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REVIEW

Metabolic, structural and biochemical changes in diabetes and the development of heart failure

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Abstract

Diabetes contributes to the development of heart failure through various metabolic, structural and biochemical changes. The presence of diabetes increases the risk for the development of cardiovascular disease (CVD), and since the introduction of cardiovascular outcome trials to test diabetic drugs, the importance of improving our understanding of the mechanisms by which diabetes increases the risk for heart failure has come under the spotlight. In addition to the coronary vasculature changes that predispose individuals with diabetes to coronary artery disease, diabetes can also lead to cardiac dysfunction independent of ischaemic heart disease. The hyperlipidaemic, hyperglycaemic and insulin resistant state of diabetes contributes to a perturbed energy metabolic milieu, whereby the heart increases its reliance on fatty acids and decreases glucose oxidative rates. In addition to changes in cardiac energy metabolism, extracellular matrix remodelling contributes to the development of cardiac fibrosis, and impairments in calcium handling result in cardiac contractile dysfunction. Lipotoxicity and glucotoxicity also contribute to impairments in vascular function, cardiac contractility, calcium signalling, oxidative stress, cardiac efficiency and lipoapoptosis. Lastly, changes in protein acetylation, protein methylation and DNA methylation contribute to a myriad of gene expression and protein activity changes. Altogether, these changes lead to decreased cardiac efficiency, increased vulnerability to an ischaemic insult and increased risk for the development of heart failure. This review explores the above mechanisms and the way in which they contribute to cardiac dysfunction in diabetes.

Keywords Cardiac metabolism · Diabetes · Fatty acid oxidation · Fibrosis · Glucose oxidation · Glucotoxicity · Heart failure · Hypertrophy · Review

Abbreviations

AR	Aldose reductase
CHD	Coronary heart disease
CVD	Cardiovascular disease
ECM	Extracellular matrix
GlcNAc	*N*-acetyl glucosamine
GLP-1	Glucagon-like peptide-1
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
miRNA	microRNAs
MMP	Matrix metalloproteinases
PDH	Pyruvate dehydrogenase
PDK	Pyruvate dehydrogenase kinase
RAGE	Advanced glycation end-product receptor
ROS	Reactive oxygen species
SERCA2	Sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a
SGLT2	Sodium-glucose cotransporter-2
SR	Sarcoplasmic reticulum
TIMP	Tissue inhibitor of metalloproteinases
XBP-1	X-box binding protein 1

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Introduction

Cardiovascular disease (CVD) is a major cause of mortality in individuals with diabetes, accounting for 44% and 52% of deaths in people with type 1 or type 2 diabetes, respectively [1]. Additionally, increased levels of HbA_{1C}, indicative of hyperglycaemia, are associated with an increased risk of developing heart failure in people with diabetes [2]. There is also a positive correlation between diabetes and the risk of coronary heart disease (CHD). Comparing the 7 year incidence of myocardial infarction among individuals with and without diabetes, people with diabetes who have not had a previous myocardial infarction have as high of a risk of myocardial infarction as individuals without diabetes who have had a previous myocardial infarction [3]. Moreover, diabetes has a negative impact on the management of CHD. For example, the 3 year risk of myocardial infarction recurrence, target lesion revascularisation, and all-cause mortality is significantly higher in diabetic patients with ST-elevation myocardial infarction who are undergoing percutaneous coronary intervention than patients without diabetes [4]. This is due, at least in part, to a reduction in coronary flow reserve and impaired coronary vasodilation, which occurs in patients with diabetes [5]. These alterations are also associated with reduced coronary capillary density and angiogenesis [6], accompanied by reduced vascular endothelial growth factor expression in the myocardium of people with diabetes [7]. In addition to macrovascular changes, microvascular changes have also been associated with an increased risk for heart failure in individuals with type 2 diabetes [8]. Specifically, diabetic autonomic neuropathy, or the impaired autoregulation of blood flow through vascular beds in the heart, contributes to decreased bioavailability of nitric oxide. Decreases in nitric oxide contribute to a vasoconstrictive microvasculature, which results in microvascular injury throughout the body, including the heart [9, 10]. Due to subsequent microangiopathy, abnormal thickening (and weakening) of capillary basement membranes can contribute to hypoxia, hypertension and delayed wound healing [11]. Together, changes in the macrovasculature and microvasculature driven by hyperglycaemia predispose the myocardium to CVD in individuals with diabetes.

Another significant impact of diabetes on cardiac function is the development of diastolic dysfunction that is unrelated to ischaemic heart disease or hypertension. Diabetes-induced diastolic dysfunction negatively influences left ventricular filling, chamber stiffness and relaxation [12]. Diastolic dysfunction is seen in people with type 1 and 2 diabetes, independent of sex, age or duration of diabetes [13, 14]. This diastolic dysfunction is associated with an increase in isovolumetric relaxation time and impaired left ventricular compliance [14]. Diastolic dysfunction can also be further aggravated when diabetes is associated with hypertension, causing severe impairment in left ventricular filling and relaxation [15]. In addition to diastolic dysfunction, systolic dysfunction can occur in individuals with diabetes, including reduced ejection fraction, decreased fractional shortening and increased left ventricular end-systolic volume [16]. Systolic dysfunction is also associated with a decrease in stress-corrected midwall shortening and reduced left ventricular fractional shortening in patients with diabetes [17]. It is important to note that diastolic dysfunction can either precede systolic dysfunction, or is associated with normal systolic function [18]. Notably, both type 1 and type 2 diabetes typically results in early-onset diastolic dysfunction (heart failure with preserved ejection fraction [HFpEF]) and is followed by late-onset systolic dysfunction (heart failure with reduced ejection fraction [HFrEF]) [13]. Together, these structural and functional abnormalities contribute to the increased risk of CVD in individuals with diabetes (Fig. 1).

Energy metabolic changes

The energy metabolic milieu in diabetes is perturbed due to hyperlipidaemia, hyperglycaemia and hyperinsulinaemia, all of which can compromise cardiac mitochondrial function and, ultimately, cardiac function.

Hyperlipidaemia While the healthy heart derives 60–70% of its energy from fatty acid oxidation, in the setting of uncontrolled diabetes, the heart relies on fatty acid oxidation for up to 90–100% of its energy needs [19–22]. This is due in part to an increase in plasma triacylglycerol-rich lipoproteins and non-esterified fatty acid (NEFA) levels in diabetes contributing to increased fatty acid delivery to the heart [22, 23]. There are also several dysregulated biochemical pathways involved in fatty acid oxidation, including increased transcription of fatty acid oxidative enzymes (i.e. increased peroxisome proliferator-activated receptor-alpha [PPARα]-peroxisome proliferator-activated receptor-gamma coactivator-1 [PGC-1] activity) and decreased allosteric inhibition of mitochondrial fatty acid uptake and oxidation, resulting in increased fatty acid oxidation [19–22]. This includes a decrease in malonyl CoA, a potent inhibitor of mitochondrial fatty acid uptake [24, 25], due to a decreased synthesis by acetyl-CoA carboxylase (ACC) [26] and increased degradation by malonyl CoA decarboxylase (MCD) [27]. The consequences of these changes are an increased reliance on fatty acid oxidation, which results in a reduction in cardiac efficiency due to fatty acids being a less efficient fuel than glucose with regards to oxygen consumption and the potential to increase the activity of uncoupling proteins in the heart [19, 28, 29]. In addition to reduced cardiac efficiency, increased fatty acid uptake and oxidation results in intramyocardial accumulation of long chain acyl CoAs, long chain acylcarnitines, ceramides, diacylglycerols and

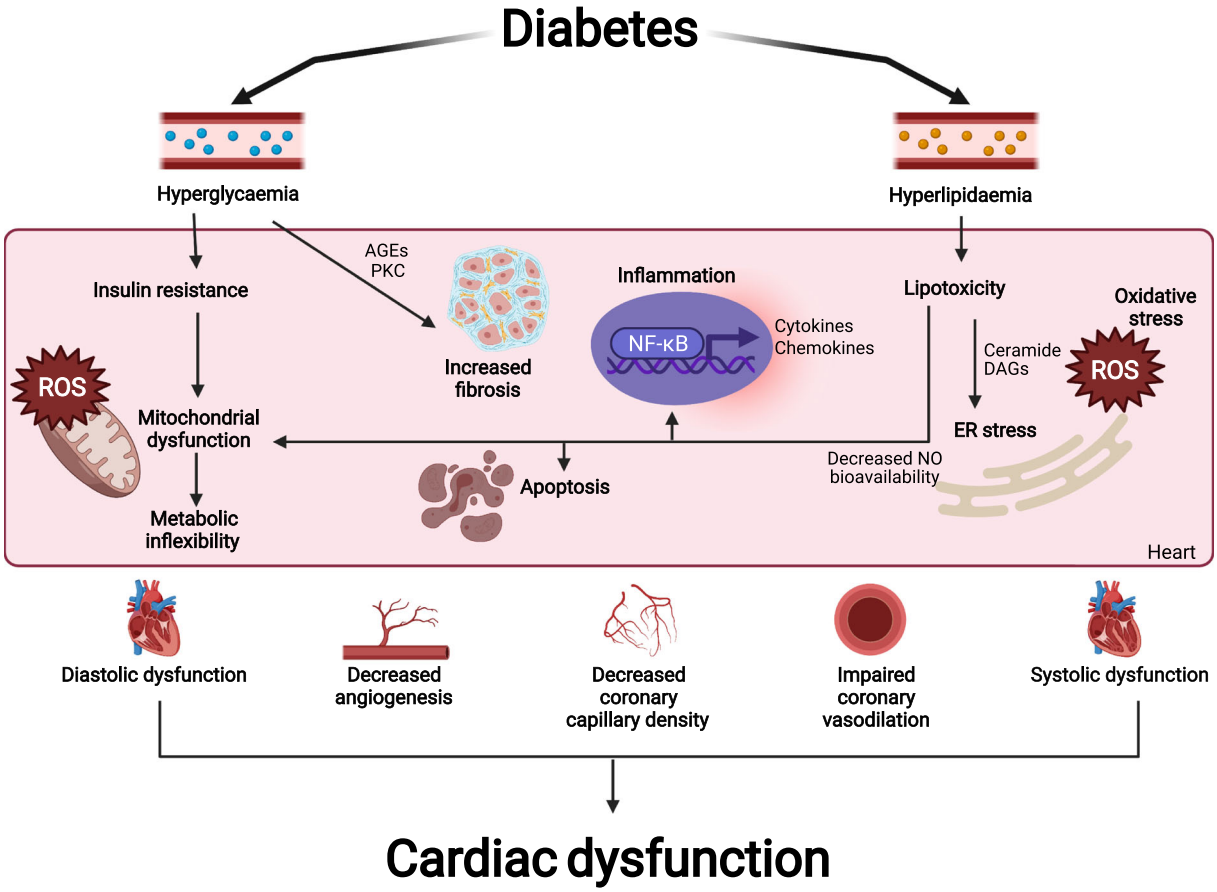

Fig. 1 Cardiac cellular and functional pathological alterations in the setting of diabetes that contribute to CVD. Diabetes is characterised by hyperglycaemia and hyperlipidaemia, both of which contribute to the development of cardiac insulin resistance, metabolic perturbations, mitochondrial dysfunction, oxidative stress, apoptosis, glucotoxicity, lipotoxicity, inflammation, endoplasmic reticulum stress, hypertrophy and fibrosis. Together, these metabolic, structural and biochemical changes contribute to cardiac dysfunction in people with diabetes. DAG, diacylglycerol; ER, endoplasmic reticulum; NO, nitric oxide; PKC, protein kinase C. Created in Biorender.com. This figure is available as part of a downloadable slideset

triacylglycerols. The accumulation of these lipids contributes to the development of lipotoxicity, fibrosis, apoptosis and cardiac dysfunction (see [30, 31] for reviews).

Hyperglycaemia and hyperinsulinaemia Dysinsulinaemia is an important contributor to both the abnormal metabolic profile and the development of pathological hypertrophy and mitochondrial dysfunction in diabetes. Hyperinsulinaemia may contribute to hypertrophy via activation of Akt serine/threonine kinase 1 (Akt1), as insulin treatment of mice with streptozotocin-induced type 1 diabetes worsened the progression of pathological hypertrophy and mitochondrial dysfunction due to cardiac growth not being matched with an equivalent expansion of the vasculature [32].

Myocardial glucose metabolism is decreased in diabetes at each point in its pathway: uptake, glycolysis and oxidation. Glucose uptake is depressed due to hyperlipidaemia, insulin resistance and, specifically, a decrease in both insulin stimulation and the total amount of GLUT4 levels [33, 34]. Glycolytic rates are also decreased, as are glucose oxidation rates, due to reduced pyruvate dehydrogenase (PDH) activity [20, 26, 35, 36]. PDH activity is reduced due to decreases in insulin and the increased oxidation of fatty acids in the heart of individuals with diabetes [35]. In addition, post-translational modifications of PDH, which includes increases in both inhibitory phosphorylation and glutathionylation, also impair its activity in diabetes [37, 38].

Cardiac metabolism and remodelling Through several prominent animal studies investigating HFpEF, the causal relationship between cardiac metabolism and cardiac remodelling has become more apparent, although there is still uncertainty surrounding the topic [39, 40]. Keeping in mind that, following increased fibrosis and stiffness, diabetic cardiomyopathy displays clinical features of HFpEF, the way in which HFpEF develops following metabolic changes may shed light on the link between metabolism and cardiac remodelling. HFpEF develops through a myriad of systemic and local metabolic changes which include an increased reliance on fatty acids for energy, increased inflammation and nitrosative stress [39, 40].

Specifically, the extent to which cardiac proteins are hyperacetylated dynamically changes due to alterations in the mitochondrial acetyl-CoA pool, which is directly influenced by the metabolism of different energy substrates. In a mouse model of HFpEF, aged mice treated with a high-fat diet and desoxycorticosterone pivalate developed classic HFpEF phenotypes alongside cardiac fibrosis and inflammation. The development of the fibrosis and inflammation was a result of the downregulation of the acetyl-CoA pool and overall mitochondrial acetylation [40]. In another model of HFpEF where mice were subjected to *N*-nitro-L-arginine methyl ester alongside a high-fat diet, X-box-binding protein 1 (XBP1) was found to be decreased in cardiac tissue from these HFpEF mice. Similar findings were observed in cardiac tissue obtained from humans with HFpEF [39]. Furthermore, it was found that nitrosative stress contributed to defective splicing of XBP1, and that targeting nitric oxide synthase could improve the HFpEF phenotype in mice [39]. Thus, there is possible interplay between both the peripheral and local metabolism contributing to cardiac nitrosative stress, inflammation, fibrosis and, ultimately, cardiac remodelling that occurs in diabetes.

The clinical implications of the perturbed metabolic milieu in diabetes includes a decreased cardiac efficiency, a decreased ability of the heart to withstand an ischaemic insult, and an increased risk of developing heart failure (Fig. 2). Hyperglycaemia and hyperlipidaemia together contribute to increased myocardial reliance on fatty acids for energy, while glucose oxidation rates are decreased. The increased reliance on fatty acids contributes to increases in oxygen consumption per ATP molecule produced, alongside increases in mitochondrial toxic intermediates [41]. This results in cardiac oxidative stress, inflammation and, ultimately, mitochondrial dysfunction and reduced cardiac efficiency. In a study using obese mice with induced type 2 diabetes, the progression of diabetes from 4 to 24 weeks resulted in an increase in cardiac protein expression of fatty acid metabolic enzymes, supporting the idea that as diabetes progresses, the heart relies more on fatty acids for energy [42]. With regards to ischaemia, during low flow or moderate ischaemia, hearts from rats with induced diabetes will fail faster compared with non-diabetic rat hearts due to the diabetes-induced increase in reliance on fatty acid oxidation, which inhibits glucose oxidation [33, 43]. In contrast, during no flow or severe ischaemia, diabetic rat hearts have significantly better recovery of function compared with non-diabetic rat hearts. This is because of the decreased accumulation of lactate and protons from glycolysis and changes in pH [26, 44–46].

Cardiac energy metabolic changes in diabetes

- Increased myocardial fatty acid oxidation
- Decreased myocardial glucose uptake, glycolysis and glucose oxidation
- Decreased cardiac efficiency

Structural alterations: hypertrophy and fibrosis

Diabetes is also accompanied by adverse remodelling of the heart. There is an independent association between diabetes and increased left ventricular volume and increased ventricular wall thickness [17]. These structural alterations are accompanied by an increase in myocardial fibrosis and collagen accumulation, with collagen remodelling occurring specifically in the interstitial and perivascular region of the myocardium of diabetic patients [6]. Excessive cardiac fibrosis directly contributes to increased stiffness and can worsen cardiac function and outcomes, leading to the development of heart failure in diabetic patients [17, 47, 48].

Hypertrophy Echocardiography on individuals with uncomplicated type 1 diabetes shows increased left ventricular wall thickness and mass compared with control participants [47]. Moreover, greater than 70% of patients with type 2 diabetes have hypertrophy, based on left ventricular mass relative to height [48]. The majority of hypertrophy observed is eccentric, which involves dilatation of the left ventricular chamber, rather than concentric, which involves thickening of the left ventricular wall. However, both forms of hypertrophy are present. Echocardiography of individuals with type 1 diabetes performed 2 years apart suggest that cardiac hypertrophy in diabetes may shift from concentric to eccentric remodelling as the disease progresses [47]. Notably, the hearts of individuals with diabetes that exhibit left ventricular hypertrophy often have concurrent diastolic dysfunction, as described earlier (see section 'Introduction').

Hypertension is a common comorbidity of diabetes. Higher systemic BP forces the heart to pump against a higher pressure gradient, or an increased afterload, which can lead to a compensatory hypertrophy. Nevertheless, the Strong Heart Study found that diabetes is associated with larger left ventricular mass and wall thickness independent from arterial pressure [17]. This suggests that there are other factors contributing to the development of left ventricular hypertrophy. One intriguing candidate is microRNAs (miRNAs), non-coding RNAs that have recently been implicated in diabetic hypertrophy. Diabetes or high levels of glucose trigger a downregulation of miR133a [49]. This decrease in miR133a likely enables altered gene expression that leads to the progression

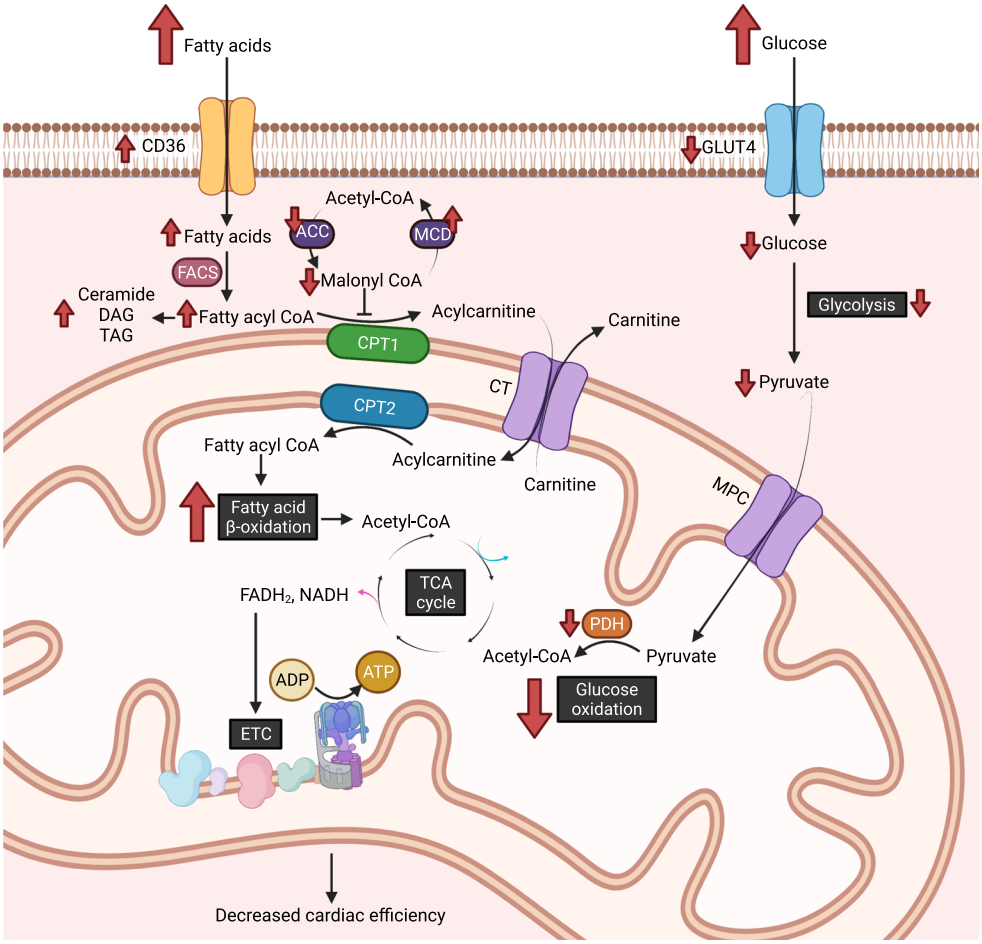

Fig. 2 Cardiac energy metabolic changes in diabetes. Diabetes leads to an increase in the supply of fatty acids and glucose to cardiomyocytes. Hyperlipidaemia results in an increase in the cellular and mitochondrial uptake of fatty acids. This is followed by an increase in fatty acid oxidation driven by the increased delivery of fatty acids and concurrent decreases in malonyl CoA levels (a potent inhibitor of CPT1). Hyperglycaemia and insulin resistance results in a decrease in total GLUT4 levels. As such, despite the supply of glucose being increased, glucose uptake is decreased resulting in decreased glycolysis and glucose oxidation rates. Notably, the rate limiting enzyme of glucose oxidation, PDH, has decreased activity due to the increases in fatty acid oxidation. Together, the increase in fatty acid oxidation and decrease in glucose oxidation decreases cardiac efficiency and contributes to the development of heart failure in diabetes. Red arrows indicate the changes that occur to metabolites and flux through their respective metabolic pathways in the setting of diabetes. ACC, acetyl-CoA carboxylase; CPT, carnitine palmitoyltransferase; CT, carnitine-acylcarnitine translocase; DAG, diacylglycerol; ETC, electron transport chain; FACS, fatty acyl CoA synthetase; MCD, malonyl CoA decarboxylase; MPC, mitochondrial pyruvate carrier; TAG, triacylglycerol; TCA, tricarboxylic acid cycle. Created in Biorender.com. This figure is available as part of a downloadable slideset

of hypertrophy. miRNAs present an appealing direction for diagnosis and treatment of diabetes-related heart disease.

Fibrosis Cardiac fibrosis is a consequence of adverse remodelling of the extracellular matrix (ECM) that results in excess deposition of ECM proteins. Fibrosis plays a role in the development of hypertrophy and can lead to impaired cardiac function [6, 50]. Studies have consistently found that collagen levels—namely type I, III and VI collagens—and fibrosis are increased in individuals with diabetes typically at late and severe stages of diabetic cardiomyopathy [6]. Studies suggest that matrix metalloproteinases (MMPs) and AGEs play a role in the pathogenesis of myocardial fibrosis [51].

Specifically, as a result of the hyperglycaemia-induced increase in production of AGEs, oxidative stress can contribute to the activation of inflammatory cells, after which AGEs can directly activate cardiac fibroblasts to become myofibroblasts. MMP-2 is a collagenase that is involved in ECM turnover and breaks down type I, II, and III collagen [50]. MMPs are inhibited by the profibrotic responses and as a result increase fibronectin and collagen. In mouse models of type 1 diabetes, the levels of the inactive MMP-2 precursor and mRNA levels of MMP-2 are downregulated [50]. Furthermore, tissue inhibitor of metalloproteinases 2 (TIMP2) is upregulated, suggesting greater inhibition of MMP-2 activity. Together, AGE causes dysregulation of both MMPs and TIMPs, and this contributes to impairments in

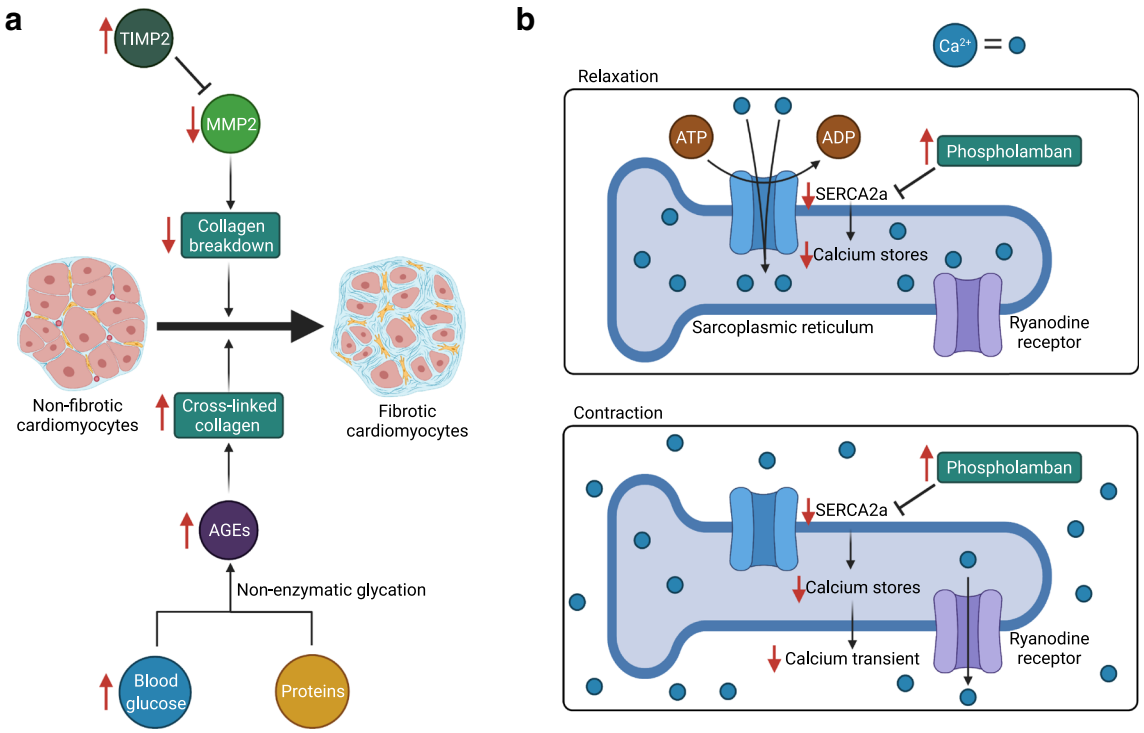

Fig. 3 Development of cardiac fibrosis and impaired cardiac Ca^{2+} handling in diabetes. Changes in ECM remodelling and Ca^{2+} signalling contribute to cardiac dysfunction in diabetes. Red arrows represent alterations observed in diabetes. (**a**) MMP2 plays a key role in collagen turnover in the ECM. Levels of MMP2 are decreased in diabetes, while the levels of its endogenous inhibitor, TIMP2, are increased. Meanwhile, hyperglycaemia leads to increased non-enzymatic glycation of proteins in diabetes, which causes increased production of AGEs. AGEs increase the cross-linking of collagen in the extracellular matrix. AGE-mediated cross-linking and decreased breakdown of collagen contribute to the formation of fibrosis in diabetes. (**b**) During cardiac relaxation, SERCA2a transports two Ca^{2+} into the SR for each ATP hydrolysed to ADP. In diabetes, SERCA2a is downregulated. Additionally, phospholamban is upregulated, resulting in enhanced inhibition of Ca^{2+} uptake into the SR. During contraction, ryanodine receptors allow Ca^{2+} to be released into the cytoplasm, leading to a Ca^{2+} transient that triggers contraction. The decreased ability to store Ca^{2+} in relaxation contributes to impaired Ca^{2+} transients in diabetes. Created in Biorender.com. This figure is available as part of a downloadable slideset

ECM degradation, increased cardiac stiffness and, ultimately, diastolic dysfunction.

After being formed through the non-enzymatic glycation of proteins, AGEs can increase cross-linking of collagen [52, 53]. In diabetes, elevated levels of glucose lead to elevated glycation, and therefore increased collagen cross-linking (Fig. 3a). AGE-mediated cross-linked collagen is less elastic and more resistant to proteolysis than normal collagen [52]. Consequently, this collagen contributes to diminished left ventricular compliance in diabetes. Importantly, higher levels of circulating AGEs are associated with cardiac stiffness and worsening diastolic dysfunction in individuals with type 1 diabetes independent of hypertension [53].

Cardiac structural changes that occur in diabetes

- Increased afterload contributes to concentric hypertrophy that progresses into eccentric hypertrophy
- Perturbations in miRNAs contribute to hypertrophy
- Hyperglycaemia-induced AGEs downregulate MMPs and upregulate TIMPs to contribute to fibrosis

Impairments in Ca^{2+} handling

Altered regulation of Ca^{2+} levels in the myocardium has been implicated in type 1 and type 2 diabetes and contributes to impaired contractile function [54–57]. Diminished rates of Ca^{2+} uptake into the sarcoplasmic reticulum (SR) have been observed in rat models of diabetes [54]. Myocytes from *db*/*db* mice, another model of type 2 diabetes, also have smaller Ca^{2+} transients with lower rates of decay [55]. Impairments in Ca^{2+} handling may occur early on in diabetes, contributing to the development of diastolic dysfunction [58]. This decrease in SR Ca^{2+} uptake can be partially explained by a reduced protein expression of sarco/endoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) [55–57], a P-type ATPase responsible

for reuptake of Ca^{2+} into SR stores following cardiomyocyte contraction. Additionally, expression of the protein that inhibits SERCA2a, phospholamban, is increased in rodent models of type 1 and 2 diabetes [55, 56]. This reduced ability to sequester Ca^{2+} in the SR following contraction helps to explain the delayed relaxation seen in the heart in diabetes (Fig. 3b) [54–57]. Consequently, having a limited reservoir of Ca^{2+} to release from the SR can weaken myocardial contraction [56, 57]. Transgenic overexpression of SERCA2a can restore systolic and diastolic function [57]. Thus, Ca^{2+} handling remains an enticing target for improving cardiac function in individuals with diabetes.

Glucotoxicity and lipotoxicity

Alongside metabolic and structural changes, there are also other pathways involving hyperglycaemia, glucotoxicity and lipotoxicity that contribute to cardiac dysfunction in diabetes.

Glucotoxicity Glucotoxicity can include alterations in aldose reductase (AR) in the polyol pathway, protein *O*-GlcNAcylation, AGEs formation, apoptosis, autophagy and mitophagy. Hyperglycaemia causes the AR enzyme to reduce a significantly greater amount of glucose (30%) into sorbitol at the expense of the NADPH cofactor, which is needed for other metabolic pathways [59]. The increased flux of glucose through this pathway reduces the activity of glutathione reductase, leading to increased susceptibility to oxidative stress. Protein *O*-GlcNAcylation, or *O*-GlcNAc, is a reversible post-translational modification that involves the attachment of *N*-acetyl glucosamine (GlcNAc) to serine or threonine residues on peptides via an O-linkage, and has been proposed to occur in the nucleus, cytoplasm, and mitochondria [60]. The *O*-GlcNAc structure is formed from the modification of glucose; therefore, changes in energy metabolism, such as those that occur during diabetes, may affect the levels of *O*-GlcNAc. Elevated mitochondrial *O*-GlcNAc is caused by hyperglycaemia and contributes to mitochondrial dysfunction in diabetes through modulating the hexosamine biosynthetic pathway (HBP) [61], which can impact left ventricular dysfunction, Ca^{2+} handling and myocardial contractility. *O*-GlcNAc can also inhibit autophagic flux, especially mitophagy, which can lead to myocardial injury in type 1 diabetes through the presence of dysfunctional mitochondria which are not removed from the cell [62]. Hyperglycaemia can have detrimental consequences on glucose deposition, which can mediate and further cause pathology in the heart of individuals with diabetes. Formation of AGEs in the heart is increased by hyperglycaemia and can be further aggravated by diabetes [63]. These form on intra- and extracellular proteins, generating protein cross-linking, and can increase free radical and reactive oxygen species (ROS) activity, leading to biochemical damage and further cardiac impairment in diabetic cardiomyopathy [64]. This increased ROS can also result in elevated cardiomyocyte apoptosis, leading to further cardiac dysfunction in diabetes [65]. AGE receptor (RAGE) activation can increase oxidative stress through the activation of the oxidative stress markers NF-κB and haem oxygenase mRNA [66]. Inhibition of RAGE by pre-treatment of antibodies to the AGE receptor or binding proteins can reduce AGE-induced oxidative stress.

Prior to the development of fibrosis, if the heart of an individual with diabetes is exposed to excess glucose, glucotoxicity may occur due to the build-up of a glucose gradient across the sarcolemma [67]. Since myocardial glucose oxidation is decreased in diabetes [20], this can lead to hyperglycaemia and the subsequent accumulation of glycolytic intermediates and products which can further contribute towards AGEs production [63], as well as increased anaplerosis and lipogenesis [68].

Lipotoxicity Excessive cardiomyocyte lipid accumulation in later stages of diabetes can lead to cardiac lipotoxicity and consequently impair cardiac efficiency, as well as promote lipoapoptosis (see [49] for review). As previously discussed, cardiac energy metabolism is perturbed in the setting of diabetes, whereby fatty acid oxidation is increased while glucose oxidation is decreased (see section 'Energy metabolic changes'). As a result of the increased reliance on fatty acid oxidation for energy, ATP/O ratios decrease, mitochondrial uncoupling increases, ROS production increases and, ultimately, cardiac efficiency decreases [28, 69]. In addition, excessive fatty acid supply to the heart can lead to lipoapoptosis in cardiomyocytes. Several mechanisms contribute to lipoapoptosis, including increased palmitate toxicity, increased ceramide formation, increased endoplasmic reticulum stress and increased systemic low-grade inflammation [70–73]. Together, decreased cardiac efficiency and increased lipoapoptosis contribute to lipotoxicity and cardiac dysfunction in diabetes.

Together, these changes in the heart lead towards increased cardiac dysfunction and pathophysiology in the hearts of individuals with diabetes. *O*-GlcNAc affects proteins that are essential in vascular function including endothelial nitric oxide synthase (eNOS), which can impair vasodilation, leading to increased BP [74]. *O*-GlcNAc can also impair cardiac contractility and calcium signalling [75]. Increased activity of the AR enzyme alongside increased AGEs formation can play a role in increasing oxidative stress [59, 66]. Lastly, increased lipid accumulation results in decreased cardiac efficiency and increased lipoapotosis. The disturbances of these various pathways manifest the detrimental effects of hyperglycaemia and hyperlipidaemia on cardiac function in individuals with diabetes.

Transcriptional and translational modifications

Genetic studies of people with diabetes have revealed a link between changes in expression of different genes and the various pathogenic pathways causing cardiac dysfunction in diabetes [76, 77].

Epigenetic and post-transcriptional modifications Growing evidence suggests that transcriptional changes are mediated by diabetes-related epigenetic modifications that include DNA methylation, post-translational histone modifications and dysregulation of non-coding RNAs (see [78] for review). Aberrant changes in histone protein acetylation, protein methylation and DNA methylation have the potential to alter the DNA-histone or DNA–transcription factor interactions, thereby leading to activation or repression of genes implicated in long-term cardiovascular complications of diabetes. In support of this, whole genome DNA methylation analysis of human heart failure revealed significantly altered DNA methylation patterns compared with healthy hearts [79]. Importantly, alterations in cardiac DNA methylation are associated with shifts in cardiac gene expression that can potentiate metabolic remodelling of heart failure, such as activation of the glycolytic pathway [79]. Decreased expression of DNA methyltransferase-1a and -3 have also been observed in diabetic rat hearts [80]. Similarly, substantial changes in histone acetylation and methylation dynamics, including enzymes involved in these processes, have been noted in various experimental mouse models of heart failure during diabetes [81, 82]. Interventions targeting these modifications such as histone deacetylase (HDAC) inhibition may be a promising therapeutic target in supressing diabetes-related myocardial remodelling [83]. However, clear mechanisms responsible for the links between diabetes or hyperglycaemia and the augmented epigenetic modification remain to be investigated.

Altered expression of non-coding RNAs, including miRNA, long non-coding RNAs (lncRNA) and circular RNAs (circRNA), are also implicated in diabetes-induced cardiac complications. Non-coding RNAs regulate transcription and post-transcriptional processing of mRNA transcripts and orchestrate several transcriptional changes seen in the hearts of individuals with diabetes. RNA microarray analysis studies have also indicated distinct changes in many of these non-coding RNAs in myocardial apoptosis, hypertrophy, fibrosis, autophagy and oxidative stress, suggesting their potential as therapeutics and diagnostic tools to address underlying pathogenesis variation in patients with diabetes and heart failure [84]. However, there is still a large gap in identifying the most reliable target from the vast number of non-coding RNAs dysregulated in diabetes-induced heart failure.

Post-translational modifications Recently, mitochondrial protein acetylation has also been shown to be important in mediating myocardial metabolic dysfunction in the hearts of mice in models of type 2 and type 1 diabetes [85, 86]. An association between hyperacetylation of mitochondrial proteins and mitochondrial metabolic inflexibility, characterised by a shift in myocardial metabolic fuel preference towards fatty acid utilisation, has been observed in these studies [85, 86]. Enhanced myocardial fatty acid oxidation during diabetes leads to an increase in acetyl-CoA generation that can potentially drive acetylation of mitochondrial proteins. While increased acetylation of enzymes involved in both mitochondrial fatty acid oxidation and glucose oxidation have been observed, the effects of this acetylation on these pathways appear to differ. Increased acetylation increases fatty acid oxidation [87], while acetylation decreases glucose oxidation in association with PDH inhibition due to hyperacetylation of its E1α subunit [85]. Thus, acetylation could contribute to the metabolic inflexibility seen in heart failure induced by diabetes through regulating metabolic enzyme activities differently. However, similar studies are lacking in patients with diabetes. Widespread lysine acetyl modification of myocardial proteins has been reported in heart failure in humans without diabetes [88], although the biological consequences of most of these modifications remains incompletely understood. Although earlier studies suggested the significant contribution of hyperacetylation in the development of heart failure [88], a recent study in mice unexpectedly found no changes in myocardial energetics and functions following a genetic model of cardiac mitochondrial protein hyperacetylation and pressure-overload hypertrophy [89]. Understanding the reasons for such discrepancies requires further investigation, although disease-specific variations and divergent methods used to measure acetylation dynamics may contribute to these differences. Considering the progression of diabetes and concurrent heart failure, previous studies in both mouse models and humans have shown that protein lysine acetylation increases in heart failure, so we would expect that as the severity of diabetes increases, so will the levels of protein lysine acetylation [88]. Increased acetylation of fatty acid oxidative enzymes, as previously mentioned, would increase their enzyme activity and perpetuate the diabetes-induced increased reliance on fatty acid oxidation as diabetes progresses [87].

Conclusion and clinical implications

With the requirement to present the risks for CVD with any new type 2 diabetes therapy, the emergence of cardiovascular outcome trials has brought attention and excitement to sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists—both of which improve

Biochemical changes that occur during diabetes

- Decreased Ca^{2+} uptake into the sarcoplasmic reticulum (SR) due to decreased SERCA2a protein levels and increased phospholamban expression. This leads to a decreased reservoir of Ca^{2+} in the SR and weakened myocardial contraction
- Hyperglycaemia contributes to increased aldose reductase (AR) enzyme activity and *O*-GlcNAcylation that leads to mitochondrial dysfunction and glucotoxicity
- Increased fatty acid oxidation contributes to decreased cardiac efficiency, increased lipoapoptosis and lipotoxicity
- DNA methylation, histone protein acetylation and dysregulation of non-coding RNAs dysregulate genes involved in metabolic remodelling
- Hyperacetylation of mitochondrial proteins contributes to metabolic inflexibility leading to increased fatty acid oxidation and decreased glucose oxidation

cardiovascular outcomes in patients with type 2 diabetes [90, 91]. While initially intended for the treatment of diabetes, the cardiovascular benefits are due to a culmination of whole-body, vasculature, renal and cardiac-specific physiological changes. Beneficial cardiovascular effects in patients with diabetes may occur secondary to optimising cardiac energy metabolism in the heart [92, 93]. Specifically, SGLT2 inhibitors are predicted to act through improving energy metabolism, reducing the pre- and afterload of the heart, decreasing NLR family pyrin domain containing 3 (NLRP3) inflammation, improving autophagy, decreasing oxidative stress and inhibiting the sodium-hydrogen exchange. This is reviewed in a state of the art review by Lopaschuk and Verma [92]. Similarly, GLP-1 receptor agonists are predicted to act through improving cardiac bioenergetics alongside decreases in inflammation, platelet aggregation, thrombosis and apoptosis; all of which contribute to improvements in vascular function [94].

Since glucose is a more oxygen-efficient energy substrate compared with fatty acids, there is potential to develop metabolic therapeutic strategies to improve cardiac insulin sensitivity via modulation of myocardial glucose oxidation. A new and promising therapeutic target is pyruvate dehydrogenase through the application of a PDH kinase (PDK) inhibitor [95]. Clinical studies have shown that the PDK inhibitor dichloroacetate increases cardiac efficiency in patients with coronary artery disease and congestive heart failure [96, 97]. In fact, a study in a rodent model of type 2 diabetes found that increasing PDH flux via dichloroacetate reversed diastolic dysfunction and normalised blood glucose levels [98]. Furthermore, decreasing PDK expression via genetic or pharmacological inhibition of forkhead box O1 (FoxO1) has also been shown to alleviate diabetic cardiomyopathy in mice [38, 99]. As such, studies that investigate whether newer PDK inhibitors can improve the metabolic profile and cardiac efficiency in diabetic humans are warranted.

Taken together, the implications of research to date would suggest that in managing the complex and multifactorial aetiology of heart disease in diabetes, attempts should be made to inhibit myocardial fatty acid oxidation and promote myocardial glucose oxidation. However, a metabolic therapeutic drug is not yet on the market. Instead, physicians can now prescribe SGLT2 inhibitors and GLP-1 receptor agonists to manage hyperglycaemia and concurrently reduce the risk of CVD. New drugs in the pipeline for the treatment of diabetes that need to be assessed for their effects on CVD include, but are not limited to, dual gastric inhibitory polypeptide and GLP-1 receptor agonist, glimins (e.g. Imeglimin), anti-CD3 monoclonal antibody and sparc-related modular calcium-binding protein 1 [100]. Overall, it is important to note that, regardless of the drug used to treat a patient with both diabetes and heart failure, systemic metabolism will influence cardiac metabolism and as such, efforts to improve whole-body systemic metabolism via lifestyle changes (i.e. exercise and diet) should go hand-in-hand with pharmacological intervention.

Supplementary Information The online version contains a slideset of the figures for download, which is available to authorised users at https://doi.org/10.1007/s00125-021-05637-7.

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