomyopathy in these patients is much more challenging than in those with type 2 DM. In the early phase, the Thousand & 1 Study included 1093 patients with type 1 DM without known heart disease, with a mean age of 49.6 ± 15 years (men, 53%; mean duration of DM, 25.5 years) [59]. Among these patients, 15.5% ($n = 169$) had abnormal systolic or diastolic function, including 1.7% with left ventricular ejection fraction < 45% and 14.4% with diastolic dysfunction ($E/e \geq 12$ or $E/e = 8$—12 and left atrial volume > 34 mL/m^2). The authors reported decreased global longitudinal strain only in patients with macroalbuminuria [60]. Using positron emission tomography imaging, increased myocardial fatty acid metabolism has been reported in patients with type 1 DM [61]. In addition, impaired myocardial energetics, as assessed by magnetic resonance spectroscopy, has been shown in young subjects with uncomplicated type 1 DM, irrespective of the duration of DM [62].

In a large case-control study based on the Swedish National Diabetes Registry, and including patients with type 1 DM, DM was associated with a HR of 4.69 (95% CI 3.64—6.04), after adjustment for time-updated age, sex, time-updated DM duration and baseline comorbidities [63]. Poor glycaemic control and impaired renal function substantially increased the risk of HF.

Therefore, clinical evidence also supports the existence of a specific diabetic cardiomyopathy in patients with type 1 DM. In these patients, because of the autoimmune process, dilated phenotype with HFrEF seems to be more common than the restrictive phenotype with HFpEF [64].

Preclinical evidence for the role of hyperglycaemia in the development of diabetic cardiomyopathy

Over the years, preclinical studies have shown that glucose toxicity participates in defective cardiac metabolism and cardiomyocyte dysfunction via oxidative stress, accumulation of AGEs and the O-GlcNAcylation pathway, leading to hypertrophy, epigenetic modifications, mitochondrial dysfunction, cell apoptosis, fibrosis and Ca^{2+} mishandling. Altogether, these alterations induce cardiac stiffness and impaired cardiac contraction and relaxation, as described below (Fig. 2).

Glucose and structural modification

Structural modification of the left ventricle, leading to cardiac stiffness and impaired cardiac function, is a common feature of diabetic cardiomyopathy [58,65]. Lombarda

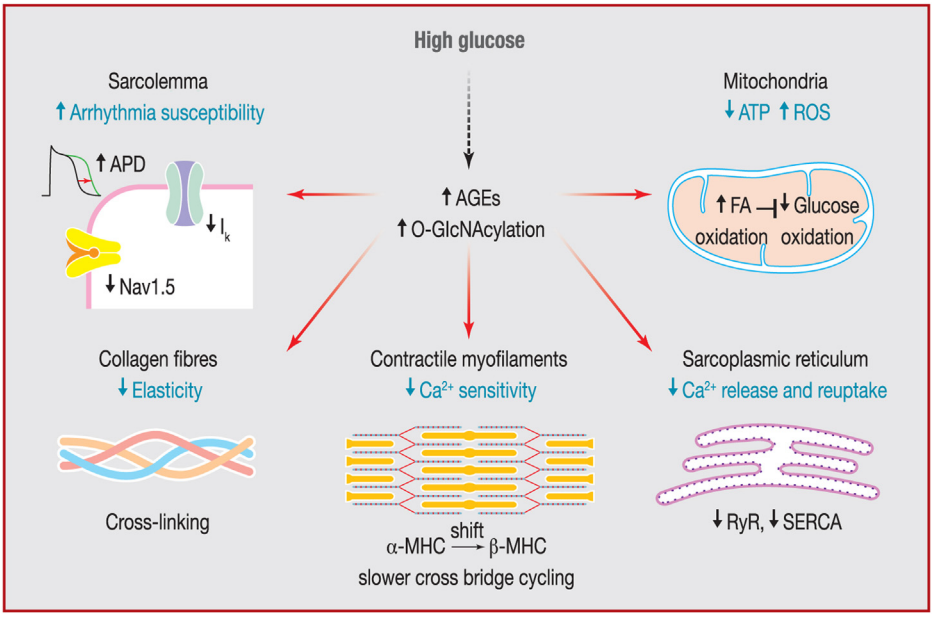

Figure 2. High glucose-mediated cellular dysfunction involved in diabetic cardiomyopathy development. High glucose induces both advanced glycated end-product (AGE) formation and upregulation of protein *O*-linked-N-acetylglucosaminylation (O-GlcNAcylation), which mediate several molecular alterations: (1) an increase in arrhythmia susceptibility related to action potential duration (APD) prolongation caused by a decrease in potassium outward current (I_k) and voltage-gated sodium channel (Nav1.5) function by O-GlcNAcylation; (2) reduced cardiac elasticity caused by AGE-mediated collagen cross-linking molecules; (3) a decrease in contractile myofilament Ca^{2+} sensitivity as a result of the shift from α-myosin heavy chain to the foetal isoform β-myosin heavy chain, as well as myosin light chain and actin O-GlcNAcylation, slowing cross-bridge cycling; (4) a decrease in Ca^{2+} release and reuptake at the sarcoplasmic reticulum, related to AGE-mediated alteration of the ryanodine receptor (RyR) and sarco/endoplasmic reticulum Ca^{2+} adenosine triphosphatase (SERCA), underlying cardiac contraction and relaxation; (5) a decrease in adenosine triphosphate (ATP) and an increase in reactive oxygen species (ROS) production in the mitochondria, as a result of fatty acid (FA) oxidation enhancement, which inhibits glucose oxidation.

et al. [66] have shown that in patients with type 1 DM, myocardial deformation is correlated with HbA1c level. Hyperglycaemia-mediated AGE formation induces loss of collagen elasticity, with subsequent reduction of myocardial compliance. In addition, AGEs increase the production of reactive oxygen species (ROS), which are known to promote myocardial fibrosis [67]. Nevertheless, the underlying fibrotic mechanisms remain unclear in diabetic cardiomyopathy. The fibrogenic agent transforming growth factor beta (TGF-β) may be involved in diabetic cardiac fibrosis (for more details see review [68]). Besides fibrosis, high glucose induces cardiac hypertrophy via, for example, the activation of the peroxisome proliferator-activated receptor gamma (PPARγ), as described in adult rat cardiomyocytes treated for 48 hours with a high glucose concentration (25 mM) [69]. The increase in fibronectin production described in rats with streptozotocin-induced type 1 DM also participates in cardiac hypertrophy and fibrosis, as seen in the diabetic heart [70].

The glucose memory

Large-scale clinical trials [36,71,72] have pointed out the importance of early tight glucose control in limiting micro- and macrovascular damage in DM, induced by persistent glucose-mediated cell damage (even after glucose normalization), which correlates with the severity of hyperglycaemic history. This concept, known as ''metabolic memory'', was first evoked by Engerman et al. [73] in 1987, who showed that early control of glucose level, using insulin, in dogs with type 1 DM, prevented retinal damage induced by hyperglycaemia, a phenomenon well described in retinal and renal cells [74]. In cardiomyocytes, a few papers have described some long-lasting high-glucose cellular effects related to ''metabolic memory''. For instance, in rats with streptozotocin-induced type 1 DM, an increase in cardiac fibronectin messenger ribonucleic acid levels persisted 2 weeks after glucose normalization by insulin [75]. Moreover, in the cardiomyocyte line H9c2, the ''metabolic memory'', induced by 25 mM glucose (24 hours), increased interleukin-6 expression, despite glucose normalization, through interleukin-6 promotor methylation [76]. This mechanism seems to be related to high glucose-mediated epigenetic alterations (long-lasting modification of chromatin structure and gene transcription without modification of gene sequence) involved in ''metabolic memory'' development [77,78]. In aortic endothelial cells and mesangial renal cells [79,80], high glucose mediates mitochondrial superoxide production to activate several glucotoxic pathways (e.g. the polyol pathway, protein kinase C and AGEs). All of these mechanisms, found in diabetic cardiomyopathy [65], might be activated, and pave the way to a better understanding of the long-lasting high-glucose deleterious effects observed in cardiomyocytes.

Glucose and metabolic alterations

Normally, the heart uses either fatty acid (60—80%) or glucose oxidation to produce adenosine triphosphate (ATP), depending on substrate availability. However, the diabetic heart lacks this substrate flexibility, which deeply impacts cardiac metabolic activity. Indeed, fatty acid oxidation increases and glucose oxidation is inhibited. Then, the increase in fatty acid oxidation promotes acetyl coenzyme A and citrate production. Through the Krebs cycle, these substrates generate nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$), which enter the mitochondrial respiratory chain to produce ATP, associated with oxygen consumption. Because these molecules are very rich in electrons, the increase in their production and, thus, mitochondrial membrane flux and hyperpolarization, inhibits the respiratory chain complex, leading to ROS generation, with less ATP production [81,82]. The O-GlcNAcylation pathway also alters mitochondrial respiratory complex I, III and IV in neonatal rat cardiomyocytes in the presence of high glucose. Indeed, 30 mM glucose (48 hours) results in lower ATP production and mitochondrial respiration efficiency [83]. Besides altering the mitochondrial respiratory chain, the excess of acetyl coenzyme A and citrate inhibits glycolysis in cardiomyocytes, and switches the glucose to the pentose pathway, promoting ROS formation, AGE production and O-GlcNAcylation upregulation. For example, in neonatal rat cardiomyocytes, hyperglycaemia mediates O-GlcNAcylation of mitochondrial transcriptional factor A [84], which is involved in mitochondrial deoxyribonucleic acid (DNA) transcription and replication. These alterations result in reduced mitochondrial activity, with greater ROS and less ATP production, and participate in cell death. Indeed, in mice with streptozotocin-induced type 1 DM and H9c2 cardiomyocytes with high glucose (48 hours), the increase in ROS production is associated with cytochrome c release and activation of the caspase 3 apoptotic pathway, leading to cell death [85,86]. Na+/K ± ATPase activation protects H9c2 myocardial cells against high glucose-induced cell apoptosis by decreasing the level of ROS and alleviating cytosolic Ca^{2+} overload [86]. A higher ROS level is also associated with high sensitivity to Ca^{2+}-induced mitochondrial permeability transition pore and activation of the caspase 9-mediated apoptotic pathway, as seen in atrial myoblasts from patients with type 2 DM [81,87]. 30 mM glucose (72 hours) also induces nuclear expression of FOXO1, a key transcription factor in insulin signal transduction, in H9c2 rat cardiomyocytes. Then, FOXO1 promotes β-adrenergic receptor kinase (GRK2) expression, which increases caspase 3-mediated cell apoptosis by promoting ROS production [88]. ROS can also promote apoptosis by inhibiting the insulin-like growth factor 1/phosphatidylinositol-3-kinase/Akt (IGF-1/PI3 K/Akt) survival pathway in H9c2 cardiomyocytes treated with 33 mM glucose (36 hours) [89]. All of these mechanisms promote ROS production, decreasing mitochondrial ATP production and promoting cell death.

Glucose and excitation-contraction coupling

Studies in animal models of type 1 and type 2 DM have clearly shown that diastolic and systolic dysfunction are associated with defective Ca^{2+} handling [90]. In cardiomyocytes, Ca^{2+} plays a key role in the initiation of contraction through excitation-contraction coupling. Indeed, during cardiomyocyte depolarization, Ca^{2+} enters into the cell through the L-type voltage-dependent Ca^{2+} channel, activating a massive release of Ca^{2+} from the ryanodine receptor of the sarcoplasmic reticulum, which binds to the myofilaments and generates contraction. Then, Ca^{2+} returns to diastolic levels through sarcoplasmic reticulum reuptake and cellular extrusion. In animal models of DM, the $[Ca^{2+}]i$ transient is reduced as a result of a decrease in expression and/or activity of L-type voltage-dependent Ca^{2+} channel Ca^{2+} entry (although this is still a matter of debate), as well as reduced expression of ryanodine receptors [90—94]. The aforementioned upregulation of AGEs has been shown to directly alter ryanodine receptor activity, participating in abnormal diastolic sarcoplasmic reticulum Ca^{2+} release and decreasing sarcoplasmic reticulum Ca^{2+} content, which is necessary for the next contraction [95,96]. In addition, in diabetic models, [Ca2 +]i transient decay time is prolonged, as a result of impaired sarcoplasmic reticulum Ca^{2+} reuptake by the sarco/endoplasmic reticulum Ca^{2+} ATPase (SERCA), impairing relaxation [90,91]. SERCA dysfunction has been attributed to modification of phospholamban (an inhibitor of SERCA activity) by O-GlcNAcylation. This O-GlcNAcylation of phospholamban decreases its phosphorylation, thus promoting its inhibition of SERCA activity [97]. Moreover, high glucose leads to transcription factor O-GlcNAcylation, notably the specificity protein 1 (Sp1), which also downregulates SERCA expression [19,98]. SERCA is also an AGE target, which reduces its activity and depresses cardiac relaxation [96]. Taken together, these mechanisms alter SERCA-dependent Ca^{2+} reuptake, leading to cardiomyocyte contractile dysfunction by emptying sarcoplasmic reticulum Ca^{2+} load [90,91,94,99]. In addition, in rats with type 1 diabetes, myofilament sensitivity to Ca^{2+} decreases, which results from a shift from α-myosin heavy chain to the foetal isoform β-myosin heavy chain messenger ribonucleic acid [100,101] and slower cross-bridge cycling [102], slowing relaxation. Myosin heavy chain, myosin light chain and actin are also O-GlcNAcylated, as observed in cardiac muscle fibres in rats with streptozotocin-induced type 1 DM [103], decreasing myofibril sensitivity to Ca^{2+} [104] and contractile dysfunction. Finally, it is worth noting that high glucose-mediated alteration of excitation-contraction coupling increases the propensity for arrhythmia in animal models. Indeed, Erickson et al. [105] have shown that hyperglycaemia induces sarcoplasmic reticulum abnormal diastolic Ca^{2+} release via calmodulin kinase II (CaMKII) O-GlcNAcylation, and exacerbates arrhythmia in diabetic rats under β-adrenergic stimulation. Moreover, studies in rat ventricular cardiomyocytes showed that 25.5 mM glucose (24 hours) prolonged the action potential duration [106] by decreasing the outward potassium current amplitude in a diabetic rat model [107,108], which is arrhythmogenic. Furthermore, in rats with type 1 DM, O-GlcNAcylation of the cardiac voltage-gated sodium channel Nav1.5 decreases its expression and slows its inactivation, participating in action potential prolongation and ventricular arrhythmia susceptibility under β-adrenergic stimulation [109].

Treatment

The Food and Drug Administration and the European Medicines Agency have required evidence of cardiovascular safety for glucose-lowering agents since 2008, using three-point major adverse cardiovascular events (MACE3), a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke, as a primary endpoint. Therefore, data regarding the cardiovascular effects of glucose-lowering therapies are increasingly available. Since 2008, none of the new cardiovascular safety trials (known as ''cardiovascular outcome trials'') of antidiabetic drugs have shown an increase in ischaemic cardiovascular risk, but in some cases have shown cardiac protection. Therefore, the Food and Drug Administration is recommending that broader safety trials are conducted, including a large spectrum of patients with diverse risk factors, thus evaluating a wide range of safety concerns, instead of focusing only on cardiovascular safety [110]. Metformin is one of the first-line treatments for patients with type 2 DM. Although there is an absence of randomized clinical trials assessing the potential beneficial effect of metformin in patients with HF, a meta-analysis of nine cohort studies, involving 34,000 patients, suggested that metformin was associated with a reduced risk of all-cause mortality and hospitalization compared with controls (mostly sulphonylurea therapy) (pooled adjusted risk estimate 0.93, 95% CI 0.89—0.98; $I^2 = 0\%$; $P = 0.01$) [111]. As for metformin, no randomized clinical trials have been undertaken to assess the cardiovascular outcomes of sulphonylurea treatment. The results from observational studies and meta-analyses are controversial, with either an increase in or no effect on cardiovascular risk [112,113]. The increased risk of HF with thiazolidinedione has been established, caused in part by fluid retention and oedema side effects [114]. The effects of dipeptidyl-peptidase-4 (DPP4) inhibitors are controversial. Although the EXAMINE [115] and TECOS [116] trials did not reveal an increase in HF hospitalization in patients with DM receiving alogliptin and sitagliptin, respectively, the SAVOR-TIMI 53 trial [117] showed an increase in HF hospitalization of patients with type 2 DM treated with saxagliptin compared with placebo. As for linagliptin, the CARMELINA trial evaluated its effect on cardiovascular outcomes as a non-inferior risk of a composite cardiovascular outcome over a median 2.2-year follow-up [118].

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists, injectable or daily oral intestinal-derived incretin peptides, stimulate postprandial insulin secretion and inhibit glucagon release. The results of GLP-1 analogue cardiovascular outcome trials are shown in Table 1. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Result) randomized trial demonstrated a decreased rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke in the liraglutide group compared with placebo in patients with type 2 DM with an established cardiovascular disease [119]. The SUSTAIN-6 [120] and PIONEER-6 [121] trials demonstrated non-inferiority in terms of cardiovascular outcomes for semaglutide, with > 80% of the

Table 1 Results of glucagon-like peptide-1 analogue cardiovascular outcome trials.

Study	MACE3		Cardiovascular mortality		Non-fatal MI		Non-fatal stroke	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
LEADER [119]	0.87 (0.78—0.97)	0.01	0.78 (0.66—0.93)	0.07	0.88 (0.75—1.03)	NS	0.89 (0.72—1.11)	NS
SUSTAIN-6 [120]	0.74 (0.58—0.95)	< 0.001[a]	0.98 (0.65—1.48)	NS	0.75 (0.51—1.08)	NS	0.61 (0.38—0.99)	0.04
REWIND [122]	0.88 (0.79—0.99)	0.026	0.91 (0.78—1.06)	NS	0.96 (0.79—1.16)	NS	0.76 (0.61—0.95)	0.017
PIONEER 6 [121]	0.79 (0.57—1.11)	< 0.001[a]	0.49 (0.27—0.92)	NT	1.18 (0.73—1.90)	NT	0.74 (0.35—1.57)	NT

CI: confidence interval; HR: hazard ratio; MACE3: three-point major adverse cardiovascular events; MI: myocardial infarction; NS: not significant; NT: not tested.
[a] For non-inferiority.

population with cardiovascular disease. Although the LEADER and SUSTAIN-6 trials reported no changes in the rate of hospitalization for HF, only a small proportion of the included patients had HF at baseline. The REWIND TRIAL [122], evaluating a weekly injection of dulaglutide versus placebo, demonstrated a favourable effect on MACE3 (HR 0.88, 95% CI 0.79—0.99; $P = 0.026$). In this trial, two-thirds of the patients were considered to be in primary prevention.

The FIGHT [123] and LIVE [124] smallest randomized trials specifically explored the effects of liraglutide in patients with HFrEF. In the FIGHT trial, including patients with and without type 2 DM, no reduction in HF hospitalization or cardiovascular death was observed. In the LIVE trial, no significant differences were observed between the groups for the primary endpoint (increase in left ventricular ejection fraction). However, liraglutide-treated patients had a higher number of serious cardiac events, probably as a result of an increased heart rate. Therefore, the effects of GLP-1 receptor agonists might differ between patients with type 2 DM and those with symptomatic HFrEF.

Sodium/glucose co-transporter 2 inhibitors

Sodium/glucose cotransporter-2 (SGLT2) inhibitors inhibit glucose reabsorption in the proximal renal tubules, independent of insulin, and reduce Na^+ reabsorption, leading to increased natriuresis [125]. SGLT2 inhibitor use reduces the rate of HF hospitalizations, as seen in cardiovascular outcome trials (Table 2) and, in the case of empagliflozin, markedly reduce cardiovascular death. The EMPAREG OUTCOME (Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 Diabetes) trial [126] included patients with type 2 DM with established cardiovascular disease who presented a reduction in MACE3 after a median follow-up of 3.1 years in the empagliflozin group versus placebo (10.5% versus 12.1%; HR 0.86, 95% CI 0.74—0.99; $P = 0.04$ for superiority). In addition, the trial demonstrated lower rates of cardiovascular mortality and hospitalization for HF (9.4% vs 14.5%; HR 0.65; 95% CI 0.50—0.85) in the empagliflozin group, a finding that was consistent across all major subgroups, including those with and without HF.

The CANVAS (Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes) programme included 10,142 patients with either established cardiovascular disease (65%) or a high risk of cardiovascular events (35%), and randomly assigned to canagliflozin (100 mg or 300 mg) or placebo [127]. The rate of the primary outcome, MACE3, was lower in the canagliflozin group than in the placebo group (26.9 vs 31.5 per 1000 patient-years). Although the reduction in cardiovascular and all-cause death with canagliflozin versus placebo did not reach significance, patients under canagliflozin showed a significant 33% reduction in the risk ratio for HF hospitalization. However, adverse effects occurred more often under canagliflozin than placebo—most notably, lower extremity amputations [127].

DECLARE-TIMI 58 [128], the cardiovascular outcome trial of dapagliflozin, included 17,160 patients (40.6% with and 59.3% without established cardiovascular disease) randomized to placebo or dapagliflozin over 4.2 years, with co-primary endpoints of MACE3 and a composite of cardiovascular death or hospitalization for HF. The trial did not show superiority for dapagliflozin in terms of MACE3

Table 2 Results of sodium/glucose co-transporter 2 inhibitor cardiovascular outcome trials.

Study	MACE3		Cardiovascular mortality		Hospitalization for HF		Cardiovascular mortality and hospitalization for HF		All-cause mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
EMPAREG-OUTCOME [126]	0.86 (0.74—0.99)	< 0.001	0.62 (0.49—0.77)	< 0.001	0.65 (0.50—0.85)	0.002	0.66 (0.55—0.79)	< 0.001	0.68 (0.57—0.82)	< 0.001
CANVAS [127]	0.86 (0.75—0.97)	0.02	0.87 (0.72—1.06)	NT	0.67 (0.52—0.87)	NT	0.78 (0.67—0.91)	NT	0.87 (0.74—1.01)	0.24
DECLARE-TIMI 58 [128]	0.93 (0.84—1.03)	0.17	0.98 (0.82—1.17)	NT	0.73 (0.61—0.88)	NT	0.83 (0.73—0.95)	0.005	0.93 (0.82—1.04)	NT

CI: confidence interval; HF: heart failure; HR: hazard ratio; MACE3: three-point major adverse cardiovascular events; NT: not tested.

compared with control but did show superiority for the composite of cardiovascular death or hospitalization for HF (Table 2). The real-life study CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors) confirmed reduced HF hospitalization with SGLT2 inhibitors compared with other glucose-lowering medications [129].

Although the effect of SGLT2 inhibitors on HF hospitalization is impressive (the EMPAREG outcome), the CANVAS and DECLARE-TIMI 58 trials enrolled very few patients with established HF. The potential protective role of SGLT2 inhibitors against hospitalization for HF and/or cardiovascular death in patients with HF has been recently evaluated in the EMPEROR-REDUCED [130] and DAPA-HF [131] clinical trials, each of which enrolled > 3000 patients with HF with or without type 2 DM, with a reduced ejection fraction ($\leq$ 40%), New York Heart Association functional class II—IV and an elevated concentration of N-terminal pro-B type natriuretic peptide (NT-proBNP), a biomarker of cardiac injury. Patients were randomly assigned to dapagliflozin (DAPA-HF trial) or empagliflozin (EMPEROR-REDUCED) or matching placebo. Both trials showed superiority of SGLT2 inhibitors in preventing cardiovascular death and/or hospitalization for HF, regardless of DM, in patients under contemporary guideline-based HF therapies. The protective effects of SGLT2 inhibitors have revolutionized the standard of care for patients with reduced ejection fraction, as observed in the European Society of Cardiology 2019 guidelines, where SGLT2 inhibitors are recommended as first-line treatment, to lower the risk of hospitalization for HF in patients with type 2 DM [132]. Furthermore, the American Heart Association/American College of Cardiology 2019 guidelines support the use of SGLT2 inhibitors in patients with DM hospitalized for HF [133]. Without doubt, in the upcoming guidelines, SGLT2 inhibitors will soon be considered the standard of care for patients with HFrEF, despite their diabetic status, in light of the EMPEROR-REDUCED and DAPA-HF trial results.

The mechanism underlying the beneficial effects of SGLT2 inhibitors in HF is still under investigation, but seems to be beyond glucose lowering or diuresis *per se* (Fig. 3). A possible mechanism could be a direct myocardial effect through cardiac energy metabolism (higher ketone body oxidation). Increasing ketone levels participate in attenuation of the inflammation profile in HF under SGLT2 inhibitors, although the underlying mechanism is not fully understood. Furthermore, SGLT2 inhibitors inhibit the cardiac Na^+/H^+ exchanger, lowering myocardial Na^+ and Ca^{2+} levels increased in HF. SGLT2 inhibitors also reduce CaMKII activity, and prevent the sarcoplasmic reticulum Ca^{2+} mishandling observed in HF. Besides their direct action on the cardiomyocyte, the beneficial effect of SGLT2 inhibitors is also related to their renal action, through higher natriuresis, lowering renal intraglomerular pressure, with a subsequent reductions in sympathetic system activation and blood pressure, which indirectly improve cardiac function. Other theories have also been proposed, such as a reduction in ROS, increasing autophagy and provascular cell progenitors, and should be further investigated [134].

Although SGLT2 inhibitors emerge as a strong therapeutic class in both DM and HF, it should be noted that they present some adverse events, such as mycotic genital infections, which are outweighed by their cardiac benefits. As already discussed, the increase in ketones bodies might explain, in part, the cardioprotective effect of SGLT2 inhibitors, with a risk, however, of diabetic ketoacidosis, which is still rare, but is twice as frequent compared with other antidiabetic drugs. The increased risk of fractures and lower limb amputations with this class remains controversial [135].

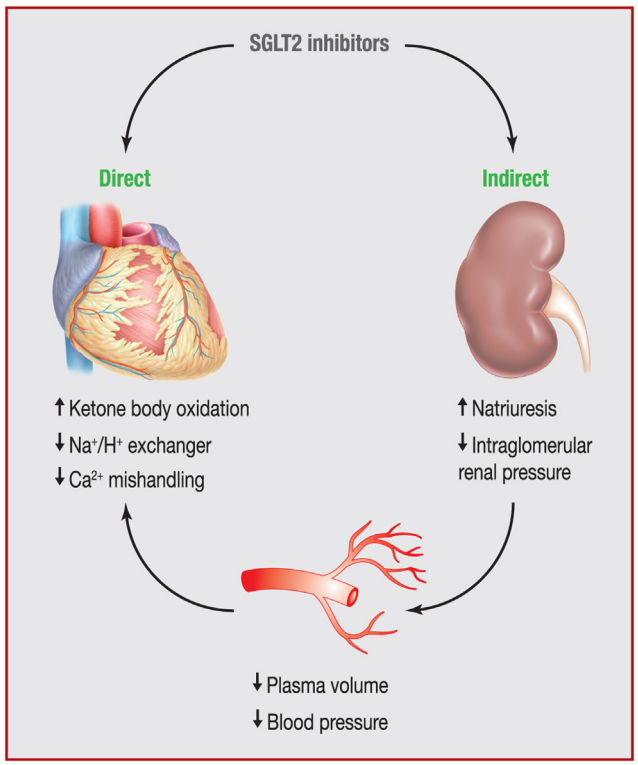

Figure 3. Schematic representation of the potential beneficial effects of sodium/glucose co-transporter 2 (SGLT2) inhibitors on cardiac function, both direct and indirect. SGLT2 inhibitors seem to have a direct effect on the heart, by increasing ketone body oxidation and decreasing Na^+/H^+ exchanger activity and Ca^{2+} mishandling via calmodulin kinase II; they also have indirect effects, related to an increase in renal natriuresis and a decrease in intraglomerular pressure, leading to lower plasma volume and blood pressure, reducing cardiac workload.

Conclusions

Several clinical studies have demonstrated a higher risk of HF during DM, caused, in part, by coronary artery disease and valvulopathy, and also specific cardiac dysfunction. Hyperglycaemia, among several factors, contributes to the development of diabetic cardiomyopathy. Although the beneficial effect of HbA1c tight control on cardiovascular event reduction is still controversial, it is well established that an increase in HbA1c level increases the risk of HF; this is correlated to glucose toxicity, leading to metabolic alterations, with a decrease in energy substrate production and an increase in oxidative stress production. The upregulation of the hexosamine pathway and the production of AGEs, mediated by high glucose, induce structure alteration and participate in Ca^{2+} mishandling, affecting cardiac compliance, contraction and relaxation. As cardiac safety is

a major challenge in drug development, several studies have deciphered the cardiovascular effects of glucose-lowering agents. Although thizolidinediones are known to promote HF, studies are still controversial regarding DPP4 inhibitors. GLP-1 agonists have demonstrated a non-inferiority effect compared with placebo, whereas the new therapeutic class of SGLT2 inhibitors seems to be promising in terms of cardiovascular outcomes.

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Disclosure of interest

The authors declare that they have no competing interest.

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