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REVIEW

Diabetic cardiomyopathy: the need for adjusting experimental models to meet clinical reality

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Abstract

Diabetic cardiomyopathy (CM), occurring in the absence of hypertension, coronary artery disease, and valvular or congenital heart disease, is now recognized as a distinct, multifactorial disease leading to ventricular hypertrophy and abnormal myocardial contractility that correlates with an array of complex molecular and cellular changes. Animal models provide the unique opportunity to investigate mechanistic aspects of diabetic CM, but important caveats exist when extrapolating findings obtained from preclinical models of diabetes to humans. Indeed, animal models do not recapitulate the complexity of environmental factors, most notably the duration of the exposure to insulin resistance that may play a crucial role in the development of diabetic CM. Moreover, most preclinical studies are performed in animals with uncontrolled or poorly controlled diabetes, whereas patients tend to undergo therapeutic intervention. Finally, whilst type 2 diabetes mellitus prevalence trajectory mainly increases at 40- < 75 years (with a currently alarming increase at younger ages, however), it is a legitimate concern how closely rodent models employing young animals recapitulate the disease developing in old people. The aim of this review is to identify the current limitations of rodent models and to discuss how future mechanistic and preclinical studies should integrate key confounding factors to better mimic the diabetic CM phenotype.

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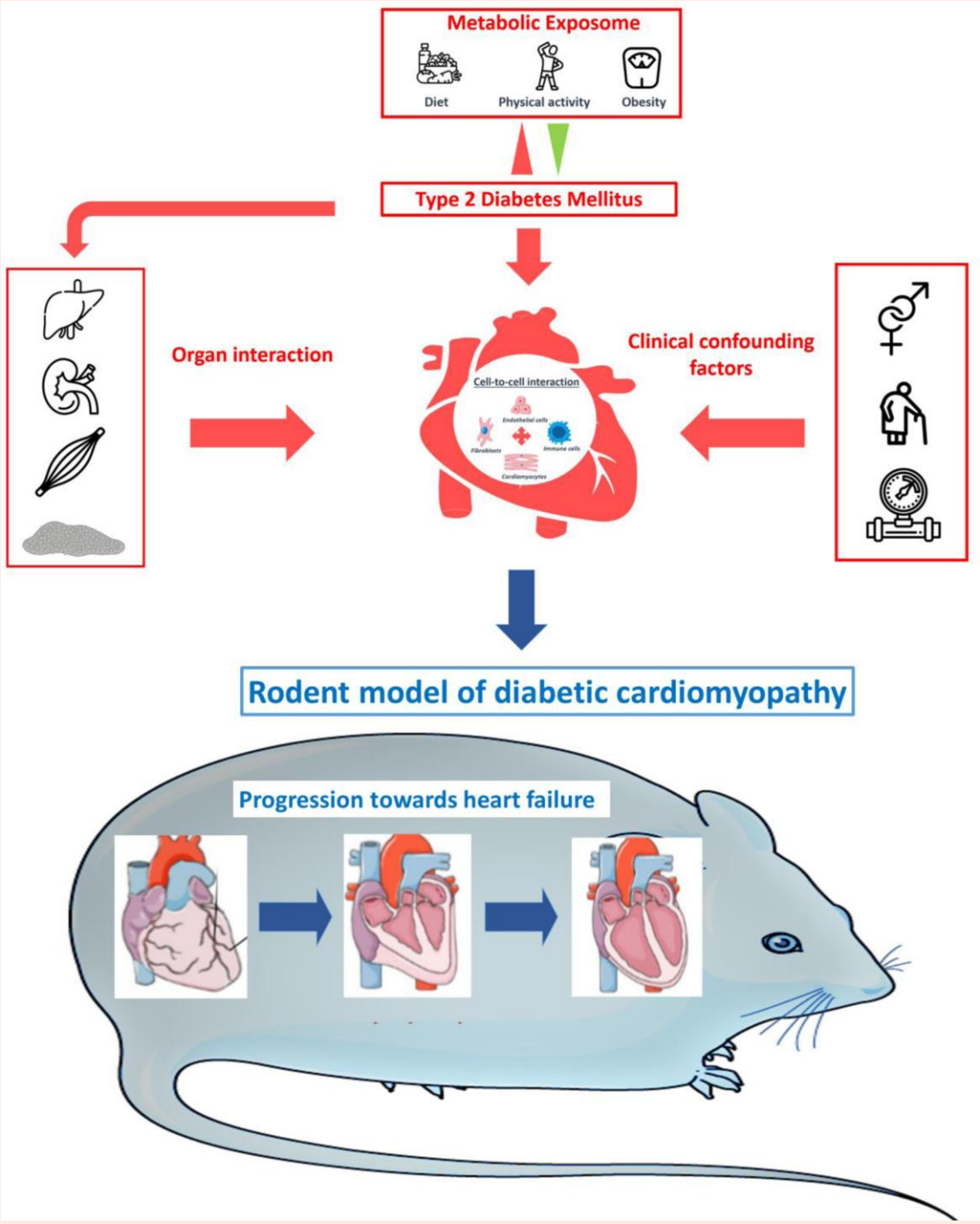
Graphical Abstract



Keywords Diabetic cardiomyopathy • Type 2 diabetes mellitus • Insulin resistance • Organ-to-organ interaction • Heart Failure

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, afflicting all ages, sexes, and socioeconomic classes, ultimately leading to frailty and unhealthy ageing.[1] Cardiovascular (CV) complications are the leading causes of morbidity and mortality in T2DM patients, accounting for about two-thirds of overall deaths as evidenced by the Framingham Heart Study.[2] One of the specific CV complications in T2DM is diabetic cardiomyopathy (CM), originally described as an early diastolic dysfunction progressing to systolic dysfunction and heart failure (HF) in the absence of hypertension, coronary artery disease, and valvular or congenital heart disease.[3] The CARDIA study provided strong evidence for the diagnosis of

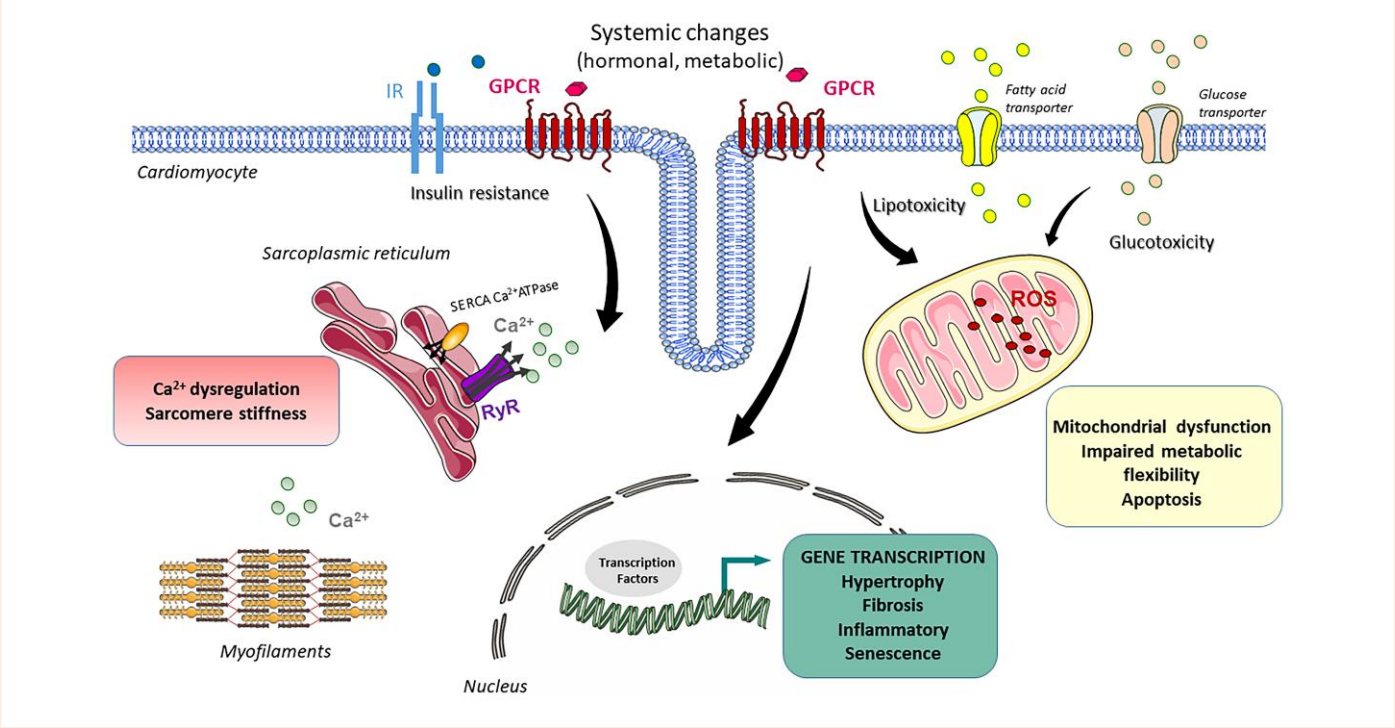


Figure 1 Mechanisms contributing to cardiomyocyte dysfunction in diabetic cardiomyopathy. Hormonal and metabolic alterations may result in hyperglycaemia, insulin resistance, and lipid overload which cause through specific signalling pathways subcellular component abnormalities. This includes mitochondrial dysfunction, impaired metabolic flexibility, Ca2 + dysregulation, and activation of gene transcription programme involved in cardiac remodelling and senescence. These molecular and cellular events contribute to diastolic and systolic dysfunction. GPCR, G protein-coupled receptor; IR, insulin receptor; ROS, reactive oxygen species; RyR, ryanodine receptor.

diabetic CM,[4] identifying subtle diastolic and/or systolic myocardial abnormalities preceding the onset of overt CM and HF.[5–7]

Diabetic CM is now recognized as a distinct, multifactorial disease leading to ventricular hypertrophy and abnormal myocardial contractility that correlates with an array of complex molecular and cellular changes (*Figure 1*).[8]

With no pathognomonic feature identified as specific to human diabetic CM, however, asserting the 'uniqueness' of diabetic CM will require a thorough consideration for the «metabolic exposome», including diet, lifestyle, glycaemia, obesity, sedentary behaviour, alongside unmodifiable confounders, such as genetic susceptibility, sex, and ageing, which are intertwined in the pathogenesis of diabetic CM.[9]

The complex impact of these factors are then magnified by other processes linking the heart to the functional state of key metabolic organs, i.e. the adipose tissue, liver, kidney, and the gut (microbiota) that may separately exert noxious cardiac effects through a crosstalk mediated by e.g. proinflammatory cytokines, profibrotic factors, microvesicles, miRNAs, and immune cells. This endocrine organ-crosstalk evolves into a paracrine cellular-crosstalk between cardiomyocytes, fibroblasts, endothelial cells, and immune cells in the myocardium (*Figure 2*).

Whilst animal models provide the unique opportunity to investigate mechanistic aspects of diabetic complications, including diabetic CM, important caveats exist when extrapolating findings obtained from preclinical models of diabetes to humans because animal models do not recapitulate the full complexity of diabetic CM. Common features, such as insulin, glucose levels, and dyslipidaemia occurring in diabetic CM, are generally well reproduced in most rodent models of diabetes (*Table 1*), but there are many open questions with clinical significance. For example, there is a clear lack of molecular data in human diabetic CM, to which we could compare findings obtained in rodent models. This is a great obstacle, as therapeutic

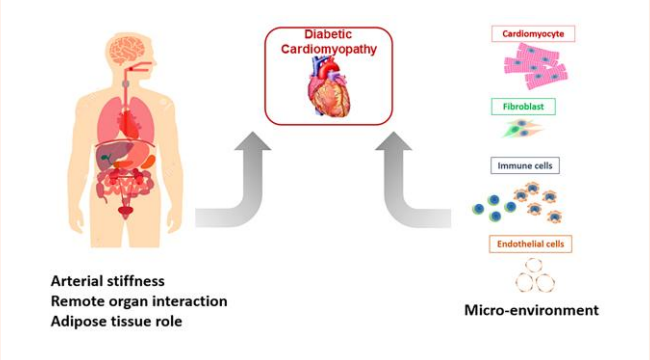


Figure 2 Diabetic heart is at the cross-road of environmental factors, organ-crosstalk, and paracrine cellular-crosstalk between cardiomyocytes, fibroblasts, endothelial cells, and immune cells in the myocardium.

responsiveness of mice and humans with diabetic CM diverge. Specifically, strict glycaemic control protects rodents from HF,[63,64] but not humans,[65] some antidiabetic agents even increase the risk for HF.[66–69] Moreover, we do not have any models to predict which diabetic patient will develop diabetic CM, what the causal factors to promote either HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF) from diabetic CM are, and to understand why strict glycaemic control does not ameliorate diabetic CM, etc. Failure to answer these burning questions suggest the possibility that there are important pathogenic stimuli in human

Table 1 Rodent models that recapitulate diabetic cardiomyopathy features found in humans

		Animal model	Cardiac/noncardiac alterations that recapitulate human features of diabetic cardiomyopathy	References
Mice	HFD	*C57BL6 mice*	Early onset of metabolic alterations and cardiac LV dysfunction (5 weeks after starting HFD), obesity, hyperglycaemia, hyperinsulinemia, dyslipidaemia. Fatty liver, combined visceral/subcutaneous adiposity with increased rate of crown-like structures, mild diabetic nephropathy.	10–14
		C57BL6/J mice + HFD + angiotensin II infusion.	Model of HFpEF (LV hypertrophy and LV diastolic dysfunction; no change in LVEF).	12
		ob/ob mice	LV diastolic dysfunction and features of lipotoxicity. Reduced circulating leptin, excessive food intake, increased insulin, hyperglycaemia, hyperinsulinemia, and triglyceride levels. Compromised immune system, reproductive ability, altered incidence of malignancies (↑ or ↓).	15–17
		C57BL/6N mice + HFD + po. L-NAME administration	Model of HFpEF (hypertrophic response, diastolic dysfunction, pulmonary congestion, reduction in contraction velocity and impaired relaxation). Reduced skeletal muscle strength.	18
	Models of lipotoxicity	*Alteration in myosin heavy chain acyl-CoA synthetase (MHC-ACS mice)*	Lipotoxicity, myocardial macrophage infiltration, inflammation, abnormal cardiac metabolism, cardiac hypertrophy, LV dysfunction and premature death.	19,20
		GPI-anchored human lipoprotein lipase transgenic mice (hLpLGPI mice)	Lipotoxicity, cardiac hypertrophy, abnormal cardiac metabolism, LV dysfunction, and cardiac fibrosis.	21
		Myosin heavy chain-peroxisome proliferator-activated receptor α mice (MHC-PPARα mice)	Lipotoxicity, cardiac hypertrophy, abnormal cardiac metabolism, LV dysfunction, and cardiac fibrosis.	22
		Myosin heavy chain fatty acid transport protein mice (MHC-FATP mice)	Lipotoxicity, LV diastolic dysfunction and prolonged QTc intervals.	23,24
		Adipose TG lipase knockout mice	Lipotoxicity. LV dysfunction and premature death. Reduced triglyceride hydrolase activity in skeletal muscle and adipose tissue. Reduced glycogen content in liver.	25
	T1DM	*Streptozotocin Intraperitoneal route*	Reduction in heart rate, amplitude of contraction and of ventricular pressure, and prolongation on the rate of ventricular myocyte contraction and relaxation. Kidney enlargement. Reduced body weight and circulating insulin levels.	26–31
		Intravenous route		32
	T2DM	*db/db mice*	Decreased systolic function, abnormal diastolic filling, and electrophysiological alterations. Leptin receptor deficiency due to a point mutation. Hyperphagia, dyslipidaemia, progressive diabetic nephropathy.	33–35
Rat	HFD	*Sprague-Dawley rats*	Lipotoxicity, cardiac fibrosis and hypertrophy. Increased plasma triglyceride, cholesterol and LDL, reduced HDL levels. Increased circulating markers of oxidative stress and inflammation.	36,37
	Obesity	*Obese Zucker rats (fa/fa)*	Lipotoxicity and increased LV end-diastolic volume and stroke volume. Reduced cardiac levels of taurine, glutamate, glutamine, and glutathione; increased cardiac lactate levels. Primarily subcutaneous obesity.	38,39
		DahlS.Z-Lepr(fa)/Lepr(fa) (DS/obese) rats	LV diastolic dysfunction, LV hypertrophy, and cardiac fibrosis, oxidative stress, and inflammation. Increased body weight, subcutaneous and visceral fat mass. Elevated serum insulin, LDL/HDL ratio and triglyceride levels.	40
	T1DM	*Streptozotocin- Intraperitoneal route*	LV systolic and diastolic dysfunction, oxidative stress increased rate of apoptosis, mitochondrial damage, and fibrosis. Reduced body weight, increased circulating glucose and HbA1c levels.	41–44
		- Intravenous route	Reduced LV systolic and diastolic function. Polydipsia, polyuria, glycosuria, proteinuria, uraemia.	45,46
	T2DM	*Zucker diabetic fatty rats (ZDF)*	Increased heart and LV weight, presence of fibrosis, depressed RV and LV systolic function. Dyslipidaemia. Respiratory muscle weakness. Diabetic neuropathy, microangiopathy, nephropathy, hypercoagulability.	47–53
			Cardiac hypertrophy, increased extracellular matrix deposition and increased	54–60

Continued

Table 1 *Continued*

Animal model	Cardiac/noncardiac alterations that recapitulate human features of diabetic cardiomyopathy	References
Goto-Kakizaki rats (GK) Intraperitoneal injection of Streptozotocin + nicotinamide	heart size. Non-obese model of T2DM with moderate hepatic triglyceride accumulation. Age-dependent development of glomerulosclerosis. Hepatic lipotoxicity (increased accumulation of triglycerides, cholesterol, and free fatty acids). Increased serum and hepatic lipid peroxidation.	
Otsuka–Long–Evans–Tokushima fatty (OLETF) rats	Late-onset hyperglycaemia, mild obesity, diabetes mostly in males, multiple recessive genes involved, age-dependent atrophy of pancreatic islets, diabetic nephropathy, primarily visceral obesity.	39,61,62

HFD, high-fat diet; LV, left ventricle; LVEF, left ventricular ejection fraction; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

patients with diabetic CM that are poorly reproduced by current rodent models.[70] Obvious additional species-specific differences include but do not limit to chronicity of insulin resistance, differences in cardiac physiology, such as heart rate, Ca^{2+} fluxes, sarcomere composition and vessel function, resistance to developing micro- and macrovascular diseases in rodents, differential hormonal milieu, concentrations of various lipid species,[71] and control of diabetes (typically no in preclinical models vs. patients). Furthermore, whilst T2DM is traditionally a disease of the elderly in humans (i.e. 40 to <75 years with increasing prevalence in the younger population,[72,73] however), most rodent models employ young adult animals. Importantly, diabetic CM emerges in the midst of multiple organ disorders, that may significantly alter cardiac function by modest yet chronic changes in ion concentration, pH, circulating abnormal proteins and metabolites, subclinical increase in afterload, liver dysfunction, skeletal muscle dysfunction, presence of obstructive sleep apnoea (OSA), etc. However, current rodent models poorly reproduce such common comorbid conditions.

The aim of this review is to identify the current limitations of rodent models and to discuss how future preclinical studies should integrate key confounding factors to better mimic the diabetic CM phenotype as it presents itself in clinic.

2. Molecular aspects of diabetic CM

Abnormalities responsible for hallmarks of diabetic CM, i.e. cardiac stiffness, hypertrophy, fibrosis, and ischaemia, eventually leading to HFpEF and/or HFrEF are highly complex. Both insulin resistance and chronic hyperglycaemia contribute to impaired cardiac contractility and structure via e.g. dysregulated intracellular Ca^{2+} homeostasis, abnormal PI3K/Akt pathway signalling, enhanced production of reactive oxygen species (ROS), advanced glycation end products (AGEs), cardiac protein O-GlcNAcylation, toxic fatty acid (FA) metabolites, as well as probably less well studied mechanisms, such as altered autophagy, and epigenetic dysregulation.[74] These abnormalities do not emerge in isolation, but are interconnected. For example, the metabolic inflexibility in cardiomyocyte metabolism with a shift towards FA oxidation and ensuing mitochondrial ROS production can trigger endoplasmic reticulum (ER) stress, cardiomyocyte death, inflammation, and microvascular dysfunction.[75]

ER stress and mitochondrial dysfunction are key factors for the development and progression of diabetic CM. Altered Ca^{2+} handling is widely believed to underlie depressed contractility, slow relaxation, and arrhythmias triggered in diabetic CM.[76] In murine models with diabetic CM, prolongation of intracellular Ca^{2+} decay and consequential decrease in Ca^{2+} transient amplitude directly correspond to delayed relaxation and abnormal contractility, respectively.[76] The development of dysregulated Ca^{2+} cycling is facilitated by altered expression and/or activity of the L-type Ca^{2+} channels, ryanodine receptor, sarcoplasmic reticulum Ca^{2+} ATPase (SERCA2a), and Na+/Ca2 + exchanger (NCX). In T2DM models, these alterations hamper mitochondrial Ca^{2+} uptake, provoking an energy supply-and-demand mismatch with excessive mitochondrial ROS production.[76] Moreover, ER stress, triggered by hyperglycaemia, free FAs, and inflammation, is an early event in diabetic CM, which may promote cardiomyocyte apoptosis and loss of function.[77] Indeed, beyond changes in Ca^{2+}-handling proteins *per se*, intercompartmental transfer of Ca^{2+} also occurs through the mitochondrial-associated membranes (MAMs; functional interaction sites between ER and mitochondria), exchanging lipids and Ca^{2+}. In a diet-induced mouse model of diabetic CM recent evidence suggests that reticular-mitochondrial Ca^{2+} uncoupling is an early trigger of mitochondrial Ca^{2+} mishandling, leading to reduced mitochondrial bioenergetics and cardiac dysfunction.[78] Mitochondrial dysfunction in diabetic hearts is further characterised by changes in mitochondrial substrate utilization (i.e. increased reliance on FA-based energy production),[79] oxidative stress,[80] fragmented mitochondria,[81] and impaired mitophagy.[82] As opposed to T2DM models,[78] hearts of streptozotocin-induced T1DM mice or neonatal murine cardiomyocytes exposed to high glucose levels, display facilitated MAM formation with mitochondrial Ca^{2+} increase,[83] underscoring important myocardial differences in intracellular Ca^{2+} homeostasis between T1DM and T2DM.

Despite the considerable advances in our mechanistic understanding, a particular concern is that the majority of these results were obtained from rodent cardiomyocytes and there is a clear lack of corresponding observations in human cells.

2.1 Investigating diabetic CM in preclinical models: the importance of clinical confounding factors

The majority of molecular mechanisms in the pathogenesis of diabetic CM has been investigated in rodent models of type 1 or T2DM (*Table 1*). The models consist of animals with defective insulin actions or signalling, altered cardiac glucose and/or FA utilization, enhanced oxidative stress, and/or cardiac fibrosis.[75,84] The most popular animal models include the chemical ablation of the β-cells of the pancreas by streptozotocin, genetic interference with leptin signalling (ob/ob and db/db mice, ZDF rats), the induction of insulin resistance by exposure to high fat diet (HFD) and transgenic animals with a cardiac-specific lipotoxicity.[75] However, important confounding factors contributing to cardiac remodelling and dysfunction are rarely considered when dissecting the signalling pathways leading to diabetic CM in rodent models. Experimental approaches that more closely mimic the clinical scenario in T2DM patients are detailed below:

2.1.1 Ageing

Many of the cardiac abnormalities (i.e. increased wall thickness and interstitial myocardial fibrosis, cardiomyocyte hypertrophy) found in diabetic CM are analogous to those induced by ageing.[85,86] Recent studies suggest that T2DM accelerates the ageing of the heart and may therefore represent a

form of premature senescence leading to premature onset of HF.[87] Indeed, T2DM has a dramatic impact on cellular senescence of different types of stem cells, including cardiac stem cells and potentiates the accumulation of senescent cells in the heart.[88]

Senescent cells display a complex phenotype including DNA damage and genomic instability, ER stress, mitochondria dysfunction, impaired contractile function, hypertrophic growth, and change in gene expression involving a rise of a unique secretory phenotype (senescence-associated secretory phenotype) and induction of senescence-associated beta-galactosidase positivity. Senescent cardiomyocytes secrete growth factors, creating a profibrotic microenvironment and promoting activation of cardiac fibroblasts, which is harmful to the myocardium and triggers processes associated with maladaptive cardiac remodelling.[86,89] Furthermore, T2DM induces epigenetic alterations, such as hypermethylation of CpG islands, increased trimethylation of Histone 3 (H3) at lysine (K)4, H3K9, H3K27, and H4K20, as well as a decreased monomethylation and acetylation of H3K9. These epigenetic modifications contribute to senescence through changing the access of transcription factors to promoter/enhancer regions and are complemented by noncoding RNA regulation by microRNA (i.e. miR34a) and long-noncoding RNA.[90] For practical and financial reasons, most animal studies make use of animals of young or moderate age. Data is accumulating that aged animals respond differently to perturbations associated with diabetic CM, and we therefore advocate to evaluate the role of aging in relevant models.[91]

To further underscore the importance of senescence in the pathogenesis of diabetic CM, senolytic drugs have been shown to alleviate myocardial hypertrophy, fibrosis, and diastolic dysfunction in db/db obese mice.[92] Such observations have suggested diabetic CM as a model of premature cardiac ageing and that senolytic therapy can prevent this T2DM-related complication.[93]

2.1.2 Sex

Independent of age, women with T2DM are at higher risk of developing CV diseases (CVD) compared to age-matched men and tend to manifest a more severe cardiac remodelling in diabetic CM.[94,95] Interestingly, this sex-dependent aggravation of diabetic CM has been successfully recapitulated in several female rodent models. For instance, ZDF female rats exhibit cardiac hypertrophy with reduced capillary density and increased myocardial structural damage, even though males develop more pronounced fibrosis.[96] Increased cardiac hypertrophy and endothelial dysfunction have also been shown in female GK rats compared to males.[97] In the db/db mouse model left ventricular pro-hypertrophic and pro-oxidant gene expression were exaggerated in females leading to increased cardiomyocyte size compared to males.[98] This difference is probably due to sex hormones and neurohormonal diversity coupled with gender-specific activation of molecular pathways involved in cardiac metabolism/remodelling.[99,100] In support of this possibility, animal studies show a sexual dimorphism during the progression of CVD induced by diabetes. Based on the few experimental studies conducted on both sexes of humans and animals, differences in diabetic response seem to be related to relevant sexual dimorphism already present in the non-diabetic state, as demonstrated by differential lipid concentrations and profiles, insulin and glucose control, antioxidant system, nitric oxide (NO) production, energy metabolism, myocardial contractility, and structure.[99,101,102] The impact of this sex-dependent effect in diabetes is not fully understood, but differences in metabolic (e.g. glucose, lipid and insulin) control are likely to be pivotal.[103] Specifically, in females, the interaction between cardiac insulin and oestrogen signalling, which share common pathways, may modulate many structural and functional features in healthy and diabetic states.[103] An illustrative example is the sex-specific dichotomous FA handling pattern: increased accumulation of acylcarnitine (AC) and triglyceride (TG) metabolism with enhanced ROS production in cardiomyocytes has been reported in female GK rats compared to males,[104] suggesting a sex-specific FA metabolism and redox biology with potential consequences in diabetic CM. Taken together, considering the equality in prevalence but disparity in clinical presentation, preclinical studies are highly recommended to study both sexes.[100,105]

2.1.3 Obesity/adiposity

Adipose tissue represents an intersection of pathways involved in longevity, genesis of age-related chronic diseases, metabolic dysfunction, and low-grade inflammation. Obesity and adiposity are causally linked to the development of T2DM and strongly contribute to diabetic CM.[106] The cardiac risk of obesity *per se*, without diabetes and other co-morbid conditions, is underscored by its close association with structural, functional, metabolic, and haemodynamic changes in the heart, leading to a condition clinically termed as obesity CM.[107] Obesity CM hearts are characterised by progressive increase in left ventricular (LV) mass, LV remodelling with interstitial fibrosis, and systolic dysfunction that may lead to HF in both patients and rodent models.[10,108] Moreover, obesity CM has been recently described as energetic inefficient with reduced ATP delivery in human patients.[109] Several wild type high-fat diet (HFD) or genetically modified rodent models have shown to partially recapitulate features of human obesity CM (*Table 1*). Although conflicting data exists as per the ability of HFD to induce myocardial dysfunction, these are likely explained by differences in mouse strains, the duration and timing of dietary intervention, and composition of diet.[109,110] Overall, the mechanisms by which adiposity contributes to cardiac alterations largely overlap with those reported for diabetic CM and include oxidative stress, inflammation, apoptosis, dysregulated autophagy, hypertrophy, interstitial fibrosis, lipotoxicity, and metabolic disturbances. Observations indicate that not only the degree of adiposity counts but the location of body fat accumulation also influences the risk of cardiac dysfunction: ectopic adiposity (visceral, pericardial and epicardial) carries a higher risk than subcutaneous fat,[111,112] probably through the release of pro-inflammatory and pro-fibrotic factors.[113,114] Interestingly, the effects of HFD on cardiac remodelling seem to be reversible, as a switch from HFD to standard diet for 8 weeks reduced lipid accumulation, myocardial hypertrophy, and fibrosis, and improved myocardial function in 16-week HFD mice.[78] These preclinical data are in line with clinical intervention studies, such as gastric bypass, caloric restriction or exercise, intended to reduce myocardial structural and functional consequences of diabetes or obesity.[115,116]

2.1.4 Sedentary life/exercise

Physical exercise is an important non-pharmacological treatment in T2DM, with high efficacy in delaying or preventing diabetic CM.[117] Preclinical studies have identified some mechanisms underlying the exercise-related benefits. Exercise inhibits the pathological processes of myocardial apoptosis, fibrosis, and microvascular alterations through improving myocardial metabolism (improved glucose oxidation and reduced FA oxidation), restoring the physiological regulation of Ca^{2+} (normalizing depressed expression and function of SERCA2a in HFD + streptozotocin rats) and protecting mitochondrial function.[118] Beneficial cardiac effects of exercise are proposed to be mediated by a decrease in adipose tissue senescence with its related pro-fibrotic secretome, independent of improvement in metabolic status in HFD mice.[119]

2.1.5 Left ventricular pressure overload

Left ventricular pressure overload occurs in a variety of conditions, such as vascular stiffness in advanced age, hypertension, valvular heart disease, often in association with obesity, and diabetes. Its deleterious consequences, i.e. myocardial fibrosis and hypertrophy, are mediated by neurohormonal factors involving the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS). The sympathetic nervous system provides the most powerful, but also deleterious, stimulation of cardiac function, via catecholamines and their post-synaptic β-adrenergic receptors (β-AR) including β1-AR, β2-AR, and β3-AR subtypes.[120] Interestingly, diabetic CM, similar to other forms of HF, displays alterations of autonomic control with reduction of parasympathetic activity and an increased activity of sympathetic nervous system, which promotes decreased β-AR responsiveness.[121–123] The latter increases heart rate, stroke volume, and peripheral vascular resistance and stimulates the RAAS, exacerbating left ventricular dysfunction. At the molecular level, elevated sympathetic drive enhances

β1-AR signalling, which promotes hypertrophy, interstitial fibrosis, cardiomyocyte apoptosis and impairs energy metabolism and myocardial function.[120] Additional mechanistic studies suggested that a canonical downstream effector of β-AR, the cyclic AMP-dependent protein kinase A (PKA) may be involved in the deficient ventricular performance and metabolism in the mouse diabetic heart,[124] potentially giving way to other cAMP effectors, such as the Epac proteins.[125] Interestingly, the relationship between insulin resistance and β-AR signalling is emerging as an important focal node in the pathogenesis of diabetic CM since hyperinsulinemia may play a role in desensitization of β-AR signalling in T2DM. This is well illustrated in a study showing that in a diabetic CM murine model induced by HFD, myocardial injury and dysfunction could be reversed by pharmacologically inhibition of β2-AR or G protein-coupled receptor kinase 2 activity.[126] In contrast to cardiac β1- and β2-AR, the role of the β3-AR in the diabetic heart has been hardly investigated. It was reported that a β3-adrenoceptor-mediated negative inotropic effect contributes to the altered positive inotropic response induced by β-adrenoceptor activation in diabetic rat heart.[127]

2.1.6 Chronic intermittent hypoxia

Prevalence and severity of OSA is higher among diabetic individuals compared to non-diabetic subjects.[128] OSA is associated with metabolic and CV co-morbidities including hypertension, arrhythmia, stroke, coronary heart disease, which supports OSA as a major health burden. Mechanistic studies in rodents subjected to chronic intermittent hypoxia (the pathophysiologic basis of OSA) found that OSA-induced CV dysfunction (vascular remodelling, endothelial dysfunction, early atherosclerosis and increased arterial blood pressure) depends on oxidative stress- and HIF1α-driven sympathetic overactivity. Specifically, increased levels of ROS and HIFα activate chemoreflex and suppress baroreflex, thereby stimulating the sympathetic nervous system, increasing LV afterload, and contributing to insulin resistance and T2DM.[129]

2.2 Crosstalk between metabolic organs and the heart beyond cardiac glucose toxicity

To date, there is a need to consider each major organ, i.e. heart, liver, adipose tissue, skeletal muscle, lung, kidney, and brain operating as an integrated network within the human body in response to dysregulated metabolism. In particular, T2DM is associated with progressive microvascular disorders and systemic inflammatory processes, inducing fibrosis in several organs, including the CV system, liver, adipose tissue, kidney, and skeletal muscle. During the progression of these fibro-inflammatory processes, there are significant haemodynamic and metabolic interactions between these organs, which need to be assessed to predict health trajectories in T2DM patients,[130] and more specifically the progression towards diabetic CM and HF with preserved ejection fraction (HFpEF).[131,132] Indeed, dysregulation of both the immune system and microcirculation through endothelial cell dysfunction and procoagulant changes contributes to diabetic CM beyond hyperglycaemia, insulin resistance, and metabolic derangements.[74,130] Importantly, the microcirculation impacts on insulin sensitivity by affecting the delivery of insulin and glucose to skeletal muscle. Thus, endothelial dysfunction and extracellular matrix remodelling promote the progression from prediabetes to diabetes and the development of diabetic CM and other T2DM complications, including HFpEF and chronic kidney disease (CKD).[133,134] Thus, whilst HFpEF was initially considered as a disorder characterized by hypertension, cardiac hypertrophy, and diastolic dysfunction, the pandemics of obesity and T2DM have modified the HFpEF syndrome. As a result, HFpEF is now recognized as a multisystem disorder involving the heart, lungs, kidneys, skeletal muscle, adipose tissue, vascular system, and immune and inflammatory signalling.[131,135] We acknowledge that in clinical practice, HFpEF and diabetic CM are often difficult to distinguish. HFpEF can be the result of a large number of triggers, including diabetes, whereas diabetic CM refers to myocardial structural abnormalities that are predominantly caused by diabetes (*Table 2*).

Table 2 Comparison between diabetic cardiomyopathy and heart failure with preserved ejection fraction

Clinical presentation or factor	DCM	HFpEF
Diabetes	Mandatory	Very common (>50%)
HFpEF	Common, but also be HF(m)rEF	Mandatory
Age	Elderly(>60 years)	Very elderly (>75 years)
Sex distribution	50:50%	Female dominance(~70%)
Hypertension	Very common	Very common
Coronary artery disease (CAD)	No obstructive CAD	Obstructive CAD common (30%)
Obesity	Very common (>80%)	Common (>50%)
Diastolic LV dysfunction	By default	Common
Myocardial metabolism	Significantly altered Favouring FA over glucose Lipotoxity Ketone utilization	Usually altered Switch from FA to glucose Lipotoxicity
Mitochrondial dysfunction and lower biogenesis	+++	++
Autonomic neuropathy	++	–
Fibrosis	++	+

DCM, diabetic cardiomyopathy; HFpEF, heart failure with preserved ejection fraction; LV, left ventricular.

How interorgan crosstalk during T2DM specifically contributes to diabetic CM requires further exploration. Animal models of T2DM represent a unique approach to test the mechanisms of such organ interactions and to assess how the pathological state developing in one organ, can lead to deleterious functional and structural consequences in the heart (Table 3).

2.2.1 Kidney

T2DM is directly related to both CKD and CVD. Patients with diabetes and CVD are twice as likely to develop CKD than those without CVD.[133–136] Furthermore, the co-incidence of HFpEF and CKD is very strong since approximately 50% of the patients with HFpEF also suffer from CKD.[132,137] To further underscore a pathophysiological crosstalk, activated inflammatory cascades and endothelial dysfunction in renal injury promote features of HFpEF, such as cardiomyocyte stiffening and myocardial fibrosis.[132] Beside clinical evidence, causal relationship between CKD and HFpEF came from an experimental rat model of CKD induced by nephrectomy, which resulted in a cardiac HFpEF-like phenotype, with left ventricular hypertrophy and diastolic dysfunction.[138] The kidney-heart relationship is also achieved by complex interactions involving neurohormonal pathways.[139] This is well illustrated with the RAAS system, which is overactivated during CKD and causes a cascade of events leading to vasoconstriction, increased sodium retention, and reduced water excretion. All of which increase blood volume expansion and restore perfusion pressure and therefore may contribute to the development of HFpEF.[139] Beside its renal effects, aldosterone directly promotes cardiac fibrosis, left ventricular hypertrophy, and coronary microvascular dysfunction.[135] Additional renal factors such as uremic toxins and galectin 3 may also have a direct impact on the heart and/or coronary microvasculature and therefore may play a role in the pathogenesis of HFpEF.[140,141] Finally, in indirect support of a kidney involvement, large clinical studies established

Table 3 Subcellular hallmarks in major experimental rodent models of diabetic cardiomyopathy

	MICE					RATS		
	HFD		*Transgenic*	*T1DM*	*T2DM*	*T1DM*	*T2DM*	
	C57BL6	*ob/ob*	*MHC-PPARα*	*STZ*	*db/db*	*STZ*	*ZDF*	*GK*
Fatty acid oxidation	↑	↑	↑	↑	↑	↑	↑	↑
Glucose oxidation	↓	↓	↓	↓	↓	↓	↓	↓
Lipotoxicity	↑	↑	↑	↑	↑	↑	↑	↑
Oxidative stress	↑	↑	↑	↑	↑	↑	↑	↑
Inflammation	↑	↑	N/A	↑	↑	↑	↑	↓
Apoptosis	↑	↑	N/A	↑	↑	↑	↑	↑
Calcium handling	↓	↓	↓	↓	↓	↓	↑/=	↓
Mitochondrial function	↓	↓	↓/=	↓	↓	↓	↓	↓
Molecular changes (expression/activity)	↑CD36	Leptin mutation	↑Cardiac *PPARα* ↑CD36	↑NADPH oxidase (subunit 47) ↑PPARα ↑creatinine kinase ↓miR-133 ↑miR-195	Leptin receptor mutation	↑NLRP3	↑SERCA	
References	10,83,84, 220–227	84,220,221,228–232	22,84,233	22,84,220,234–243	84,220,232,244–248	84,222,249–254	84,220,221,255–261	84,237,262–269

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; HFD, high-fat diet; GK, Goto-Kakizaki rats; MHC-PPARα, mice with cardiomyocyte-specific overexpression of peroxisome proliferator activated receptor α (PPARα), STZ: streptozotocin; ZDF, Zucker diabetic fatty rats; SD, Sprague-Dawley; miR, microRNA; N/A, data not available.

that whereas tight glycaemic control alone does not,[65–69] but GLP-1 receptor agonists[142] and SGLT-2 inhibitors,[143,144] which also improved kidney disease,[142,144,145] lowered the risk for HF in diabetic patients. Thus, these important interactions between T2DM, renal dysfunction and diabetic CM seem to induce a downward spiral of deleterious events, whose interruption represents a novel therapeutic opportunity.[146]

2.2.2 Adipose tissue

A growing body of evidence supports the existence of a two-way adipose-myocardial axis in which products released from fat affect myocardial metabolism and function, whilst peptides secreted from the heart affect FA disposal. Accumulation of ectopic fat in various organs, e.g. in heart, liver, pancreas and kidney has been identified as an important marker in the pathogenesis of T2DM in both human and animal studies.[147–149] Although the causal relationship between the pathophysiological status of white adipose tissue and cardiac lipotoxicity remains elusive, elevated lipolytic rate in adipose tissue has been demonstrated to contribute to the overall augmentation of plasma lipid levels, as observed in the majority of patients suffering from HF. Excessive release of FA from adipose tissue contributes to myocardial insulin resistance with subsequent metabolic inflexibility characterised by a shift in cardiac energy expenditure towards a near-exclusive and less oxygen-efficient FA oxidation. The perpetuation of this metabolic deregulation leads to the development of cardiac lipotoxicity.[150,151] Cardiac lipid overload promotes the formation of cytotoxic intermediates (diacyl-glycerols and ceramides) and enhances ROS generation through exacerbated peroxisomal and mitochondria FA oxidation. Both intermediate lipotoxic species and ROS affect mitochondrial function and Ca^{2+}-handling proteins promoting cardiac dysfunction.[152,153]

Adipose tissue is an important source of inflammatory mediators (Tumor Necrosis Factor: TNF-α, Interleukin 6: IL6, Interleukin 8: IL-8, Monocyte chemoattractant protein-1: MCP-1) and adipokines (leptin, resistin, and omentin), which may act in an autocrine, paracrine, and endocrine manner, ultimately furthering cardiac injury.[114,154] In contrast, the anti-inflammatory adipokine, adiponectin is inversely correlated with myocardial adiposity. Whilst visceral adipose tissue contributes to a low-level and sustained systemic inflammation, pericardial and epicardial fat can directly affect the underlying myocardium by local diffusion of secreted inflammatory mediators.[155–157] Another ectopic fat source known to influence the heart is the perivascular adipose tissue (PVAT), whose volume increases proportionally to visceral adipose tissue.[158] In obesity, PVAT has been shown to shift from an anti-inflammatory and vasodilatory profile towards a proinflammatory status with impaired vasodilation favouring the progression of vascular disease.[159,160]

Finally, a prominent role for atrial and B-type natriuretic peptides (ANP and BNP, respectively) has been proposed in the crosstalk between the heart and the adipose tissue.[161] As such, the induction of lipolysis by natriuretic peptides secreted by the damaged heart has been suggested to counteract obesity, with a disproportionately greater effect in reducing visceral adipose tissue than subcutaneous adipose tissue.[162] On the other hand, increased release of adipocyte FA may contribute to cardiac steatosis and cardiac cachexia.[163]

Further analysis of the crosstalk between adipose tissue and the heart may identify new treatment options, such as targeting lipolysis and cardiac lipid metabolism in diabetic CM to avoid its progression towards HFpEF.

2.2.3 Liver

Several studies support the bidirectional crosstalk between the heart and liver and the consequences of simultaneous development of hepatic metabolic diseases, diabetic CM, and HF. A better understanding of this hepato-cardiac axis is required to ensure an effective management of T2DM patients with heart or liver diseases in order to improve overall prognosis.

Whilst T2DM and metabolic diseases (obesity and non-alcoholic fatty liver disease) are important risk factors to induce cardiac dysfunction,[108,164] a growing body of evidence suggests that the dysfunctional heart per se could affect both systemic metabolism and liver function, and thus, create a vicious injurious cycle between heart and liver. The close association among cardiac and metabolic diseases suggests a common pathophysiological basis. Notably, in metabolic diseases, the heart and liver share similar intracellular defects such as mitochondrial dysfunction, ER stress, lipotoxicity, and disrupted Ca^{2+} homeostasis. Interestingly, MAM exchange phospholipids and Ca^{2+} as well as regulate metabolic homeostasis and signalling.[165] Of note, reduction of ER-mitochondria communication was observed in both heart[78] and liver[166] of HFD mice. In the heart, decreased ER-mitochondria communication caused mitochondrial dysfunction

leading to diabetic CM, whereas in the liver, disrupted ER-mitochondria interactions undermine hepatic metabolic flexibility and insulin sensitivity. Therefore, targeting MAM could be a new strategy to concomitantly improve both heart and liver function in T2DM.

In addition, the heart secretes proteins referred to as cardiokines, which go beyond local cardiac effects, and mediate changes in extracardiac tissues, including liver function. For example, the cardiac ANP attenuates glycolysis and increases gluconeogenesis in rat liver.[167] Other studies showed that the heart controls systemic metabolism via the cardiac-specific microRNA-208a and the mediator complex subunit 13 (MED13) signalling in rodent cardiomyocytes.[168] Overexpression of MED13 or inhibition of miR-208a in cardiac tissue of transgenic mice enhanced lipid uptake, β-oxidation, mitochondrial content, and other genes involved in FA utilization in adipose tissue and liver,[169] supporting the existence of a functionally relevant, metabolic crosstalk between the heart and liver.

2.2.4 Skeletal muscle

Sarcopenia is characterized by a loss of skeletal muscle strength due to reduction in the quality and quantity of muscle mass, replacement of myofibers with fat, changes in muscle metabolism, oxidative stress, degeneration of neuromuscular junctions, and increased fibrosis. Whilst sarcopenia has been described in elderly individuals, mounting evidence suggests a higher prevalence in T2DM patients. Sarcopenia in T2DM patients may be caused by different mechanisms, such as impaired insulin sensitivity, chronic hyperglycaemia, advanced glycosylation end products, subclinical inflammation, microvascular, and macrovascular complications.[170] It seems that the opposite also applies; patients with sarcopenia are at increased risk to develop T2DM due to reduced organismal capacity to catabolise high-energy nutrients.[170,171] In addition, sarcopenia is associated with CVD[172,173] and both share common risk factors, such as altered glucose metabolism, insulin resistance, inflammation, and metabolic syndrome.[174] For instance, T2DM patients with chronic HF exhibit severe skeletal muscle fibre atrophy, capillary remodelling and impaired mitochondrial function, characterized by mitochondrial complex I dysfunction with ROS overproduction.[175]

2.2.5 Brain

Recent studies shed light on the relationship between the brain and CV system, and how the brain-heart axis regulates T2DM.[176] Cohort studies highlight the link between Alzheimer's disease and T2DM,[177] whilst drugs that are currently approved for the treatment of T2DM, such as metformin, have shown promising results in improving cognitive function, and even preventing the development of Alzheimer's disease in diabetic patients.[178]

2.3 Investigating diabetic CM in preclinical models: the role of cellular crosstalk within the heart

In analogy to interorgan signalling, adjacent cells also communicate in a paracrine and autocrine fashion, where a given cell can detrimentally affect neighbouring cells, leading to a vicious cycle and subsequent cardiac dysfunction. In addition to its signature parenchymal cells, the contracting cardiomyocytes, the heart contains many other cells, including fibroblasts, smooth muscle cells, endothelial cells, and resident macrophages. Healthy crosstalk between these different cells ensures myocardial homeostasis, but a pathologically altered cell-cell communication may initiate and propagate adverse cardiac remodelling leading to the development of diabetic CM.[135,179]

2.3.1 Fibroblasts/cardiomyocytes

Cardiac fibroblasts play a crucial role in extracellular matrix (ECM) turnover, as they are involved in both synthesis and degradation of ECM components through matrix metalloproteinasesand tissue inhibitors of metalloproteinases. Fibroblasts adhere to ECM proteins through integrins that are critical mediators of cell attachment, adhesive signalling, and remodelling of collagen fibrils. Excessive cardiac ECM deposition is a key feature of the remodelling response in diabetic CM and promotes myocardial stiffness and cardiac dysfunction in rodent models of diabetes.[180] Experimentally, high glucose levels induce cardiac fibroblasts into a state of increased proliferation,[181] with increased DNA and collagen synthesis as well as fibronectin and TGF-beta-1 gene expression.[182,183] Genetic inhibition of α11β1 integrin in STZ diabetic mice prevents the progression of fibrosis and abnormal cardiomyocyte growth, indicating that this specific integrin plays a critical role in modifying fibroblast-cardiomyocyte-ECM interactions.[184] Crosstalk between cardiomyocytes and fibroblasts is also associated with a cardiomyocyte switch to a fibrogenic phenotype, characterized by increased synthesis and release of cytokines that induce fibroblast proliferation and activation, as well as proinflammatory molecules that trigger fibrosis through activation of immune cells.[180]

2.3.2 Endothelial cells

Diabetic CM is associated with coronary microvascular dysfunction, which impairs coronary blood flow and myocardial perfusion.[185] Abnormalities in the coronary microcirculation result from endothelial cell dysfunction, which is considered a central mechanism in HFpEF pathophysiology.[8,160] Indeed, endothelial cells have altered paracrine signalling to cardiomyocytes by reducing the bioavailability of vasodilator molecules, NO and endothelium-derived hyperpolarizing factors (EDHFs), thereby limiting blood flow and promoting leukocyte infiltration in the myocardium.[186] The latter leads to activation of myofibroblasts and interstitial collagen deposition. As part of T2DM-associated glucotoxicity and lipotoxicity, endothelial cells generate ROS and reactive nitrogen species (RNS) that uncouple endothelial NO synthase (eNOS) activity (by oxidizing eNOS cofactor tetrahydrobiopterin) leading to decreased NO bioavailability.[187] This effect together with insulin resistance converges on and minimizes the activity of guanylate cyclase and cyclic guanosine monophosphate- protein kinase G signalling that results in deranged titin phosphorylation and increased cardiomyocyte hypertrophy, exacerbating wall stiffness in diabetic hearts.[188] Endothelial cells can also contribute to the development of cardiac fibrosis through endothelial-to-mesenchymal transition to myofibroblasts.[189]

2.3.3 Immune cells

Numerous experimental and clinical studies have reported a role of adaptive immunity in diabetic CM pathogenesis.[190–192] T2DM is associated with chronic systemic inflammation, which leads to leukocyte activation and recruitment to various organs, further aggravating inflammatory cardiac tissue remodelling over time.[191] This chain of events results in cardiac fibrosis as resident fibroblasts become activated in response to pathophysiologic conditions, which for the heart, leads to wall stiffening and decreased contractility.[180] Although the role of B cells is still unclear, T cell-derived immune response has been shown to contribute to the progression of diabetic CM.[192] In particular, in STZ-induced rodent models of diabetic CM, increased infiltration of T lymphocytes into the myocardium is positively correlated with increased collagen deposition and wall stiffness,[191] whilst genetic depletion of CD4+ T cells protects against cardiac fibrosis and impairment in LV function.[192,193] Yet, recent studies have further delineated the contribution of each T-lymphocyte subset in diabetic CM. Proinflammatory T helper cells Th1, Th17, and Th22 subtypes are increased in diabetic CM,[194] whereas the activation of anti-inflammatory Th2 and Foxp3+ Treg subtypes is delayed or impaired,[195] overall promoting chronic inflammatory tissue damage. Increased neutrophil/lymphocyte ratio (an indicator of systemic inflammation) is associated with the occurrence of subclinical diabetic CM.[196] As per potential mechanisms involved, the sphingosine-1-phosphate (S1P)/S1P-receptor signalling axis regulating T cell trafficking, activation, and polarization may be of importance.[197] Indeed, targeted deletion of T-cell S1P-R or administration of fingolimod (an S1P-receptor modulator) both reduce myocardial fibrosis and improve cardiac function in STZ-induced diabetic CM mice.[192,198]

Macrophages also play a key role in regulating inflammatory responses and homeostatic maintenance of the myocardium. Normally in injured

tissue, efferocytosis allows macrophages to engulf apoptotic cells and cellular debris to reduce inflammation.[199] Efferocytosis is regulated by many processes in high-glucose milieu. In particular, the metalloproteinase disintegrin and metalloproteinase domain-containing protein 9 (ADAM-9) were shown to be upregulated in macrophages, secondary to a downregulation of miR-126, which increased MER proto-oncogene, tyrosine kinase (MerTK) cleavage with a net effect of reduced efferocytosis.[200] Interestingly, human diabetic hearts display the same molecular signatures in terms of miR-126, ADAM9, and cleaved MerTK expression, suggesting that this pathway may be involved in regulating human diabetic CM progression. Recently, cardiac-resident MHCII^{high} macrophages showed a pathogenic role in cardiac remodelling through production of IL-10. The profibrotic effect of IL-10 autocrine loop promotes macrophages to secrete osteopontin and TGFβ, which induce cardiac fibroblasts into producing collagen that results in cardiac fibrosis with increased cardiac stiffness.[201] Therefore, a new understanding of communication between cardiac macrophages and fibroblasts could lead to novel therapeutic strategies for diabetic CM and its progression towards HF.

2.4 Investigating diabetic CM in preclinical models: identifying new biomarkers and therapeutic targets

2.4.1 Biomarkers

Since T2DM patients at high risk of developing HF display altered metabolism in cardiomyocytes, with underlying changes in protein and metabolite profiles related hyperglycaemia, lipotoxicity and oxidative stress, a systems biology approach may identify a specific signature of diabetic CM. To reduce disease burden, it is imperative to develop non-invasive biomarkers to detect and characterize diabetic CM processes at their early and possibly reversible stages in order to reveal new therapeutic targets and to follow disease progress. These last years, new methods have emerged, which offer a great potential to identify such biomarkers. Big datasets derived from *in silico* predictive models, imaging, and OMICS technologies (metabolomics, lipidomics, transcriptomics, proteomics) may be used for developing multiparametric datasets to assist improved diagnostic and therapeutic decisions.

Metabolic alterations and insulin resistance are early signs of future cardiac dysfunction and have a causative role in the development of diabetic CM.[202] Metabolomics using different analytical techniques such as magnetic resonance spectroscopy, mass spectrometry and chromatography[203] are powerful approaches to follow simultaneous changes in multiple metabolite levels occurring in the diabetic heart. Indeed, cardiac energetic metabolism assessed by the PCr/ATP ratio, is reduced in some studies,[204] although some discrepancies exist depending on the models.[205,206] In parallel, lipid metabolism is altered with increased FA oxidation and lipid accumulation.[147]

In silico predictive methods have the potential to reveal or to confirm effective biomarkers. Using this approach and exploiting meta-analysis of transcriptomic datasets, differential expression levels of lysyl oxidase like 2 (LOXL2) and electron transfer flavoprotein beta subunit (ETFβ) in serum and heart tissue of 6–16-week-old db/db mice correlated closely with a reduced LV diastolic dysfunction, supporting the use of LOXL2 and ETFβ as early predictive biomarkers for diabetic CM.[207]

Moreover, systematic multiorgan biobanking of porcine models of diabetes and obesity subjected to molecular profiling by transcriptomics, proteomics and metabolomics has been proposed to better understand tissue-specific pathogenic mechanisms and organ crosstalk with the prospect of revealing novel molecular targets.[208]

In the field of imaging technologies, the development of machine learning algorithms aims to provide more accurate biomarkers.[209] Thus, combining imaging, radiomics and multi-OMICS data with machine learning will provide large datasets of parameters allowing to find biomarkers for early diagnosis and monitoring progress of diabetic CM.

2.4.2 New therapeutic targets

Drug development is time-consuming and costly, urging the use of precision medicine to replace the 'one size fits all' paradigm with more patient tailoring approaches. Understanding T2DM-specific mechanisms shall lead to opportunities of developing better therapies. Mechanistic studies have demonstrated dramatic glucotoxicity in the heart, and linked it to accelerated sugar-related protein modifications, such as O-GlcNAcylation[210] and AGE formation,[211] as well as increased ROS formation.[212] Yet, most interventional studies focusing on the reduction of plasma glucose in T2DM patients found at most modest improvement[213] and even deleterious effects in HF outcomes.[66–69] To underscore the importance of alternative mechanisms, recent benefits obtained with SGLT2 inhibitor (SGLT2i) treatment for HF and CKD were partly independent of their hypoglycaemic effects.[143,144] Many potential mechanisms have been proposed for SGLT2i.[214–216] For example, it has been suggested that a nephroprotective effect with natriuresis, diuresis and decreased blood volume that reduced preload and afterload are possible mechanisms.[143,144] Reduced cardiac oxidative stress and fibrosis have also been observed with SGLT2i treatment.[217] Occurrence of ketoacidosis prompted the idea that plasma ketone bodies may serve as an alternative and efficient source of cardiac fuel.[218] It has also been proposed that SGLT2 inhibitors have off-target pharmacology by directly inhibiting cardiac NHE1 activity and protect the myocardium under ischaemic conditions.[219] Nevertheless, confirmation of SGLT2i's specific cardioprotective mechanisms remains elusive to date.

Research efforts need therefore to focus on finding therapeutic strategies to inhibit pathophysiological pathways and reduce the risk of diabetic CM. In addition, the understanding of diabetic CM pathophysiology should generate awareness regarding its multiorgan nature. Thus, holistic approaches considering the complexity of myocardial damage induced by T2DM along with the functional interplay between different key organs will advance our knowledge of diabetic CM. This type of multidimensional approach will increase the likelihood of early diagnosis and the translational success of new drugs in development. Currently, there are no specific therapies for diabetic CM. Further refinement of diabetic CM molecular signatures derived from improved preclinical models should provide new mechanistic insights leading to specific targets, drugs, biomarkers, and effective patient management in the future.

3. Future perspectives

Animal models have provided valuable insight into the initiation and progression of diabetic CM, including the revelation of some underlying molecular mechanisms. In addition, they are irreplaceable for testing new treatments and identifying possible side-effects. Despite these undeniable virtues, experimental models have failed to reproduce all structural, functional, and molecular alterations of human diabetic CM, posing as one of the obstacles to advance patient care. An additional intriguing issue with pathophysiological relevance is the failure of antidiabetic drugs to combat diabetic CM. Given the myriads of confounding factors in clinical reality, it is probably impossible to propose a single best model of rodent diabetic CM recapitulating human diabetic CM in its entirety. Indeed, diabetic patients experiencing various additional 'stresses' (advanced liver or kidney disease, sarcopenia, OSA, Alzheimer's disease, etc.) may therefore develop different versions of diabetic CM, hence would mostly benefit from tailored therapeutic interventions. Thus, the design of rodent models for studies on diabetic CM is complex and should involve commonly coexisting comorbidities in humans to reflect specific endotypes. Such new models may include but do not limit to middle-aged or old animals (10–12 months or and ~ 2 years of age) fed with HFD and undergoing intermittent hypoxemia, or HFD model with experimental renal impairment (i.e. 1K1C, 2K1C), or HFD + carbon tetrachloride to induce additional liver injury to cover the full spectrum of NAFLD. Models also need optimizing in terms of duration and composition (e.g. Omega 3/Omega 6 ratio) of HFD, use of rodents with different ages, both genders, etc. We believe that the development of endotype-specific models will be the preclinical response to personalised medicine, facilitating the discovery of new targets and translation to bedside.'

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