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INVITED REVIEW

Concurrent diabetes and heart failure: interplay and novel therapeutic approaches

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Abstract

Diabetes mellitus increases the risk of developing heart failure, and the co-existence of both diseases worsens cardiovascular outcomes, hospitalization, and the progression of heart failure. Despite current advancements on therapeutic strategies to manage hyperglycaemia, the likelihood of developing diabetes-induced heart failure is still significant, especially with the accelerating global prevalence of diabetes and an ageing population. This raises the likelihood of other contributing mechanisms beyond hyperglycaemia in predisposing diabetic patients to cardiovascular disease risk. There has been considerable interest in understanding the alterations in cardiac structure and function in diabetic patients, collectively termed as 'diabetic cardiomyopathy'. However, the factors that contribute to the development of diabetic cardiomyopathies are not fully understood. This review summarizes the main characteristics of diabetic cardiomyopathies, and the basic mechanisms that contribute to its occurrence. This includes perturbations in insulin resistance, fuel preference, reactive oxygen species generation, inflammation, cell death pathways, neurohormonal mechanisms, advanced glycated end-products accumulation, lipotoxicity, glucotoxicity, and post-translational modifications in the heart of the diabetic. This review also discusses the impact of antihyperglycaemic therapies on the development of heart failure, as well as how current heart failure therapies influence glycaemic control in diabetic patients. We also highlight the current knowledge gaps in understanding how diabetes induces heart failure.

Keywords Diabetes • Diabetic cardiomyopathy • Heart failure • Mitochondria • Energy metabolism

1. Introduction

Cardiovascular disease is the leading cause of death and complications in diabetic patients worldwide,[1–6] the prevalence of which is increasing despite therapeutic and pharmacological advances.[5,7] Diabetes mellitus, a metabolic disorder characterized by hyperglycaemia resulting from insulin deficiency (type 1) or resistance (type 2).[8] is a major independent risk factor in the development of heart failure[9–11] and is becoming a global epidemic with increasing prevalence.[12–15] There are two main types of diabetes mellitus: type 1 and type 2; gestational diabetes mellitus is also part of this category but is not a major focus of this review. Type 1 diabetes mellitus, also called insulin-dependent diabetes, is an autoimmune disease where pancreatic beta cells are destroyed, and therefore, the body is unable to produce insulin.[16] Type 2 diabetes mellitus, also called non-insulin-dependent diabetes, is characterized by a deficit in the function of insulin produced by pancreatic beta cells; this is also referred to as insulin resistance. Type 2 diabetes is the more common form of diabetes, and factors such as age, obesity, diet, and pre-existing hypertension affect its development and its risk of development. Therefore, due to either the elimination of insulin secretion or the reduction in insulin function, blood glucose levels are, as a result, elevated, leading to chronic hyperglycaemia if left untreated. The Framingham Study was one of the first epidemiological studies to show an increased risk of heart failure in patients with diabetes mellitus,[10,17,18] with other clinical trials supporting this conclusion (see refs[19,20] for reviews). The presence of both diabetes and heart failure in individuals leads to poor cardiovascular outcomes.[5,6,21–24] Diabetic patients have higher mortality from coronary artery disease than non-diabetics[25] and show a worse prognosis,[26,27] which may be associated with increased atherosclerosis,[25] and can lead to ischaemic heart failure.[28] Heart failure is the major adverse cardiovascular outcome in diabetic patients.[18] Poor glycaemic control is associated with increased risk of heart failure in individuals with type 2 diabetes,[29] indicated by

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elevated haemoglobin A_{1C} levels, an index of glycaemic control.[30] Therefore, it is critical to mediate and treat cardiovascular conditions in diabetic patients. The prevention and treatment of cardiovascular disease and heart failure remains a considerable challenge in the treatment and management of diabetes mellitus.

Diabetic cardiomyopathy is a condition characterized by ventricular dysfunction and hypertrophy in diabetic patients independent of hypertension, ischaemia, or coronary artery disease.[31] The term originated from a Rubler *et al.* study that identified diabetic patients with congestive heart failure without the aforementioned risk factors or other causes. Non-invasive studies show impaired diastolic and systolic function,[32–35] especially with the presence of hypertension. Multiple mechanisms contribute to the development of heart failure in diabetic individuals, including increased inflammation[36] and oxidative stress,[37,38] changes in cardiac myocardial energy metabolism,[39–41] cardiac lipotoxicity,[42–45] impaired cardiomyocyte calcium handling, and apoptosis.[46,47] Diabetic cardiomyopathy may progress to either heart failure with preserved ejection fraction (HFpEF), where there is diastolic dysfunction,[48,49] or heart failure with reduced ejection fraction (HFrEF), where there is systolic dysfunction.[11,50,51] Each phenotype can be distinguished by the various mechanisms involved in contributing to it. Hypertrophy,[52–54] insulin resistance,[55] and lipotoxicity[56,57] have been shown to contribute to the development of HFpEF, while oxidative stress,[58] fibrosis,[59,60] and autoimmunity caused cardiomyocyte cell death[61] are involved in contributing to HFrEF. Coronary deposition of advanced glycation end-products is involved in both phenotypes.[62] Diastolic dysfunction, which is part of the diagnosis of HFpEF,[48,49,63] can precede the development of HFrEF alongside comorbidities of impaired coronary vasculature and endothelial function, and hypertrophy.[64,65] Although diastolic dysfunction is mostly predominant in diabetic cardiomyopathy, systolic dysfunction may also occur in later stages of diabetic cardiomyopathy, which can contribute to the development of HFrEF.[50,51] Studies have demonstrated a metabolic link between the two heart failure phonotypes whereby abnormal mitochondrial function and oxidative stress can lead from an HFpEF phenotype into an HFrEF phenotype by mediating cardiac hypertrophy, inflammation, fibrosis, and further endothelial cell damage, which has adverse consequences on systolic function, and ultimately more severe manifestations of diabetes and heart failure.[52,66–75]

The aim of this review is to highlight the changes that occur in diabetic cardiomyopathy, alongside the mechanisms involved its development and progression. The effect of antihyperglycaemic drugs on heart failure risk in diabetic individuals, and heart failure drugs on glycaemic control will also be discussed, as well as novel therapeutic approaches.

2. Structural and functional characteristics of the failing heart in diabetics

The failing heart in the context of diabetes is characterized by multiple alterations including impairments in diastolic and subsequent systolic function,[32–34,48] cardiac hypertrophy and fibrosis,[76] and impaired coronary microvascular perfusion.[77]

2.1 Diastolic and systolic dysfunction

Heart failure in diabetes is characterized by cardiac dysfunction, with diastolic dysfunction as a hallmark of the failing myocardium in diabetics.[32,78] Echocardiography and Doppler imaging assessments of diastolic dysfunction,[79] have shown that left ventricular (LV) dysfunction is manifested in type 2 diabetic patients through altered LV filling,[80] abnormal LV relaxation,[32,81,82] reduced LV end-diastolic volume,[83] and LV chamber stiffness.[84] Studies in type 1 diabetics demonstrate abnormalities in LV diastolic filling,[33,85,86] lower *E* to *A* ratios, prolonged isovolumetric relaxation times,[33] and reduction in end-systolic volumes.[34] Thus, there is no single parameter to indicate and quantify diastolic dysfunction. Moreover, Attali *et al.*[87] showed in both type 1 and 2 diabetic patients that abnormalities in diastolic function, including increased isovolumetric relaxation time and impaired LV compliance, were not related to additional factors such as age, sex, duration of diabetes, or presence of other complications. Impaired diastolic function has also been shown in type 1 diabetic children.[34,88] Additionally, the presence of hypertension can aggravate diastolic dysfunction, as demonstrated through further and severe impairment of LV relaxation and abnormal LV filling.[48] Speckle tracking echocardiography has emerged as a novel beneficial diagnostic method for early detection of LV dysfunction in diabetes, therefore being useful to detect LV abnormalities.[89] This method has been shown to overcome some of the limitations of transthoracic Doppler imaging[90] and can be an equally, if not better, powerful approach to assessing myocardial velocities and strain.[90–92] Studies have shown it's usefulness through examining LV strain in hypertensive and type 2 diabetic patients,[93] and LV rotational mechanics in hypertensive type 2 mellitus diabetic patients.[89] This echocardiography method has also been utilized in animal models of diabetes, namely assessing systolic strain and contractile function in db/db mice by Li *et al.*[94] and assessing cardiac dysfunction in rat models of type 1 and type 2 diabetes mellitus by Matyas *et al.*[95]

Experimental evidence in animals complements these observations in human studies, showing a decrease in end-diastolic volume in alloxan diabetic dogs,[96] a reduced *E* and *A* transmitral flow in *db*/*db* mice[97]; and an increased isovolumetric relaxation time and increased LV end-diastolic pressure in streptozotocin-induced non-insulin-dependent rats compared to controls.[98] Additionally, Otsuka Long-Evans Tokushima fatty rats show increased deceleration time.[99]

Systolic dysfunction is also present in diabetic cardiomyopathy, although in both human and animal studies it has been shown to take longer to develop and usually occurs after diastolic dysfunction.[34,97] In human studies, this manifests mainly as a reduction in ejection fraction,[100,101] along with increased LV end-systolic volume[100] and reduced fractional shortening.[102] The Strong Heart Study showed systolic dysfunction to occur, as evidenced by lower LV fractional shortening and decreased stress corrected midwall shortening in diabetic patients.[103] Animal studies are consistent with this, demonstrating impaired systolic function through lower peak-developed pressures,[98] $+dP/dt$, peak emptying rates,[104] peak filling rates, fractional shortening,[105] and systolic blood pressure in streptozotocin-induced diabetic rats.

Impaired diastolic function is either associated with normal systolic function[48,81,82,106,107] or can precede systolic dysfunction.[34] In support of this, Raev[34] showed diastolic damage and abnormalities to be more prevalent than systolic damage and abnormalities in type 1 diabetic patients, while systolic dysfunction occurred much later in the progression of diabetes. However, Fang *et al.* believe the use of less sensitive techniques to measure systolic dysfunction accounts for the reason behind studies demonstrating diastolic dysfunction with normal systolic function.

2.2 Cardiac hypertrophy

Diabetic cardiomyopathy is often associated with LV hypertrophy.[76] The Strong Heart Study showed an independent association between diabetes and cardiac hypertrophy.[103] Increased myocardial wall thickness can be seen in type 1 and 2 diabetes, alongside ventricular dysfunction.[82,103,108] Additionally, myocardial hypertrophy is linked to adverse cardiovascular outcomes, including being a predictor of cardiovascular death.[109,110] The Framingham study demonstrated that increased LV mass is associated with increased risk of cardiovascular outcomes of mobility and mortality.[110] Moreover, Solomon *et al.*[111] observed a slightly greater wall thickness in diabetic patients alongside decreased ventricle size, which they believe may be associated with higher filling pressures and diastolic dysfunction. These findings have been confirmed in animal studies showing an increase in LV mass alongside impaired LV relaxation and increased chamber stiffness.[98] The observed LV hypertrophy in diabetics may precede the onset of systolic dysfunction, and can additionally be used as a diagnostic indicator in the development of heart failure in diabetics.[112]

2.3 Cardiac fibrosis

Myocardial fibrosis and collagen accumulation can manifest as a major structural alteration in the setting of diabetes,[113,114] which can lead to myocardial damage and heart failure.[115–118] Multiple human studies demonstrate the presence of fibrosis in the left ventricle, alongside collagen accumulation in the interstitial and perivascular region of diabetic patients.[76,113,119] This cardiac fibrosis is associated with cardiac dysfunction,[53,117] and may lead to worsened cardiac outcomes including developing congestive heart failure.[53,116,120]

Increased cardiac fibrosis in diabetes is supported by animal studies, where multiple mechanisms may be responsible for the cardiac fibrosis observed in diabetes. Otsuka Long-Evans Tokushima Fatty rats, a model of type 2 diabetes, show increased myocardial collagen content that is associated with impaired diastolic function through prolonged deceleration times and decreased early filling wave peak velocities.[99] Streptozotocin-induced diabetic rats have increased collagen and interstitial fibrosis due to oxidative stress, alongside decreased cardiac contractility.[121,122] Additionally, streptozotocin-induced diabetic mice show a time-dependent increase in LV collagen content, alongside impaired diastolic and systolic function.[115] This is suggested to be due to reduced matrix metalloproteinase 2 levels. Spiro *et al.*[123] also showed an increase in type IV collagen in the myocardium of diabetic rats. The increase in cardiac collagen in diabetes may be due to increased transforming growth factor-B1 (TGF-B1) receptor II expression.[69,99,124] Another factor that can mediate this collagen accumulation and fibrosis development in diabetes is the myocardial accumulation of advanced glycosylation end products (AGEs)[125,126] which will be discussed in more detail in a subsequent section of this review.

2.4 Impaired coronary microvascular perfusion

Abnormalities in coronary artery function and circulation are highly prevalent in diabetes,[127] which may predispose the diabetic myocardium to cardiac damage and disease, including ischaemia due to impaired blood circulation and flow.[127,128] Coronary flow reserve (CFR) is reduced in both type 1 and 2 diabetic patients,[77,129] along with a reduction in coronary vasodilation[130] due to reduced nitric oxide (NO) production.[131,132] Marciano *et al.*[133] showed that type 2 diabetic patients without coronary artery disease have impaired coronary microvascular function, demonstrated by a lower CPT-CF ratio (cold pressure test to coronary flow), compared to non-diabetic individuals. Additionally, Bagi *et al.*[134] showed enhanced superoxide production and decreased NO production, leading to reduced coronary dilation in coronary arterioles isolated from *db/db* mice. Hyperglycaemia may be a cause for this, as shown by an association between CFR and HBA1c levels.[135] Additionally, Durante *et al.*[136] showed lower coronary flows in diabetic BB rats in response to stimulation by noradrenaline, calcium, or tachycardia. Coronary microvascular perfusion may be further impaired by the presence of hypertension-induced vascular lesions.[137] A reduction in coronary capillary density in the diabetic myocardium has also been observed, due to lower angiogenesis as a result of decreased vascular endothelial growth factor (VEGF) expression.[138–140] VEGF and VEGF receptor mRNA and protein expression were shown to be significantly decreased in diabetic and insulin-resistant non-diabetic rats,[138,139] and was accompanied by decreased myocardial perfusion and LV dysfunction.[139] Together, this suggests that structural abnormalities occur alongside functional abnormalities in the coronary microvasculature in diabetes. However, it is not clear which precedes the other, as some studies suggest structural changes in coronary arterial vasculature may be involved in causing further cardiac dysfunction[141] and also concurrently progress as diabetic cardiomyopathy progresses.[139,142] Additionally, Giordano *et al.*[143] showed that VEGF is a critical determinant of cardiac function as a VEGF knockout mouse model resulted in contractile dysfunction. Therefore, further studies need to be done to fully elucidate the interplay in sequence of events between abnormalities in coronary capillary density and cardiac function.

Additionally, impaired CFR and vasodilation may be an early marker of atherosclerosis, which can lead to progressive deterioration of the myocardium[128] and an increase in the risk of cardiovascular disease[129] and ischaemia.[130] Impaired vasodilation in diabetes,[132] which may also be due to NO production inhibition due to hyperglycaemia[144] through the generation of oxygen-derived free radicals,[145] can also lead to arterial atherosclerosis. Therefore, this abnormal coronary flow may greatly increase the risk and likelihood of myocardial ischaemia.[130,136,146]

3. Underlying mechanisms contributing to the development of diabetic cardiomyopathy

3.1 Insulin resistance

Insulin resistance is one of the early contributing factors to the development of diabetic cardiomyopathy.[147] The decreased efficacy of insulin to lower blood glucose levels occurs as a result of hyperinsulinaemia-mediated excessive insulin receptor signalling or down-regulation of insulin receptor signalling. This insulin resistance contributes to a number of adverse changes in the heart that include alterations in cardiac energy metabolism, increased inflammation and hypertrophy, lipotoxicity, glucotoxicity, alterations in mitochondrial function and reactive oxygen species (ROS) production, accumulation of advanced glycation products and O-GlcNAcylation, alterations in cardiac cardiomyocyte Ca^{2+} handling, systemic hyperglycaemia and hyperlipidaemia,[148] and neurohormonal changes (all of which are discussed below).

It is important to note that cardiac insulin resistance precedes the development of cardiac dysfunction and heart failure. A study in mice with heart failure developed diastolic dysfunction at 2 weeks and systolic dysfunction at 3 weeks.[41] Notably, the decline in function was preceded by

significant cardiac insulin resistance which was determined via serial and direct measurements of insulin-stimulated glucose metabolism in isolated working hearts.[41] These findings are supported by epidemiological studies that also found that insulin resistance is a predictor, rather than a biomarker, of heart failure. In an epidemioloical study of 1187 elderly men that did not have congestive heart failure, between 1990 and 1995 found that insulin resistance significantly increased the risk and predicted congestive heart failure.[149] Another study in 431, 50-year-old men with a 20-year follow-up, patients that developed heart failure at age 70 presented increased plasma proinsulin at age 50, signifying that insulin resistance preceded cardiac dysfunction.[150]

Insulin signalling begins with insulin binding to the insulin receptor, resulting in activation of the insulin receptor substrate (IRS)-1/2, PI3K/PKB (Akt) activation, GLUT4 translocation to the cell membrane, stimulation of mitochondrial glucose oxidation, and inhibition of fatty acid oxidation.[151] Cardiac muscle biopsies from type 2 diabetic patients have depressed PI3K/PKB signalling and decreased GLUT4 expression.[152] In addition to decreased translocation of GLUT4, impaired PI3K engagement and stimulation of Akt also occur, due to increased phosphorylation of the serine residue on IRS-1/2.[153]

Activation of forkhead box-containing proteins regulates insulin signalling, leading to insulin resistance. FoxO proteins are elevated in mice with high-fat diet-induced diabetes, which down-regulates IRS1, consequently leading to decreased Akt signalling, insulin resistance and the development of diabetic cardiomyopathy.[154] Also important in the regulation of insulin signalling, and is perturbed in diabetic cardiomyopathy, is the E3 ubiquitin ligase—mitsugumin 53.[155] In support of this, cardiac-specific overexpression of mitsugumin 53 in mice results in severe diabetic cardiomyopathy and insulin resistance, due to degradation of the insulin receptor and IRS-1. Mitsugumin 53 overexpression is involved in transcriptionally up-regulating peroxisome proliferator-activated receptor-α (PPARα), contributing to lipid accumulation.[156] This accumulation of lipid intermediates [diacylglycerol (DAG) and ceramides] contributes to the development of insulin resistance.[157,158] Conversely, decreasing myocardial levels of ceramide and DAG is accompanied by improvements in insulin sensitivity and myocardial glucose utilization.[159]

3.2 Altered cardiac energy metabolism

The heart has a very high energy demand despite having very low ATP stores (ATP levels effectively turnover in the heart every 5–10 s).[160] The heart has the ability to continually generate large amounts of ATP from various energy substrates, including fatty acids, glucose, lactate, ketone bodies and amino acids, regardless of workload, nutritional status, and hormonal status.[160,161] However, this metabolic flexibility is impaired in many forms of heart disease, including diabetic cardiomyopathy.[160] Insulin resistance results in an increase in myocardial fatty acid oxidation rates in diabetic cardiomyopathy and impaired glucose oxidation rates (*Figure 1*).[162–164] This increases myocardial oxygen consumption, decreases cardiac efficiency and strongly correlates with impaired cardiac contraction and diastolic function.[39,40,165–167]

Multiple mechanisms contribute to the increased reliance of the heart on fatty acid use during diabetes. The first such mechanism is increased supply of fatty acids to the heart. The lack of insulin suppressive action on adipose tissue results in the release of fatty acids from adipocyte to the circulation, leading to elevation of blood plasma free fatty acid levels. Fatty acid delivery and uptake to the heart is also increased in diabetes, due to an increase in cardiac myocyte lipoprotein lipase (LPL) activity and increases in sarcolemmal CD36 protein expression, respectively.[168,169] The increased uptake of fatty acids across the sarcolemma is facilitated by at least three proteins, namely, CD36, fatty acid transport protein (FATP), and fatty acid binding protein plasma membrane (FABPpm).[170] In STZ-induced type 1 diabetic rats and type 2 *db/db* mice an up-regulation of CD36 and FABPpm protein expression occurs.[171,172] While CD36 alone accounts for more than half of the total fatty acid taken up by cardiomyocytes,[173] both its expression and membrane localizations are increased in diabetes.[171,173]

Activation of transcription regulators such as PPARs can promote expression of genes that facilities fatty acid uptake, storage and oxidation in the heart.[151,174,175] Myocardial PPARα expression is increased in type 2 diabetes, and mice lacking PPARα are protected from the development of diabetic cardiomyopathy.[39,176] In contrast, a recent study found no differences in the risk of cardiac dysfunction between wildtype and PPARα deficient mice subjected to a low dose of streptozotocin (STZ).[177] The discrepancy in the findings could be due to the different methodology followed for inducing Type 1 diabetes (one single injection of high STZ dose vs. five daily injections of lower dose) and/or the different time points of cardiac function assessment (6 weeks vs. 9–12 weeks post-STZ administration). Interestingly, it has been shown that PPARα/γ alterations may contribute to cardiac dysfunction independent of changes in fatty acid oxidation or lipid storage in non-diabetic animals.[178,179]

One effect of increased PPARα in diabetes is an increase in mitochondrial carnitine palmitoyltransferase I (CPT-1) expression, a key enzyme involved in mitochondrial uptake and oxidation of fatty acids.[180] In addition, perturbations in CPT-1 regulation also occur in diabetes. CPT-1 is inhibited by malonyl CoA produced from acetyl CoA by acetyl CoA carboxylase (ACC).[181] Activation of AMP-activated protein kinase (AMPK) in diabetes inhibits ACC activity. Decreased ACC activity with parallel increases in malonyl-CoA decarboxylase activity[182] decreases malonyl CoA levels, resulting in decreased inhibition of CPT1 and accelerated fatty acid oxidation rates (*Figure 1*).[182–184] Post-translational modification of fatty acid oxidative enzymes also occurs in diabetes, resulting in an increase in fatty acid oxidation.[185] Increased acetylation of major fatty acid metabolic enzymes due to decreased SIRT3 also leads to up-regulation of fatty acid oxidation and impaired glucose metabolism in the heart.[186–188] In addition to increases in myocardial fatty acid oxidation, an increase in myocardial triacylglycerol content is seen in diabetics.[189] Increased myocardial uptake of fatty acids leads to the increased accumulation of lipids and their intermediate metabolites, such as long and short fatty acyl-CoAs, and diacylglycerol (DAG).[174,190] However, studies on the turnover of endogenous fatty acid in hearts from diabetic animals have generated variable results. We have shown an increased myocardial lipolysis rate in diabetic hearts irrespective of exogenous fatty acid concentration while endogenous synthesis rate remains unaffected.[189] This is further supported by a ^{13}C-NMR isotopic enrichment study in diabetic rat hearts.[191] In contrast, others reported reduced or unchanged lipolysis and increased synthesis in the hearts of diabetics in the presence of high levels of exogenous free fatty acids.[192,193] On the other hand, decreased levels of myocardial phospholipids is seen in diabetes together with impaired synthesis.[194] While the precise contribution of altered phospholipid metabolism is less clear in diabetes, various studies have suggested the etiologic role of phospholipid (membrane lipid) metabolic dysregulation in lipotoxic cardiomyopathy and other forms of myocardial dysfunction.[195,196]

In contrast to the increased myocardial uptake and oxidation of fatty acids seen in diabetes, myocardial glucose transport, glycolysis and glucose oxidation are decreased in diabetes.[197–200] Total myocardial GLUT4 and GLUT1 expression are decreased in diabetes.[201] Decreased myocardial glycogen content along with a reduced myocardial glycogen

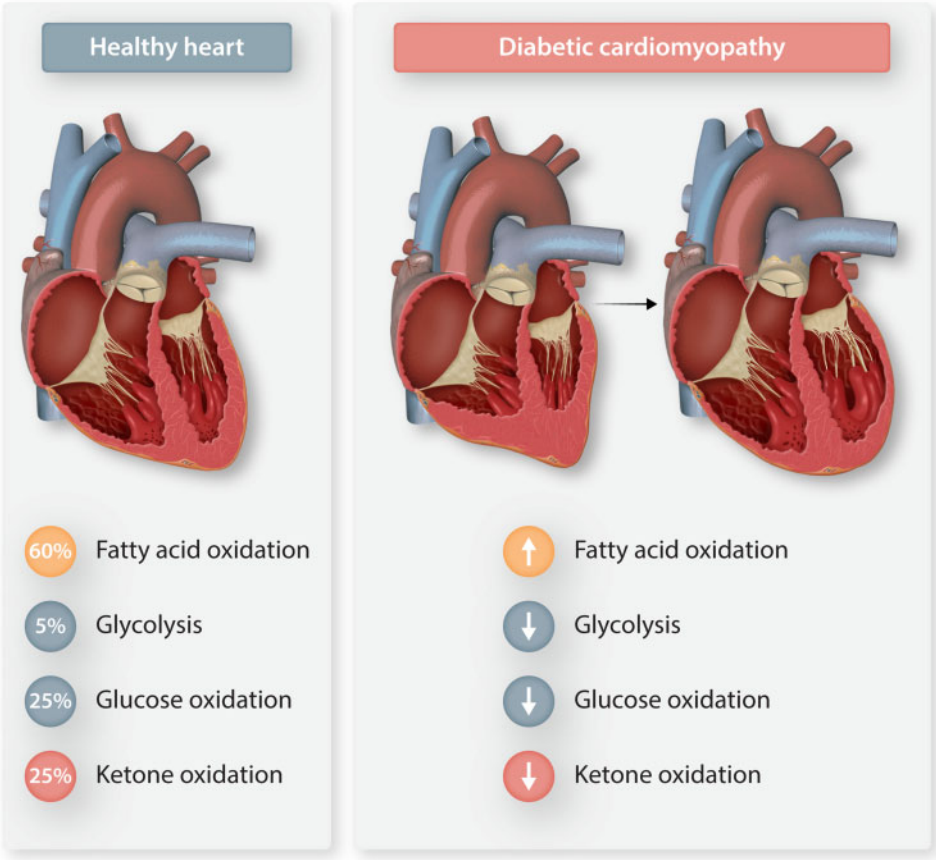

Figure 1 Energy metabolic changes in a healthy setting vs. diabetic cardiomyopathy. In the healthy heart, approximately 60% of the heart's energy comes from the oxidation of fatty acids, followed by approximately 5% by glycolysis and 25% from glucose oxidation, and 10% by ketone oxidation. However, in diabetic cardiomyopathy, due to systemic and local changes in energy substrate concentrations as well as insulin resistance, the metabolic protein machinery is perturbed and subsequently, the heart's overall energy metabolic profile is impaired. As such, diabetic cardiomyopathy results in an increase in fatty acid oxidation, decreased glucose metabolism, and decreased ketone oxidation. AGEs, advanced glycation end products; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction.

synthesis rate and impaired glycogen synthase enzyme activity is also reported in hearts of diabetics.[202–204] Insulin deficiency or resistance compromises the glucose transport and utilization in the heart. Also, the presence of excess fatty acid derivatives, such as fatty acyl CoA, DAG, and ceramide, leads to the inhibition of insulin signalling in the heart.[205,206] In addition to decreased glucose transport, inhibition of cardiac phosphofructokinase (PFK-1), the rate limiting enzyme in glycolysis, is seen in diabetes.[207,208] PFK-1 is inhibited allosterically by high levels of citrate, high ATP levels, and increases in NADH that are derived from increased fatty acid oxidation. Glucose oxidation is also decreased, due in part to increases in fatty acid oxidation, which inhibits the rate limiting enzyme of glucose oxidation—pyruvate dehydrogenase (PDH).[164,197,209] PPARα activation also suppresses glucose uptake and utilization by increasing the expression of pyruvate dehydrogenase kinase 4 (PDK-4), which inhibits PDH.[45,210]

Similar trends of fatty acid and glucose metabolic shifts have been also observed in type 1 and 2 diabetic patients.[57,211–214] In ^{31}P and ^{1}H magnetic resonance spectroscopy studies, a significant reduction in myocardial glucose utilization accompanied by reduced myocardial energetics [phosphocreatine to ATP ratio (PCr/ATP)] and increased myocardial fatty acid metabolism and triacylglycerol content is seen in type 2 diabetic patients.[212,213] The increased rates of myocardial fatty acid oxidation persist even after insulin treatment in human type 2 diabetic patients.[211] The levels of circulating free fatty acids are also negatively correlated with altered PCr/ATP ratios in patients with diabetes.[215] Earlier studies recognized myocardial PCr/ATP ratios as a predictor of cardiovascular mortality in patients with dilated cardiomyopathy.[216] Likewise, increased myocardial fatty acid utilization with a concomitant decrease in glucose utilization is seen in type 1 diabetic patients.[57,214]

Since fatty acids and glucose are the two important fuels for the heart, their balanced use is critical for maintaining normal contractile function. As a result, the decreased 'metabolic flexibility' and increased reliance of the heart on fatty acid as source of energy is associated with impaired myocardial function in diabetes.[198,217–220] Enhanced fatty acid oxidation increases myocardial O_2 consumption and decreases cardiac efficiency.[221] Enhanced fatty acid oxidation also alters the mitochondrial NADH to NAD^+ ratio and acetyl CoA levels which can further modify several intracellular signalling processes.[186] Although evidence suggests a detrimental effect of increased fatty acid oxidation on heart function in diabetes, there are still opposing views on the role of glucose and fatty acid alterations and pathologic significance in non-diabetic heart failure. Relatively few studies have combined diabetes and heart failure to study the impact of

energy metabolism in the hearts during diabetes. By combining high-fat feeding with pressure overload hypertrophy in mice we observed a marked decrease in insulin-stimulated glucose oxidation that was associated with both diastolic and systolic dysfunction.[222,223] Furthermore, nutritional strategies that increase insulin-stimulated glucose oxidation are accompanied by a decreased severity of heart failure.[222,223]

The contribution of alterations in the use of other fuels such as ketone bodies and branched chain amino acids (BCAAs) is increasingly being recognized in heart failure pathogenesis.[224–226] While ketone oxidation is increased in HFrEF and may be an adaptive process to maintain energy production,[226,227] in diabetes myocardial ketone oxidation is impaired, and may result in a decrease in metabolic flexibility and a decrease in energy production in the heart.[228,229] A decrease in BCAA oxidation in insulin resistant hearts also contributes to an impaired insulin signalling and a decrease in insulin-stimulated glucose oxidation.[230–232]

3.3 Cardiac lipotoxicity and glucotoxicity

Under normal circumstances, the uptake and oxidation of fatty acids are finely regulated resulting in only little myocardial lipid storage. However, in diabetes, a persistent elevation in circulating free fatty acids supplies the heart with excess fatty acids and promote accumulation of lipids in the cardiomyocytes (cardiac lipotoxicity) (*Figure 2*).[233,234] The causative role of excess lipid accumulation in diabetic cardiomyopathy has been demonstrated using genetic or pharmacological approaches that modify uptake or oxidation of fatty acids. For instance, mice with cardiac-specific overexpression of PPARα exhibit increased uptake and utilization fatty acid and typical features of diabetic cardiomyopathy, including ventricular hypertrophy and systolic dysfunction.[45] Recently, an increased activity of LPL was shown in epicardial adipose tissue from type 2 diabetic patients.[235] Interestingly, elevated activity of LPL was associated with increased epicardial adipose tissue volume, suggesting increased fatty acids uptake. Of interest, deletion of CD36 or cardiac LpL rescues mice from a lipotoxic-induced cardiomyopathy caused by PPARα overexpression.[236,237]

In contrast, overexpression of CD36, FATP1, or acyl CoA synthetase results in lipotoxocity.[238,239] This lipotoxicity correlates with diastolic dysfunction and other pathophysiological findings related to diabetic cardiomyopathy.[240,241] Despite their contributing role in inducing cardiac lipotoxicity in diabetes, PPARα agonists (fibrates) are still in use clinically to treat hypertriglyceridaemia.[242] In theory, lipotoxicity could arise either due to increased uptake or decreased oxidation of fatty acids. However, studies on pharmacological inhibition of FA oxidation or genetic manipulation of fatty acid oxidation enzymes revealed that decreased fatty acid oxidation does not actually lead to lipid accumulation.[243] It has been hypothesized that the reduction in oxidative function may inhibit the uptake of fatty acid by feedback mechanism.[244]

In addition to fatty acid overload, cardiac lipotoxicity is also dependent on the type of fatty acids or lipids accumulated.[244] Ceramide is one fatty acid derivative strongly associated with cardiac lipotoxicity. Inhibition of ceramide synthesis, either by deletion of serine palmitoyltransferase or pharmacologically by myriocin, results in significant metabolic and structural changes to the heart. Decreasing cardiac ceramide levels decreases heart weight, PDK4 expression, fatty acid oxidation rates and LV diameter, while improving glucose oxidation.[245] DAG is another lipid derivative associated with cardiac lipotoxicity. Increased levels of DAG in the heart is associated with biochemical changes and macrovascular remodelling, indicating its possible role in the development of diabetic complications.[159,246] Increased levels of both ceramide and DAG can also activate and facilitate the translocation of protein kinase C (PKC) to the cell membrane.[246,247] Activation of PKC by excess lipids impairs β-adrenergic signalling in the heart by phosphorylating its receptor.[248,249] Phosphorylation of the β-adrenergic receptor leads to its desensitization, resulting in reduced myocardial contractility in response to catecholamines.[250] Increased PKC activity and its translocation to the cell membrane can also attenuate insulin signalling. Previous studies have shown that PKC can phosphorylate IRS-1 at its serine residue and blocks insulin-stimulated tyrosine phosphorylation and downstream Akt signalling.[251,252]

On the other hand, although triacylglycerol is the most abundant lipid that accumulates in the heart, studies suggest that its accumulation is not associated with toxic effects in the heart.[253,254] Overall, these data demonstrate that excess fatty acid storage and utilization in the heart are detrimental to heart function, although the mechanistic link between lipid accumulation and cardiomyopathy development are not clearly defined.

In contrast to lipotoxicity, less is known about glucotoxicity. Although myocardial glucose transporters are down-regulated in diabetes, the heart can be still exposed to excess glucose. The increased extracellular glucose concentration results in the build-up of a glucose gradient for its transporter across the sarcolemma by mass action.[255] As myocardial glucose oxidation is inhibited in diabetes,[164,197,256] the increased glucose flux can lead to the accumulation of glycolysis intermediates and products. This imbalance can drive the diversion of glycolytic intermediates into pathological pathways in diabetes including PKC stimulation, the hexosamine pathway, the polyol pathway, and the formation of advanced glycation end products.[255,257] Increased glucose uptake in GLUT4 transgenic mice also contributes to mitochondrial dysfunction via O-GlcNAcylation of the transcription factor ST1 and many electron transport chain subunits.[258]

3.4 Impaired mitochondrial function

The impact of heart failure and diabetes on mitochondrial bioenergetics has long been established. Perturbations in mitochondrial oxidative metabolism and mitochondrial ROS generation occur in both heart failure and diabetes.[259–262] The reduction in cardiac function and efficiency along with impaired cardiac mitochondrial bioenergetics in obesity and diabetes is due to, at least in part, the excessive reliance on fatty acid oxidation and increased uncoupling protein content in these hearts, that contribute to ROS production.[222,263] Many studies have proposed that ROS overload is a major culprit of diabetic cardiomyopathy.[264–267] Mitochondria are a major source of ROS production, and increased fatty acid oxidation can promote ROS production.[222,261,263,268–270] Excessive cardiac ROS production induces inflammation and activates many crucial mediators of pathological signalling cascades,[271–278] such as PKC, apoptosis signal-regulating kinase-1, p38 mitogen-activated protein kinase, NH2-terminal Jun kinases (JNK), and JAK-STAT. Activation of these signalling cascades can contribute to the complications of diabetic cardiomyopathy.[279,280] Furthermore, a recent study demonstrated that enhanced activity of Krüppel-like factor-5 is linked to an increase in oxidative stress in diabetic cardiomyopathy.[177] This occurs through an up-regulation in the expression of NOX4 via direct binding to the NOX4 promoter.[177] The accumulation of ROS, increased ceramide production and low mitochondrial abundance contributes to impaired cardiac function in the hearts of the diabetics.[177]

There have been many studies that have looked at the efficacy of antioxidants in managing diabetic cardiomyopathy.[281–288] Antioxidants can mitigate ROS-mediated mitochondrial uncoupling, a characteristic of diabetic cardiomyopathy, in animal studies.[289,290] Similarly, antioxidants are protective against mitochondrial ROS in the failing heart.[291–293]

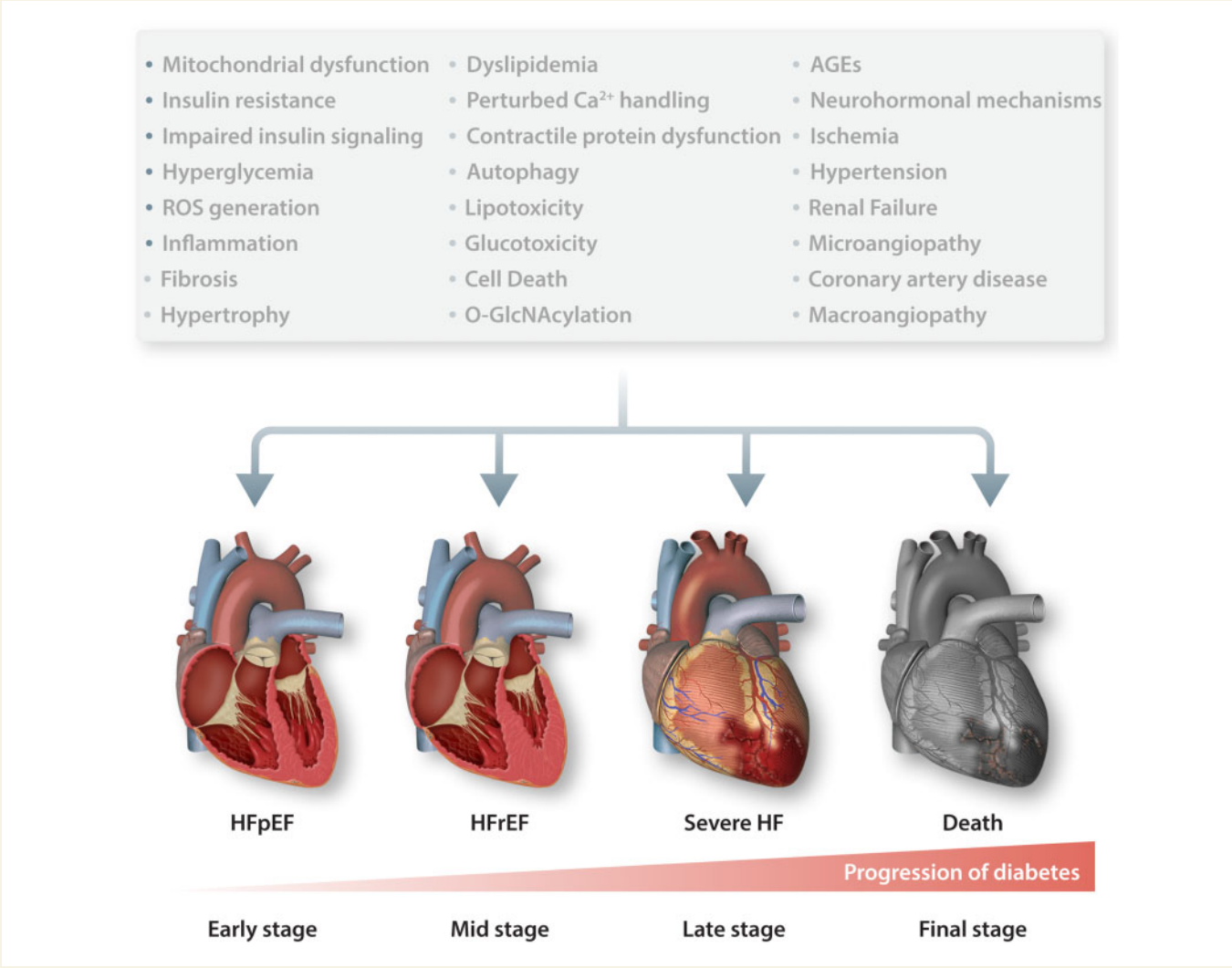

Figure 2 The different stages of diabetic cardiomyopathy. AGEs, advanced glycation end products; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF heart failure with reduced ejection fraction.

Additionally, preclinical trials specifically targeting mitochondrial ROS respiratory complexes have been positive,[294–296] but further clinical trials are necessary to confirm the efficacy of mitochondrial ROS scavenger under the contexts of both general heart failure and diabetic cardiomyopathy. Additionally, the use of Nrf2 activators and NOX inhibitor have shown to be effective in animal models,[297,298] and calorie restriction can lower ROS production and UCP expression in Type II diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats.[275,299] Unfortunately, human clinical trials have failed to replicate these observations from animal models.[300–303]

3.5 Inflammation and hypertrophy

Diabetes leads to increases in intramyocardial inflammation, characterized by increases in cell adhesion molecules [intercellular adhesion molecule-1, vascular cell adhesion molecule 1 (VCAM-1)] and increased macrophage infiltration resulting in the release of inflammatory cytokines [interleukin (IL)-1β, IL-6, IL-18, TGF-β1, tumour necrosis factor-α (TNF-α)].[267] Plasma concentrations of the cytokine acute-phase mediators, TNF-α and IL-6, are increased in the circulation in settings of impaired glucose tolerance, and thus, inflammation has been shown to be predictive for type 2 diabetes.[304–306] This is due to an excess level of glucose and free fatty acids stressing both pancreatic islet cells and adipocytes, resulting in the release of pro-inflammatory cytokines and chemokines into the circulation that promote inflammation in other tissues such as the heart.[307] Plasma TNF-α and IL-6 levels are increased and are associated with LV diastolic dysfunction in patients with diabetes.[308]

Systemic and local inflammation leads to fibrosis in the myocardium as well as hypertrophy and apoptosis at the level of the cardiomyocytes.[309] An up-regulation of inflammatory signalling results in macrophage infiltration, cardiomyocyte apoptosis, hypertrophy, and a profibrotic response via extracellular matrix remodelling—all of which lead to impaired cardiac contractility and diabetic cardiomyopathy.[310–312] Macrophage and lymphocyte infiltration into the cardiac cell are followed by secretion of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, TGF-β, interferon-γ), which leads to adverse cardiac remodelling.

Due to systemic accumulation of advanced glycation end products, angiotensin II and lipotoxicity, an increase in toll-like receptor 4 (TLR4) and tumour necrosis factor receptor 1 occurs in diabetes, leading to secretion of pro-inflammatory cytokines and subsequent cardiomyocyte

death, hypertrophy, metabolic imbalances, contractile dysfunction, oxidative stress, and mitochondrial dysfunction.[312,313] More specifically, high mobility group protein B1 mediates lipopolysaccharide binding to and activation of TLR4, resulting in downstream activation of nuclear factor-KB (NF-κB) and the NLRP3 inflammasome.[314] Activation of the pleiotropic transcription factor, NF-κB, results in the transcription of genes that are pro-inflammatory [monocyte chemoattractant protein-1, Cyclooxygenase-2 (COX-2), VCAM-1], pro-hypertrophic [atrial natriuretic peptide (ANP), myosins], and pro-fibrosis (TGF-β, collagens, fibronectin).[315,316]

Hypertrophy follows inflammation in the heart of diabetics, since cytokines can induce cardiomyocyte hypertrophy.[312,317–319] The pro-inflammatory cytokine TNF-α can activate the JNK and AKT/NF-κB pathway to promote cardiomyocyte hypertrophy.[320] Activation of the NF-κB pathway can also result in cardiomyocyte growth.[321] IL-1β, through IGF-1 downstream release from cardiac fibroblasts, promotes cardiomyocyte hypertrophy.[322] Furthermore, IL-6 also contributes to cardiomyocyte hypertrophy through activation of the CaMKII and gp130 pathways which then activates the STAT3 pathway.[323] Lastly, TGF-β can activate the TAK1-MKK3/6-p38MAPK pathway and PKC-ATF2 to promote cardiomyocyte hypertrophy.[324,325]

Myocardial inflammation can also lead to cardiomyocyte apoptosis which subsequently contributes to cardiac remodelling. TNF-α activates both extrinsic and intrinsic apoptotic pathways, as well as NF-κB, to promote cardiomyocyte death.[326,327] Additionally, through NO synthase activation or C/EBP homologous protein (CHOP), IL-1β promotes apoptosis in cardiomyocytes.[328] The NLRP3 inflammasome also induces apoptosis via caspase-1 activation.[329] The inflammasome produces active caspase 1, that when activated results in cleavage of pro-IL-1β and pro-IL-18 and the production of active cytokines. In rats with high-fat diet and streptozotocin-induced diabetic cardiomyopathy, silencing of the NLRP3 inflammasome decreases the levels of IL-1β, and this observation is mirrored when silencing CMKLR1, a G-protein-coupled receptor for chemerin. Concurrent silencing of both NLRP3 and CMKLR1 potentiates the decrease in mature IL-1β, as well as the levels of pyroptosis, underlining the important role the NLRP3 inflammasome and chemerin/CMKLR1 axis plays in mediating inflammation and pyroptosis in the setting of diabetic cardiomyopathy.[330]

Myocardial inflammation not only results in the secretion of cytokines but also pro-fibrotic factors that activate fibroblasts and promotes cardiac fibrosis.[317] TGF-β, a major cardiac pro-fibrotic cytokine, activates fibroblasts which results in the production of extracellular matrix proteins, increases collagen production, and decreases extracellular matrix degradation.[310] Furthermore, IL-6 can suppress mir-29 and promote cardiac fibroblast proliferation and collagen production.[331] TNF-α also similarly promotes cardiac fibrosis through WISP1 activation.[332]

Myocardial inflammation can also impair cardiac energy metabolism as IL-6 has been shown to impair myocardial glucose metabolism via SOCS3-dependent inhibition of IRS-1.[333] Furthermore, NF-κB activation by TNF-α can inhibit PGC-1α and consequently, increase glucose metabolism via down-regulation of PDK4.[334,335]

Inflammation can also result in endothelial and microvascular damage, resulting in myocardial ischaemia and contributing to diastolic and systolic dysfunction in diabetic cardiomyopathy.[267,317,336] Furthermore, inflammation promotes ROS generation and down-regulates SERCA2 (via IL-1β and IL-6), resulting in impaired Ca^{2+} handling and ultimately, diastolic dysfunction.[337] Myocardial inflammation can also depress cardiac contractility as TNF-α, IL-6, IL-1β and IL-2 exert negative inotropic effects on the heart.[338] Interestingly, a study in Zucker diabetic fatty rats treated with a β2-adrenergic receptor agonist decreased pro-inflammatory and pro-fibrotic responses in the heart and kidneys.[339] β-arrestin can bind to the β2-adrenergic receptor and promote internalization, subsequently promoting desensitization. While this may imply a negative role in the setting of diabetic cardiomyopathy, β-arrestins have previously been reported to inhibit NF-κB activity via IκBα. As such, inhibition of NF-κB in the setting of diabetes via β-arrestin and modulation of inflammatory mediators via sympathetic nervous system regulation may offer an alternative therapeutic strategy for diabetic cardiomyopathy. Further studies that investigate the interplay between β-arrestin and NF-κB in the setting of diabetic cardiomyopathy are warranted.

Hyperinsulinaemia, via increased pancreatic production of insulin, follows insulin resistance in order to compensate for impaired cellular insulin actions. An excess of insulin can contribute to cardiomyocyte hypertrophy by acutely stimulating growth via the P13K/Akt-1 pathway.

3.6 Cardiac stiffness

Impairments in insulin signalling due to insulin resistance result in decreased GLUT4 translocation to the membrane and impaired PI3K/Akt signalling which results in decreased Ca^{2+}-ATPase activity, consequently increasing intracellular Ca^{2+} levels contributing to cardiac stiffness and diastolic dysfunction.[153]

PI3K/Akt can activate endothelial NO synthase (eNOS), which results in an increase in NO that subsequently increases coronary vasodilation.[153] However, insulin resistance decreases activation of eNOS and consequently decreases NO levels.[340] Decreased NO results in impaired coronary microcirculation, due to impairments in coronary vascular smooth muscle cell relaxation.[341,342] Therefore, insulin resistance alongside hyperinsulinaemia can contribute to cardiac stiffness and diastolic dysfunction.

3.7 Advanced glycation end products

Diabetes-induced chronic hyperglycaemia significantly increases the formation of AGEs in the heart.[343] Protein glycation occurs after prolonged exposure to high concentrations of glucose, where amino groups of proteins bond non-enzymatically to glucose.[344] A correlation exists between formation of glycosylated tissue proteins in the heart and the period of hyperglycaemia.[345] Compared to non-diabetics pathologies, hearts from diabetic patients also show a higher abundance of AGE formation in the myocardium.[346] A high abundance of AGEs also occurs in small intramyocardial arteries of the hearts of diabetic patients.[347] This suggests that diabetes can exaggerate AGE formation and increase the susceptibility of myocardial vasculature to glycation.[343] Formation of collagen cross-linking is a major determinant in the development of diabetic cardiomyopathy. Of relevance, an association between AGEs formation and decreased cardiac collagen solubility, and increased collagen III gene and protein expression, is seen in diabetes.[348,349] AGE-induced increases in cross-linked collagen may lead to myocardium and arterial wall stiffness and eventually atherosclerotic plaque formation.[350] Moreover, AGEs are also linked with other pathological pathways in diabetic cardiomyopathy, including oxidative stress[351,352] and impaired Na^{+}/K^{+}-ATPase activity.[353] Chronic hyperglycaemia increases both formation of AGE and expression of AGE receptors (RAGE), which in turn induces oxidative stress by activating transcription factor NFk-β.[354] A strong association has been observed between increased RAGE elicited by diabetes and LV contractile dysfunction typical of diabetes cardiomyopathy, which is rescued by RAGE gene knockdown or blocking.[355,356]

3.8 Hexosamine biosynthesis pathway O-GlcNAcylation (O-GlcNAc)

O-GlcNAc is a post-translational modification that is responsible for regulating the activity of proteins.[357] This process is initiated when N-acetylglucosamine (GlcNAc) is attached to a serine or a threonine residue of a peptide via an O-linkage (O-GlcNAc). The substrate for O-GlcNAc is uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc), which is synthesized via the hexosamine biosynthetic pathway (HBP). It has been estimated that 5% of intracellular glucose contributes to the HBP,[358] although this has been debated as to whether it is an accurate estimation for cardiomyocytes.[359,360] Nevertheless, O-GlcNAc levels are closely related to glucose availability.[357] Glucose, after entering the cell is converted to fructose-6-phosphate (F6P) by hexokinase and isomerase. F6P is further processed to UDP-GlcNAc by four enzymatic reactions. UDP-GlcNAc is the substrate for O-GlcNAc transferase (OGT), which is responsible for catalysing O-GlcNAc to targeted proteins. Similar to other post-translational modifications, O-GlcNAc is a highly dynamic and reversible process, with the removal of O-GlcNAc from targeted proteins being accomplished by O-GlcNAcases.[361]

O-GlcNAc has been proposed to occur in the nucleus, cytoplasm, and mitochondria,[357] as opposed to other types of glycosylation which can take place in the extracellular matrix.[362] Chronic activation of the HBP is often associated with diabetic cardiomyopathy,[363] as evidenced by increases in both gene expression and protein levels of Glutamine-fructose-6-phosphate transaminase (GFAT) in the myocardium of diabetic patients.[364,365] Genetic modulation of Protein O-GlcNAcase (OGA) to a truncated, less effective form can exacerbate O-GlcNAc, inducing a higher chance of developing diabetes.[366,367] Vascular dysfunction is a common feature of diabetes, and such dysfunction can be attributed to excess O-GlcNAc of proteins, such as transcription factor Sp1 and eNOS.[368,369] Both protein levels and activity of OGT are elevated in rat aortic smooth muscle cells subjected to hyperglycaemia. Additionally, excessive O-GlcNAc can lead to improper Ca^{2+} handling.[370] One specific target of O-GlcNAc is phospholamban, a protein regulating the function of SERCA2. Impairment of the function of phospholamban prevents the normal Ca^{2+} pumping after excitation from SERCA2, leading to improper contraction of heart muscle. The level of O-GlcNAc on cardiac proteins is carefully regulated by changes in OGT and OGA activity.[371,372] O-GlcNAc may also affect complexes I, III, IV involved in mitochondrial respiration.[371,373] O-GlcNAc may also impact ketone body metabolism by down-regulating β-hydroxybutyrate dehydrogenase mRNA levels as well as succinyl-CoA: 3-oxoacid CoA transferase protein levels.[229] Of interest, ketone oxidation is decreased in the myocardium of diabetic mice.[256]

An increasing body of evidence suggests an increase in O-GlcNAcylation levels in diabetic cardiomyopathy. Cardiac β1-adrenoceptors (β1AR) can be modified by O-GlcNAcylation, and its signalling transduction negatively correlates with its O-GlcNAcylation level in adult rat cardiomyocytes.[374] While circulating levels of N-terminal proteolytic fragment of histone deacetylase 4 (HDAC4) have been shown to be elevated in patients with diabetes, O-GlcNAcylation of HDAC4 is cardioprotective in a mouse model of diabetes.[375] This cardioprotection is associated with a reduction in pathological Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signalling.[375] O-GlcNAcylation also plays a role in regulating autophagy by modifying the synaptosomal-associated protein 29 (SNAP29).[376] Increased O-GlcNAcylation of SNAP29 inhibits autophagic flux and causes further deterioration of cardiac diastolic dysfunction in STZ-induced diabetic rats.[376] Furthermore, O-GlcNAcylation can modulate ionic homeostasis by targeting the activity of a number of ion channels. For example, acute hyperglycaemia can enhance K^+ channel recovery via CaMKIIδ-S[280] O-GlcNAcylation.[377] Hyperglycaemia also increases O-GlcNAcylation of $Nav_{1.5}$, which lead to the abnormal expression and distribution of $Nav_{1.5}$, loss of function of the sodium channel, and prolongation of the PR/QT interval in the hearts of diabetics.[378] In patients with T2D, increased O-GlcNAcylation is linked to the dynamic of glucose-induced impairment of eNOS activation in endothelial cells that could contribute to vascular dysfunction in T2D.[379]

3.9 Cardiac cell death pathways

Three main pathways are involved in cell death, apoptosis, necrosis, and autophagy.[380] A controlled rate of apoptosis and autophagy is necessary for removing unwanted cells.[267] However, in diabetes, cardiac cell death occurs at an accelerated rate.[217,381,382] This is due to both a hyperactivated cellular death pathway and an impaired cellular defense mechanism.[383] Cardiac apoptosis is elevated in diabetes,[267,281,384,385] which is important since an apoptotic rate as low as 0.023% is sufficient to induce lethal cardiomyopathy.[385] There are two main pathways of apoptosis: intrinsic or extrinsic. Intrinsic pathways can be initiated by various kinds of mitochondrial insult.[380,386,387] After formation of a mitochondrial permeability transition pore (mPTP), cytochrome C leaks into the cytoplasm and assemble with Apaf-1, ATP, and procaspase-9, forming apoptosome.[388,389] The final product activates the effector caspase: caspase-3, which will go on to cleave target proteins.[390,391] Additionally, p53 is able to sense damage of DNA strands and up-regulate the transcription of two essential proteins: Bax and Fas.[392] Bax is a pro-apoptotic protein that resides on the mitochondrial membrane,[393] whereas Fas contributes to the extrinsic cellular death pathway. Fas will act on death receptors located on cellular membrane.[394] Soluble extracellular protein, such as TNF-α can also bind to death receptors.[326] Ligand binding initiates the assembly of multiprotein complex termed the death-inducing signalling complex (DISC), which recruits procaspase-8.[395] Such movement results in procaspase-8 activation.[396,397] Caspase-8 cleaves Bid, leading to the formation of the active form, truncated-Bid (T-Bid),[398] that is pro-apoptotic by assisting the leak of cytochrome C into the cytoplasm. There is still debate regarding the relative contribution of apoptosis vs. necrosis to cardiomyocyte cell death in dilated cardiomyopathy.[399] It has been reported that necrotic cardiomyocytes are more dominant compared to apoptotic cells in dilated cardiomyopathy and severe aortic stenosis.[400,401] In line with this, irreversible opening of the mPTP also induces cell necrosis by ATP depletion, although it potentially triggers apoptosis via outer membrane rupture and cytochrome c release into the cytosol. Whether cardiomyocyte cell death by ischaemia-induced mPTP opening has a significant contribution to cardiomyocyte loss and subsequent interstitial fibrosis in diabetic hearts warrants further investigation.

The cellular death pathways described above are altered in diabetic cardiomyopathy (*Figure 3*). Direct exposure of high levels of glucose in myoblast H9c2 cells induces significant apoptotic cell death. The observations of hyperglycaemia increases caspase 3 activation and cytochrome C release in cardiac cells are consistent with previous findings where high levels of glucose elevated the expression of Bax and its translocation from cytosol to mitochondria-enriched heavy membrane fraction in vascular endothelial cells.[402] On the other hand, the use of the caspase-3-specific inhibitor, Ac-DEVD-cmk, can suppress hyperglycaemia-induced apoptosis.[402,403] Additionally, up-regulation of p53 in myocytes, due to hyperglycaemia, occurs at very early stages in the development of

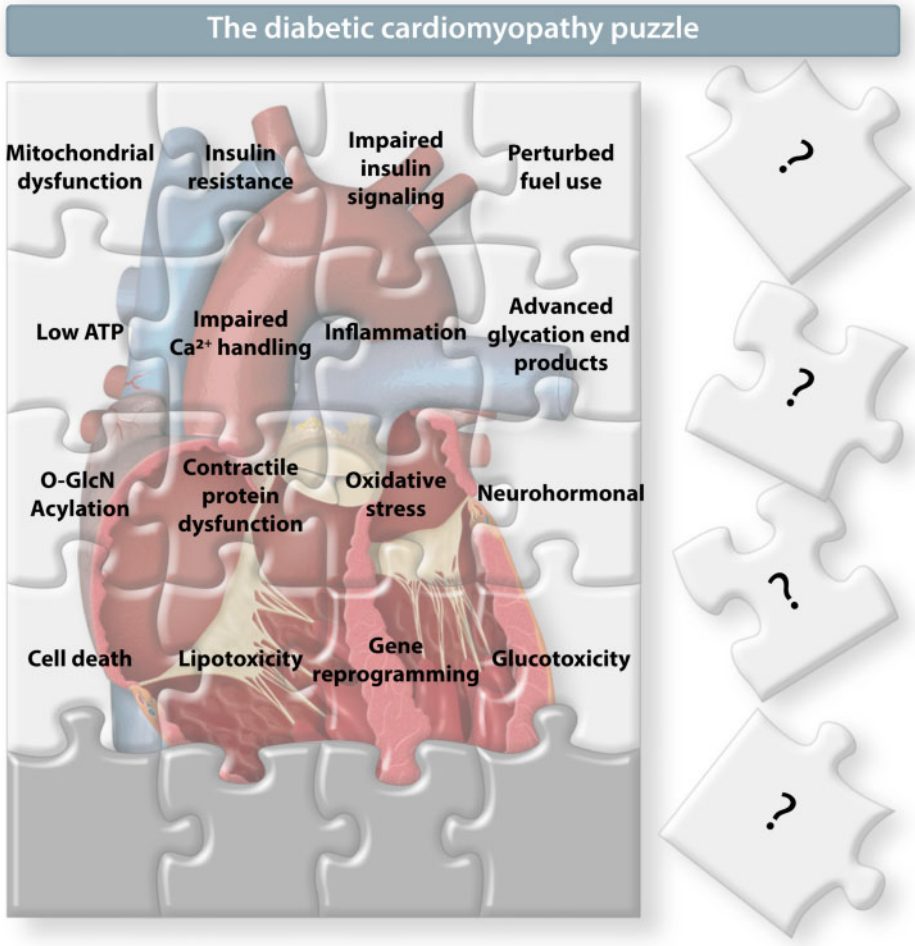

Figure 3 Mechanisms that contribute to diabetes-induced heart failure. While the exact pathophysiology of the diabetic-induced heart failure still not fully defined, there are a number of mechanisms that play important roles in its occurrence. This includes mitochondrial dysfunction, cardiac insulin resistance, and impaired cardiac insulin signalling pathway, perturbed fuel use, low ATP levels, inflammation, advanced glycation end products, O-GlcNAcylation, cell death, neurohormonal mechanism, contractile proteins dysfunction, oxidative stress, gene reprogramming, lipotoxicity, glucose toxicity, and perturbed Ca^{2+} handling.

diabetic cardiomyopathy,[404] whereas attenuation of p53 transcriptional activity by Insulin-like growth factor 1 (IGF-1) prevents myocardial apoptosis in diabetic mice.[405] Besides high glucose, exposure to high levels of palmitate can also increase mitochondrial cytochrome C release, caspase-3 activation, followed by apoptotic cell death.[406] The formation of ROS and reactive nitrogen species (RNS) in the heart is another critical mediator of diabetes-induced myocardial cell death.[407] Both ROS and RNS may be involved in many aspects of the cell death pathway, such as activation of caspase 3, the PKC pathway, release of cytochrome C and death receptor activation.[403,408,409] The antioxidant, metallothionein, can ameliorate this hyperglycaemia-induced myocardial cell death.[38]

Unlike apoptosis, the role of autophagy in diabetic heart is still controversial. With some evidence suggesting that the induction of autophagy may convey protective effects,[410] other studies proposed that excessive autophagy may accelerate the process to heart failure.[411] Autophagy is believed to be impaired in diabetic heart. One major regulator of autophagy is insulin and impaired insulin signalling stimulates myocardial autophagy.[411,412] Given that many different animal models have not shown the blunted myocardial autophagy in diabetes,[413–415] it is surprising that there has not been any approved treatment that targets autophagy specifically. However, some available medicines, such as metformin, rapamycin and resveratrol,[416–418] have been found to promote autophagy indirectly, in addition to their main mechanism of action. Recently, Mst1 (macrophage stimulating 1) was found to be responsible for dictating the cardiomyocyte towards either apoptosis or autophagy in diabetes.[419]

Study suggested that mitochondria-dependent, calcium overload-induced necrosis might contribute to the progression of heart failure.[420] Although necrosis has been suggested to be a passive and unregulated form of cell death, targeting the pathways of necrosis has potential for treating cardio-cerebrovascular injury.[421] Regulated necrosis can be classified into many categories, including but not limited to pyroptosis and ferroptosis. Both forms have been proposed to correlate with diabetic cardiomyopathy development. Pyroptosis is characterized by formation of plasma membrane pores and extracellular release of inflammatory cytokines. High glucose promoted cardiomyocytes pyroptosis by increasing ROS production.[422] Elevated level of pyroptosis also induces cell death via the miR-214-3p/caspase-1/TGF-β1 pathway in diabetic

mice.[423] Among the many protective actions exerted by metformin, inhibition of pyroptosis by suppressing the mTOR pathway via AMPK activation, may decrease pyroptosis-induced cell death in diabetic cardiomyopathy.[424] Therefore, therapies targeting pyroptosis may be an effective approach. On the other hand, ferroptosis is a newly discovered form of cell death, which can be initiated by either iron overload or oxidative stress.[425] Of interest, hydrogen sulfide is an endogenous gaseous signalling molecule that is capable of inhibiting ferroptosis. One recent study proposed that treatment with the ferroptosis inhibitor ferrostatin-1 can prevent hyperglycaemia-induced ferroptosis.[426]

3.10 Alterations in cardiac Ca^{2+} handling

One of the early perturbations in Ca^{2+} homeostasis in diabetic cardiomyopathy that precedes LV dysfunction is a slow decay of the Ca^{2+} transient.[427–430] Possible mechanisms that contribute to the occurrence of these disarrangements in Ca^{2+} handling include perturbations in the activity of SERCA2a,[431,432] as well as malfunctions in Ca^{2+} handling proteins due to post-translational modifications, namely AGEs,[433] O-GlcNacylation[434] and carbonylation.[281,435] Impaired Ca^{2+} handling between the sarcoplasmic reticulum and the mitochondria and alterations in Ca^{2+} influx and efflux to/from the cytosol and extracellular tissue and reduced activity of phospholamban and ryanodine receptors also contribute to the Ca^{2+} mishandling in diabetic cardiomyopathies.[428,436–438] Ca^{2+} reuptake via SERCA2a is impaired in hearts from diabetic rats[439–441] and ob/ob mice.[442,443] Interestingly, overexpression of SERCA2a improves Ca^{2+} handling in animal models of diabetic cardiomyopathy.[47] A recent study also demonstrated that insulin resistance impairs SERCA2a activity and cardiac function via inhibiting protein kinase B/striated muscle preferentially expressed protein kinase signalling.[444] It has also been shown that oxidative stress in the hearts of diabetics could contribution to the development of diabetic cardiomyopathy via impairing SERCA2a activity,[445] and that enhancing SERCA2a activity is associated with improved cardiac function in the hearts of diabetics.[444–446]

Diabetes is also accompanied by alterations in contractile proteins that are associated with the changes in contractile function in the diabetic heart.[113,447,448] The decrease in contractile function in the diabetic heart is also positively liked to the decrease in cardiac ATPase activity.[438,449,450] Along with the disturbances in cardiac ATPase proteins, it has also been shown that there are disturbances in isomyosin distribution and shifts from V_1 to V_3 in the diabetic heart.[451–453] There are also decreases in Ca^{2+} sensitivity along with troponin T-band shift in the diabetic heart.[454,455]

3.11 Neurohormonal mechanisms

The role of the renin–angiotensin–aldosterone system and endothelin-1 system in the pathophysiology of both heart failure and diabetes has long been recognized.[456–458] Diabetes is accompanied by an up-regulation of the renin–angiotensin–aldosterone pathway that causes an increase in afterload, an important contributor to cardiac remodelling in diabetic cardiomyopathy. Consistent with this, a number of animal studies have shown that inhibiting activity of the renin–angiotensin–aldosterone system limits the progression of diabetic cardiomyopathy.[457,459,460] As a result, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor antagonists are recommended to treat heart failure in diabetic and non-diabetic patients.[461] Moreover, diabetes is also associated with alterations in systemic autonomic function and perturbations in cardiac rhythm.[462,463] Despite the detrimental effect of these irregularities in the neurohormonal system, there are no therapeutic approaches presently used to target this system in the setting of diabetic cardiomyopathy.

3.12 Changes in cardiac gene regulation

In diabetic cardiomyopathy, there is differential expression of several genes involved in inflammation, fibrosis, insulin signalling, cell death, and metabolism (*Figure 4*).[464,465] The advancements in microarray technology facilitates extensive gene expression profiling to uncover genetic mechanisms of diabetic cardiomyopathy and its therapeutic implication. Genes that are often dysregulated in diabetic cardiomyopathy are discussed in the respective section and are summarized in *Figure 4*.

Studies both in type 1 and type 2 diabetes have shown abnormal cytosolic Ca^{2+} homeostasis and decreased SERCA2a expression in cardiomyocytes along with diminished contractile function.[466] This is important in the development of diabetic cardiomyopathy, as SERCA2a gene transfer or overexpression can reduce diabetes-related contractile dysfunction, hypertrophy, and can differentially modulate the expression of genes involved in insulin signalling, glucose metabolism and cardiac remodelling.[467] Genes involved in inflammation and immune response are also affected by diabetic cardiomyopathy. For instance, IL6 and STAT3 genes are up-regulated in patients with diabetic cardiomyopathy. On the other hand, down-regulation of SOCS3 (Suppressor of cytokine signalling 3) is observed in diabetic cardiomyopathy patients compared to healthy controls.[468]

Mitofusin 1 and 2 (Mfn1 and Mfn2) are mitochondrial dynamics proteins that controls fusion of the mitochondrial outer membrane.[469] In *db/db* diabetic mice hearts, Mfn2 is down-regulated and contributes to an imbalance in mitochondrial dynamics. On the other hand, Mfn2 overexpression relieves diabetic cardiomyopathy by promoting mitochondrial fusion.[470]

Activation of PPARα expression, a transcription regulator, also occurs in diabetic cardiomyopathy.[45,471] Importantly, over expression of PPARα activates genes involved in cardiac fatty acid utilization, while suppressing genes in glucose metabolic pathways. This suggests that dysregulation of PPARα expression contributes to the metabolic derangements observed in diabetic cardiomyopathy.[45] Increased mitochondrial biogenesis has also been implicated in diabetic cardiomyopathy, and PPARα-dependent activation of PGC-1α may be a key driver of mitochondrial biogenic response in diabetic cardiomyopathy.[471] An increase in PGC-1α gene expression occurs in hearts of *db/db* mice.[39] In addition, the up-regulation of PPARα-dependent PGC-1α is associated with increased expression of proteins of the mitochondrial electron transport chain and oxidative phosphorylation such as nuclear receptors families NRF-1 and NRF-2 and mtDNA transcription and replication (mtTFA).[471]

Recently, changes in the levels of non-coding RNAs have been recognized as important mediators of altered gene expression. The largest portion of the genome consists of non-coding RNAs. Although they are not directly transcribed to protein products, these RNAs regulate the transcription and post-transcriptional processing of many proteins. These regulatory RNAs consist of microRNAs (miRNA), long non-coding RNAs (lncRNA) and circular RNAs (circRNAs).[472] Over 4500 lncRNA genes, and 2000 microRNA genes has been identified in human genome alone.[473] Although the function of the majority of non-coding RNAs are still unknown, mounting evidence suggests that these molecules play a significant role in a number of diseases processes and many of them are dysregulated in diabetic cardiomyopathy.[464,465,474,475] Thus, their differential expression and role in diabetic cardiomyopathy pathogenesis is being actively investigated, partly because they may be potential biomarkers and therapeutic tools to treat diabetic cardiomyopathies.

LncRNAs are non-coding RNAs longer than 200 nucleotides in length. In addition to regulating other RNA functions, lncRNAs play an important

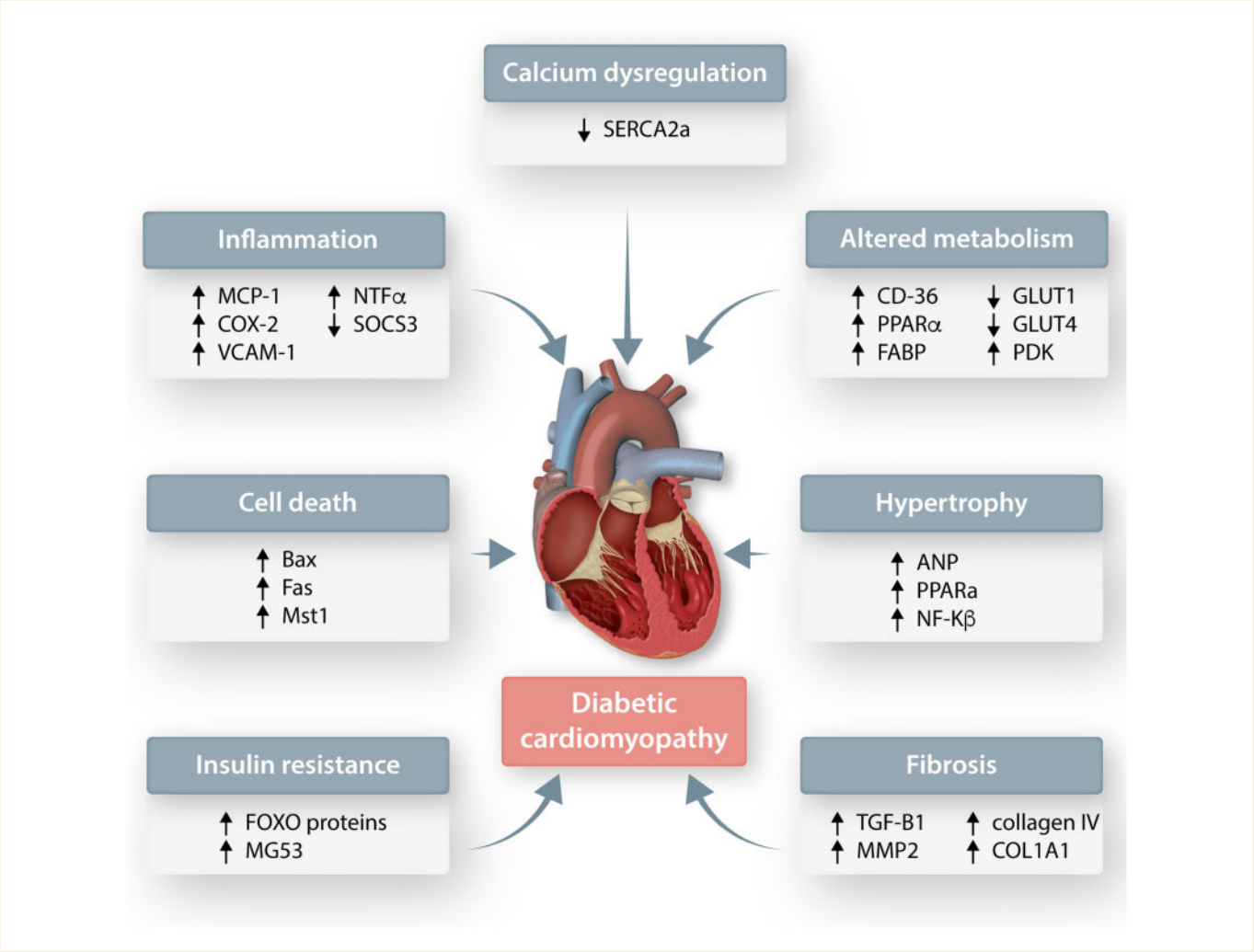

Figure 4 Gene expression dysregulation in diabetic cardiomyopathy. ANP, atrial natriuretic peptide; CD36, cluster of differentiation 36; COL1A1, collagen type 1 alpha1; FABP, fatty-acid-binding proteins; GLUT1, glucose transpoter 1; GLUT4, glucose transporter 4; MCP-1, monocyte chemoattractant protein-1; MG53, mitsugumin 53; MMP2, matrix metalloproteinase-2; Mst1, macrophage stimulating 1; NF-kB, nuclear factor kappa B; PDK, pyruvate dehydrogenase kinase; PPARα, peroxisome proliferator-activated receptor; SERCA2a, sarcoplasmic- endoplasmic reticulum Ca^{2+} ATPase 2a; SOCS3, suppressor of cytokine signalling-3; TGF-β1, transforming growth factor beta 1; TNFα, tumour necrosis factor; VCAM-1, vascular cell adhesion molecule 1.

role in epigenetic regulation by interacting with histone modifiers or chromatin remodellers or DNA.[476] These lncRNAs also forms nucleic acid-protein complexes thereby regulating the activity or localization of these proteins or serves as a precursor for other miRNAs and circRNAs.[477] Differential expression of lncRNAs has been reported in diabetic cardiomyopathy and their abnormal expression has a role in promoting or inhibiting the development of diabetes. In diabetic cardiomyopathy, there are significant alterations of a large number of lncRNAs that control apoptosis,[478–480] fibrosis,[481] and inflammation.[478,482] Detailed data on lncRNA changes and their function are summarized in *Table 1*.

Alterations in many microRNAs (miRNAs) are also linked to changes in gene expression patterns in diabetic cardiomyopathy. MiRNAs are short non-coding RNAs that regulate gene expression by binding to the 3′ untranslated region of target messenger RNAs (mRNAs).[426] Upon binding, miRNAs repress gene expression by destabilizing or degrading the target mRNAs. To date, over 2650 mature miRNAs have been identified in humans that are implicated in various diseases.[427] The role of various miRNAs in mediating diabetic cardiomyopathies have been studied broadly and is summarized in *Table 1*. Of importance, these studies have suggested the contribution of specific miRNAs to hypertrophic,[483–487] fibrotic,[488–490] apoptotic,[491–494] inflammatory, and oxidative stress[490,495–497] changes in diabetic cardiomyopathy.

Circular RNAs (circRNAs) are produced during the processing of pre-mRNA.[473] They are involved in the regulation of pre-mRNA splicing and RNA polymerase II.[498,499] Analysis of the circRNA expression profiles in diabetic cardiomyopathy has shown differential regulation of several circRNAs in tissues from *db/db* mice hearts.[500] Up-regulation of these circRNAs has also been shown in association with myocardial fibrosis[501–503] and pyroptosis.[504]

Epigenetics-mediated dysregulation of gene expression also contributes to the development of diabetic cardiomyopathies. Modification of histone proteins by lysine acetylation is a major epigenetic mechanism that regulates expression of many genes. For instance, increased acetylation of cardiac histone H3 leads to increased mRNA expression of multiple cardiomyopathy-related genes, together with cardiomyocyte hypertrophy, in diabetic mice.[505] Increased acetylation of histone H3 and

Table 1 Alterations in miRNA, LncRNA, CircRNA, and their role in diabetic cardiomyopathy

Pathological pathway	Alteration	Altered non-coding RNAs			References
		lncRNAs	miRNAs	circRNAs	
Apoptosis	Up-regulated	*MALAT1, MIAT*	*miRNA-1, miRNA-208a, miR-195, miR-34a, miR-483-3p*	*circRNA_010567, circHIPK3*	479,491–493,502,503,605,606
	Down-regulated	*HOTAIR, LncRNA H19*	*miR-29*	–	478,480,482,494
Fibrosis	Up-regulated	*Zfas1*	–	–	481
	Down-regulated	*Crnde*	*miR-133a, miR-15a/b, miR-146a*	–	488–490,607
Hypertrophy	Up-regulated	–	*miR-451*	–	487
	Down-regulated	–	*miR-150, miR-373, miRNA133a, miR-30c, miR-181a*	–	483–486
Oxidative stress	Up-regulated	–	*miR-1, miR-144*	–	495,496
Inflammation	Up-regulated	–	*miR-200*	–	497
	Down-regulated	*HOTAIR*	*miR-146a*	–	478,490
Pyroptosis	Up-regulated	–	*miR-30d*	*circ_0076631*	504,608
Angiogenesis	Up-regulated	–	*miR-193-5p*	–	609
Autophagy	Down-regulated	–	*miR30c*	–	610

circRNA, circular-RNA; Crnde, colorectal neoplasia differentially expressed; HOTAIR, HOX antisense intergenic RNA; lncRNA, long non-coding RNA; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; MIAT, myocardial infarction-associated transcript; miRNA, micro-RNA.

H4 in diabetes also leads to the recruitment of inflammatory genes promoters, including TNF-α and COX-2.[506] Augmented histone acetylation at promoter regions of natriuretic peptide genes is also associated with increased expressions of ANP and brain natriuretic peptide in the heart of diabetics.[507] Diabetes-specific alterations in DNA methylation is also associated with altered in the phenotype of the heart in diabetes.[508] This suggests that diabetes-associated epigenetic modification may be an independent risk factor for diabetic cardiomyopathy.

4. The effect of antihyperglycaemic drugs on diabetic cardiomyopathy severity

Although antihyperglycaemic drugs significantly improve glycaemic control in diabetic patients, use of these therapies does not necessarily equate to a reduced risk of developing heart failure.[509,510] This highlights that lowering blood glucose alone is not sufficient to prevent diabetic cardiomyopathy development.[510] However, a number of antihyperglycaemic drugs can alter the course of cardiovascular complications in the diabetic (*Table 2*). The impacts of these therapies on glucose and fatty acid oxidation are also summarized in *Figure 5*.

4.1 Metformin

Metformin is a first-line therapy in the majority of type 2 diabetic patients. In addition to its primary role in lowering blood glucose, beneficial effects of metformin have been shown on stimulating insulin action, decreasing inflammation,[511] and improving myocardial energy metabolism.[512,513] However, its effect on heart failure development remains uncertain. Some studies indicated that metformin is contraindicated in diabetic patients with heart failure due to lactic acidosis.[514] A recent systematic review of nine RCTs studies that examined metformin on heart failure-related outcomes in patients with or without diabetes suggest some beneficial effects of metformin, but the overall evidence were not strong enough to make a solid conclusion about metformin decreasing heart failure severity.[515] Other studies have suggested that metformin therapy does not decrease the risk of heart failure development.[516,517]

4.2 Sulfonylureas

Sulfonylureas, especially older generation ones, increase the risk of adverse events in type 2 diabetic patients and are associated with a greater prevalence of hypoglycaemia.[518,519] A meta-analysis of 115 selected trials showed that sulfonylureas are associated with increased mortality, although major adverse cardiovascular events (MACE) did not appear to be affected.[520] Another meta-analysis investigating the association of metformin and sulfonylureas on both all-cause and cardiovascular mortality in type 2 diabetic patients, showed that combination therapy resulted in an increase in relative risk for cardiovascular hospitalization, as well as fatal and non-fatal events.[521] Similarly, a retrospective cohort analysis investigating the addition of insulin or a sulfonylurea in diabetic patients suggests that sulfonylureas increase the risk of non-fatal cardiovascular outcomes and all-cause mortality.[522] This was also seen in a metformin and sulfonylurea combination therapy study of type 2 diabetic patients, in which patients newly treated with sulfonylureas possessed a higher risk for adverse cardiovascular events.[523] Recently, a meta-regression analysis of 18 studies on the risk of cardiovascular events associated with sulfonylureas found that there was an increased risk of cardiovascular mortality and events with sulfonylurea treatment.[524] In a network meta-analysis, 167 327 patients were studied to evaluate the risk of cardiovascular events with different sulfonylureas. Gliclazide and glimepiride were shown to have a lower risk of both cardiovascular-related mortality and all-cause mortality vs. glibenclamide.[525] Therefore, differences in the risk of mortality exist within the class of sulfonylureas. This is further reinforced by a cohort study of patients with type 2 diabetes on monotherapy with sulfonylureas, where glyburide and glimepiride did not

Table 2 The effects of different classes of antidiabetes drugs on the cardiovascular system and the development of diabetic cardiomyopathy

Class of the therapy	Main effect	References
Metformin	Beneficial	515,611,612
	Neutral	613,516
	Detrimental	614
Sulfonylureas	Beneficial	525
	Neutral	–
	Detrimental	518,520–524,526
Thiazolidinediones	Beneficial	528
	Neutral	–
	Detrimental	528–530
Dipeptidyl-peptidase 4 (DPP4) inhibitors	Beneficial	560,561,563,615,566
	Neutral	555,557,559,567
	Detrimental	554,564,565
Glucagon-like peptide 1 (GLP-1) receptor agonists	Beneficial	539,542,616,617,618
	Neutral	540,541,543
	Detrimental	544
Sodium-glucose transport protein 2 (SGLT2) inhibitors	Beneficial	571,573–578
	Neutral	
	Detrimental	
Insulin	Beneficial	–
	Neutral	582,583
	Detrimental	–

increase the risk of adverse cardiovascular events vs. glicazide, glipizide, and tolbutamide.[526]

4.3 Thiazolidinediones

Thiazolidinediones (TZDs) are known to cause fluid retention and as such, can increase the risk of congestive heart failure.[527] In the Pioglitazone Clinical Trial In Macrovascular Events (PROACTIVE) study, patients with type 2 diabetes and a history of macrovascular disease were randomized to receive pioglitazone or placebo.[528] Pioglitazone increased heart failure hospitalization, although this was associated with less cardiac ischaemic events.[528] The Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) study, consisting of patients with impaired fasting glucose/glucose tolerance and no known cardiovascular disease, found that while rosiglitazone reduced diabetes and the development of renal disease, it increased new-onset heart failure.[529] In the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes (RECORD) trial, a multi-centre open-label study with type 2 diabetic patients, rosiglitazone increased the risk of heart failure or hospitalization by over two-fold.[530] As such, rosiglitazone increases the risk of heart failure and alongside other TZDs, contain serious warnings regarding the increase in fluid retention and risk of congestive heart failure.[527]

4.4 Glitazars

A dual PPARα and γ agonist designed to concurrently treat hyperlipidaemia and hyperglycaemia, glitazars combine the beneficial effects of agonizing both peroxisome proliferator-activated receptors. However, glitazars present a paradox and while addressing diabetic concerns with hyperlipidaemia and hyperlycaemia, they have been shown to worsen congestive heart failure in diabetic patients.[531,532] Specifically, muraglitazar increases MACE, congestive heart failure and death in a review of several clinical trials that included 3725 patients.[533] Another glitazar, aleglitazar, while presenting effective antidiabetic effects, also increases the risk of heart failure.[534] As such, concurrent agonism of PPARα and γ results in cardiac dysfunction, which may be due to inhibition of PGC1α and mitochondrial biogenesis.[178]

4.5 GLP-1 receptor agonists

Glucagon-like peptide-1 (GLP-1) agonists improve glycaemic control in diabetics by mimicking GLP-1 action.[535–537] These include Exenatide, a partial structural analogue of GLP-1, with other GLP-1 analogues including liraglutide, lixisenatide,[538] and semaglutide.[539] Some of these GLP-1 analogues have efficacy in mediating heart failure risk in diabetics, as shown by results of multiple phase III/IV large scale double-blind randomized clinical trials. The Exenatide Study of Cardiovascular Event Lowering (EXSCEL) Trial showed that exenatide in type 2 patients with cardiovascular risk did not increase their overall risk and that the incidence of MACE was not worsened.[540] The Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes after Acute Coronary Syndrome during Treatment with Lixisenatide (EXLXA) Trial showed similar results, where lixisenatide treatment showed no effect on MACE in type 2 diabetic patients who had a recent acute coronary event.[541] In contrast, the Liraglutide Effect and Action in Diabetes (LEADER) trial showed a lower risk of MACE, including the rate of the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in type 2 diabetic patients with high cardiovascular risk.[542] Additionally, the Trial to Evaluate Cardiovascular and Other Long-Term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) showed a significantly lower rate of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in type 2 diabetic patients with high cardiovascular risk.[542] However, the results of the Functional Impact of GLP-1 for Heart Failure Treatment (FIGHT) Trial showed no improved post-hospitalization clinical stability with liraglutide in recently hospitalized patients with established heart failure and reduced ejection fraction.[543] Examination of the effect of liraglutide on ventricular function in stable chronic heart failure patients with and without diabetes also showed that liraglutide did not improve LV ejection fraction or systolic function, and was associated with an increase in heart rate and more serious cardiac adverse events.[544] Combined, this calls into question the benefits of liraglutide use in preventing diabetic cardiomyopathies.

4.6 DPP4 inhibitors

Incretins-based therapy has emerged as a novel treatment approach for diabetes management, with the inhibition of dipeptidyl peptidase 4 (DPP4) being used to prevent the cleavage and inactivation of GLP-1.[545] DPP4 inhibitors increase insulin secretion from pancreatic B-cells, thereby improving insulin tolerance and glucose control.[546–548] Current DPP4 inhibitors include vildagliptin, sitagliptin, and saxagliptin and are similar in their efficacy in lowering HBA1C levels[549] and improving glucose tolerance in diabetes.[550–553] Despite the efficacy of DPP4 inhibitors in improving glycaemic control, the efficacy of DPP4 inhibitors in improving heart failure outcomes in diabetics remains unclear. The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR)-Thrombosis in Myocardial Infarction (TIMI) 53 trial (SAVOR-TIMI53) showed a significant increase in the rate of

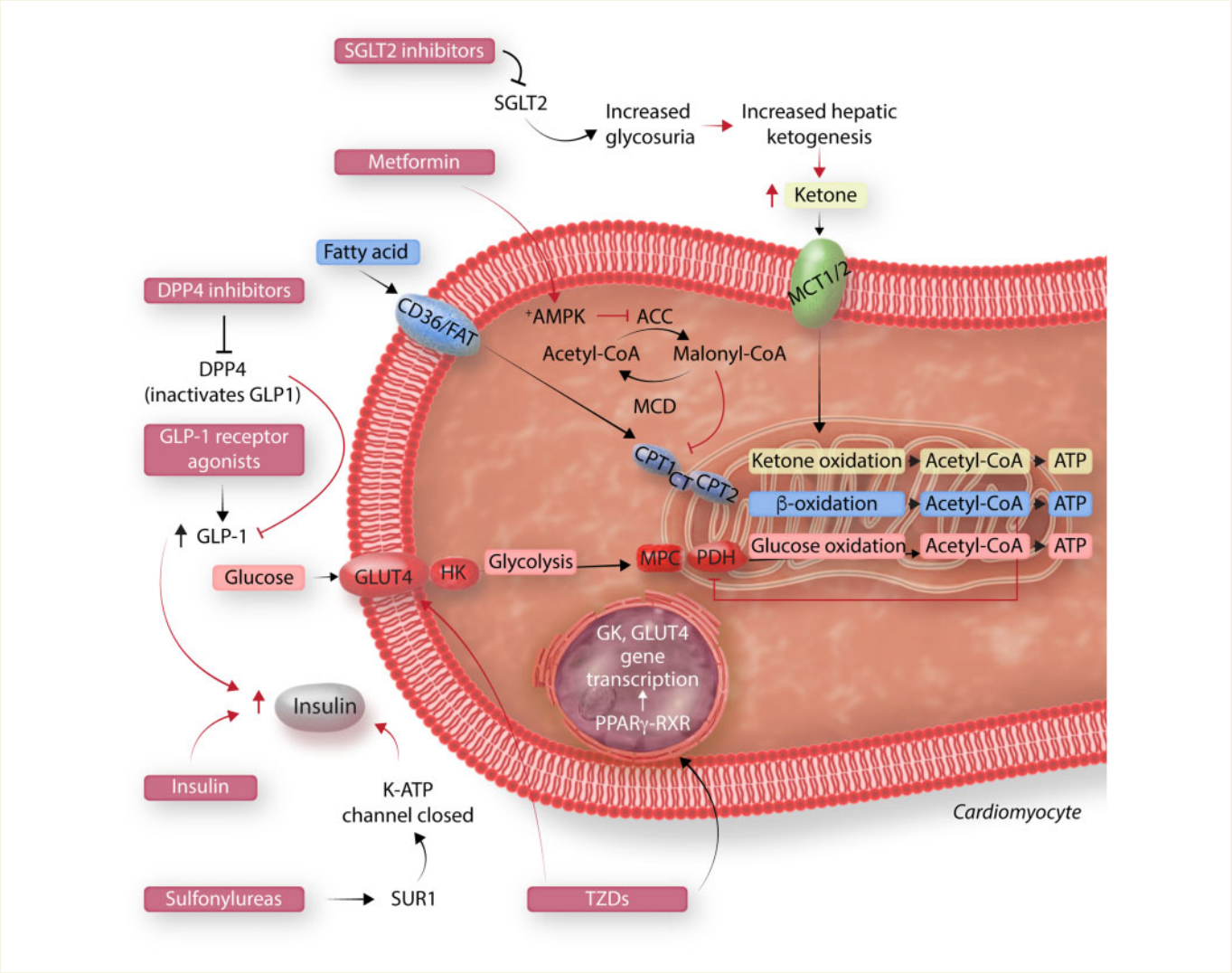

Figure 5 Summary figure of various antihyperglycaemic drugs and their mode of action in the context of the heart. Fatty acid, glucose, and ketone body metabolism are represented in this figure with the key modes of homeostasis regulation presented. SGLT2 inhibitors inhibit SGLT2 in the proximal tubules and thus, prevent renal glucose reabsorption, promote glycosuria, decreased insulin release, increased hepatic ketogenesis, and increased circulating blood ketone levels. These increased circulating ketones can subsequently modulate cardiac ketone oxidation rates. Metformin's mode of action is not well understood, although it does stimulate AMPK which inhibits ACC, decreases malonyl-CoA levels and increases fatty acid metabolism. DPP4 inhibitors prevent DPP4 from inactivating GLP-1, and thus increase GLP-1 levels to potentiate insulin secretion from pancreatic beta cells. GLP-1 receptor agonists similarly increase GLP-1 levels to increase insulin secretion. Sulfonylureas bind to SUR1, and consequently the K-ATP channel closes, depolarizing the pancreatic islet cell and increasing intracellular calcium levels to promote secretion of insulin. Lastly, TZDs have widespread actions in the body but here we focus on its role in promoting glucose metabolism and improving insulin sensitivity via binding to PPARγ and promoting the transcription of genes involved in glucose uptake and metabolism.

hospitalization for heart failure in type 2 diabetic patients treated with saxagliptin.[554] However, the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial showed non-inferiority of alogliptin to placebo on major cardiovascular events in diabetic patients with recent acute coronary syndrome.[555,556] Moreover, the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) showed that sitagliptin neither improved or decreased rates of cardiovascular events such as death, myocardial infarction, stroke, or hospitalization for heart failure in type 2 diabetics with pre-existing cardiovascular disease.[557,558] Other studies support the results of EXAMINE and TECOS trials.[559–562] although results from meta-analyses demonstrate conflicting evidence for the effect of DPP4 inhibitors on mediating cardiovascular disease.[563–565] Animals studies have also shown conflicting results on the efficacy of DPP4 inhibitors on cardiovascular disease. Sitagliptin treatment decreased LV passive stiffness and improved global LV performance in an obese type 2 diabetic mice.[566] However, long-term treatment of vildagliptin showed no cardioprotective effects on cardiac function, remodelling, or infarct size in Sprague-Dawley rats subjected to myocardial infarction induced by coronary ligation.[567] Combined, these studies suggest minimal beneficial effects of DPP4 inhibitors in reducing the risk of heart failure in diabetics, and support that certain DPP4 inhibitors may be safe in patients. However, the

cardiovascular safety and efficacy of DPP4 inhibitors needs to be further elucidated.

4.7 SGLT2 inhibitors

Sodium glucose co-transporter 2 inhibitors (SGLT2i) prevent glucose reabsorption in the proximal tubules of the kidney, therefore increasing its secretion into the urine and improving glycaemic control.[568–570] Three SGLT2i approved for clinical use include empagliflozin, dapagliflozin, and canagliflozin. Recently, large-scale clinical trials have shown cardioprotective benefits independent of its antihyperglycaemic effect in both type 2 diabetic and non-diabetic patients.[571–576] The results of the Empaglifozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOMES) showed a lower occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke, and a reduction in overall mortality and heart failure hospitalization in empagliflozin treated type 2 diabetics patients with cardiovascular risk compared to placebo.[571] The Canagliflozin Cardiovascular Assessment Study (CANVAS) and Dapagliflozin effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58 (DECLARE-TIMI58) trials supported the results of the EMPA-REG OUTCOMES study. The CANVAS trial showed a lower risk of cardiovascular events in type 2 diabetic patients with an elevated risk of cardiovascular disease,[576] while the DECLARE-TIMI58 trial showed a reduction in cardiovascular death and heart failure hospitalization in type 2 diabetic patients with or at high risk of cardiovascular disease, although it did not reduce the rate of MACE.[575] Interestingly, the Dapagliflozin and Prevention of Adverse-Outcome in Heart Failure (DAPA-HF) trial showed a reduction in the risk of mortality and heart failure reduction in patients with heart failure and reduced ejection fraction with or without type 2 diabetes.[573] These results are supported by the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) trial.[574] Combined, evidence from clinical trials show a safety and efficacy of SGLT2i as a therapeutic strategy to manage diabetes and associated cardiovascular disease, heart failure, and their risk.

Studies in animal models have also demonstrated cardiovascular benefits supporting the results from the major clinical trials. Empagliflozin improves cardiac contractility, by fractional area change, and improves microvascular function in *ob*/*ob*$^{-/-}$ mice.[577] Additionally, empagliflozin treatment attenuates cardiac fibrosis and improves haemodynamics in hypertensive rat heart failure.[578] However, despite these beneficial cardiac outcomes, the exact mechanism of the cardioprotective effects of SGLT2i are unknown.[228] Multiple mechanisms have been proposed including diuresis/natriuresis, improved cardiac energy metabolism,[256] reduction of inflammation,[579] and prevention of ischaemia reperfusion injury[580] to name a few key mechanisms. Further studies are needed to fully elucidate a mechanism to explain the observed cardioprotective effects of SGLT2i in the diabetic and non-diabetic failing heart.

4.8 Insulin

While insulin is the first-line therapy to treat T1D, it is only used to manage T2D patients when oral hypoglycaemic drugs and lifestyle do not establish glycaemic control. It has been suggested that heart failure prevalence and cardiovascular mortality is increased in patient with T2D who receive insulin.[581] Evaluation of the impact of insulin therapy on cardiovascular disease in diabetic patients has been the focus of a number of recent clinical trials. For example, the ORIGIN trial (Outcome Reduction With Initial Glargine Intervention) investigated glargine's impact compared to standard care in T2D patients with high cardiovascular risk. The trial data were neutral, and the rates of incident cardiovascular outcomes were similar in the insulin-glargine and standard-care.[582] In addition, the DEVOTE trial (A Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects With Type 2 Diabetes at High Risk of Cardiovascular Events) compared the cardiovascular safety of degludec, ultralong acting insulin, to insulin glargine in patients with T2D and high cardiovascular risk. The study showed that degludec was non-inferior to glargine concerning the incidence of major cardiovascular events.[583] While enhancing circulating insulin levels can restore cardiac insulin sensitivity in the failing heart, enhancing cardiac efficiency and reducing cardiovascular mortality, prospective studies that aim to access this possibility directly are currently lacking.

5. The effect of heart failure drugs on glycaemic control

5.1 Renin–aldosterone–angiotensin inhibitors

ACE inhibitors have been shown to improve insulin resistance and glucose intolerance via increases in GLUT4 translocation (*Table 3*).[584] Diabetic mice treated with the ACE inhibitor temocapril show decreases in plasma glucose and insulin levels, increases in skeletal muscle glucose uptake and increases in translocation of GLUT4 to the plasma membrane.[584] In a single blind, cross-over design study in type 2 diabetic patients that had arterial hypertension, the ACE inhibitor captopril increased insulin sensitivity and improved glycaemic control.[585] Captopril treatment of diabetic patients also improves glucose control.[586] However, while ACE inhibitor therapy improves glycaemic control effects, a case-control study in diabetic patients found that ACE inhibitors are associated with an increase in hospitalization for severe hypoglycaemia.[587]

5.2 Lipid-lowering agents

Statins have a propensity to induce hyperglycaemia and have been shown to cause glucose intolerance in both animals and humans. For instance, diabetic rats treated with atorvastatin or simvastatin exhibit hyperglycaemia and glucose intolerance.[588] In a meta-analysis of nine trials of patients treated with statins, mean HbA_{1C} was higher by 0.12%, indicative of a modestly increased risk for diabetes with statin treatment.[589] In another meta-analysis that investigated the effect of statin therapy on HbA_{1C} levels as well as fasting plasma glucose, statins increased HbA_{1C}.[590] Specifically, pitavastatin improved glycaemic control while atorvastatin worsened glycaemic control.[590] This diabetogenic effect was also recapitulated in a national health screening cohort of non-diabetic individuals taking statins, showing that greater adherence to the use of statins, specifically atorvastatin, rosuvastatin, pitavastatin, and simvastatin, results in increases in fasting glucose levels.[591]

5.3 ß-blockers

β-adrenergic stimulation promotes insulin and glucagon release while α-adrenergic stimulation inhibits insulin and glucagon secretion. Therefore, β-adrenergic receptor antagonism inhibits insulin release and may worsen glycaemic control especially during hypoglycaemia. The selectivity of the ß-blocker yields distinct metabolic effects and certain ß-blockers can exacerbate hypoglycaemic episodes by delaying glucose recover time.[592,593] A retrospective study that monitored glucose in patients

Table 3 The effects of different classes of heart failure therapies on glycaemic control and diabetic cardiomyopathy

Class of the therapy	Main effect on glycaemic control	References
Renin–angiotensin system inhibitors	Beneficial	584–586
	Detrimental	587
Lipid-lowering agents	Beneficial	590
	Detrimental	589,590,619
ß-receptor blockers	Beneficial	596
	Detrimental	594–596
Aldosterone antagonists	Beneficial	620
	Detrimental	621

receiving either carvedilol or a selective second-generation ß-blocker (metoprolol or atenolol) found that ß-blockers, specifically metoprolol or atenolol, increase the odds of hypoglycaemia in these hospitalized patients.[594] In hypertensive diabetic patients, treatment with propranolol or metoprolol results in mean blood sugar increases of 1.0–1.5 mM.[592,595] A randomized, double-blind parallel-group trial in patients with diabetes and hypertension showed that metoprolol increases mean $HbA_{1C,}$ but insulin sensitivity is improved with carvedilol treatment.[596] Third generation non-selective β-blockers (carvedilol) possess insulin-sensitizing properties and improve glycaemic control, while second generation β_1-selective (metoprolol) antagonism worsens glycaemic control.[597] To underline the distinct benefits between β-blockers, non-vasodilating β-blockers (metoprolol, propranolol and atenolol) have been shown to worsen glycaemic control while vasodilating β-blockers (carvedilol, labetalol, nebivolol) improve glucose profiles.

5.4 Aldosterone antagonists

Enhanced activity of the aldosterone signalling has been implicated in the development of diabetes-induced heart failure via triggering fibrosis and insulin resistance. Treatment of dilated cardiomyopathy patients with the aldosterone antagonist spironolactone resulted in a reduced collagen accumulation in the heart and improved LV function.[598] Likewise, antagonizing aldosterone can improve diastolic function and limit fibrosis in patients with hypertensive cardiomyopathy[599] and metabolic syndrome.[600] Of interest is that eplerenone is shown to limit biomarkers of inflammation and insulin resistance in patients with HIV.[601] Aldosterone antagonists have also shown promising effects by reducing apoptosis and improving diastolic function in murine models of diabetic cardiomyopathy.[602–604] The impact of aldosterone antagonism on diastolic function, cardiac insulin resistance and inflammation in patient with diabetes-induced heart failure is yet to be determine.

6. Concluding remarks

The pathophysiology of diabetes can affect the heart through multiple mechanisms that cause structural, metabolic, and functional remodelling, leading to a well-acknowledged condition called diabetic cardiomyopathy. Diabetes-induced perturbations in insulin resistance, fuel preference, ROS generation, inflammation, cell death pathways, neurohormonal mechanisms, advanced glycated end-products accumulation, lipotoxicity, glucotoxicity, and post-translational modifications contribute to the development of diabetic cardiomyopathies. Targeting these pathways is a potential therapeutic approach to lessening the likelihood of developing diabetic cardiomyopathies. A number of antidiabetic therapies can also prevent diabetic cardiomyopathy and reverse cardiac dysfunction. These advancements will help achieve personalized treatment for diabetic patients by achieving glycaemic control and managing comorbidities and limiting cardiovascular disease. Better clarity of the mechanisms involved in diabetic cardiomyopathy should lead to better therapeutics approaches to treat patients with diabetes and heart failure.

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Data availability

Data are available upon request to the corresponding author (Dr. Gary D. Lopaschuk).

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