Understanding Diabetic Cardiomyopathy: Insulin Resistance and Beyond

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Background: Diabetic cardiomyopathy (DC) is a syndrome of heart failure occurring in patients with diabetes mellitus (DM), independent of other risk factors. It is a relatively underdiagnosed condition with a prolonged subclinical phase. There is an abundance of studies put forward to explain the underlying pathogenic mechanisms observed in this condition. This review aims to summarize the evidence available in contemporary medical literature with regard to the molecular mechanisms, abnormalities in signalling and metabolism and structural and functional abnormalities manifesting as DC. **Methods:** We conducted a literature search using the terms 'diabetic cardiomyopathy', 'heart failure AND Diabetes mellitus', 'Cardiomyopathy AND Diabetes mellitus'. We searched the reference lists of included studies and relevant systematic reviews. **Results:** In this review, we elucidate all the mechanisms that have been postulated to have a role in the pathogenesis of DC, in addition to insulin resistance, such as inflammation, renin–angiotensin–aldosterone system activation and deranged protein homeostasis. **Conclusions:** DC is an underrecognized cardiac complication of DM. A comprehensive knowledge of all the pathways and mediators will aid in the development of diagnostic and prognostic markers, screening protocols and novel management strategies.

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). An estimated 60–80% of patients with T2DM die of cardiovascular events.[1,2] A bidirectional relationship has been noted between heart failure (HF) and T2DM.[3] HF was noted to be twice as high in male patients and five times as high in female patients with T2DM compared with non-diabetic controls in the Framingham Heart Study.[4] On the other hand, the prevalence of T2DM in patients with HF has been noted to be in the range of 10–30% and as much as 40% in hospitalized patients.[5] Patients with diabetes may present with features of HF with preserved ejection fraction (HFpEF), which may account for ~50% of all HF.[6] Multiple studies have revealed variations in left ventricle (LV) mass and wall thickness with increased systolic and diastolic dysfunction in patients with diabetes mellitus (DM) compared with those without.[7–10] Each 1% increase in glycated haemoglobin A1c (HbA1c) was linked to a 30% and 8% increase in the risk of HF in patients with type 1 and type 2 DM, respectively, independent of other risk factors.[11,12]

Lundbaek was the first to propose the existence of a specific diabetic myocardial disease, independent of coronary artery disease (CAD) or hypertension (HTN), in 1954.[13] In 1972, Rubler et al. presented the post-mortem findings of four patients with T2DM associated with renal microangiopathy (Kimmelstiel–Wilson disease) who were noted to have cardiomegaly and advanced HF due to diffuse myocardial fibrosis without significant CAD.[14] This condition was named diabetic cardiomyopathy (DC) and was postulated to be secondary to diffuse myocardial fibrosis, cardiac hypertrophy and diabetic microangiopathy. Later, experimental animal models also demonstrated abnormal cardiomyocyte function, which was postulated to be a possible mechanism contributing to the pathogenesis of DC.[15,16] In this review, we shall focus on the notable structural and functional abnormalities as well as the underlying pathophysiological mechanisms of DC.

Definition

DC has been defined by the American College of Cardiology Foundation, the American Heart Association and the European Society of Cardiology as a clinical condition of ventricular dysfunction that occurs in the absence of coronary atherosclerosis, HTN, valvular heart disease and congenital heart disease in patients with diabetes.[17,18] Traditionally, two stages of DC have been described: an early stage characterized by concentric LV hypertrophy, increased myocardial stiffness, increased atrial filling pressure and impaired diastolic function; and a late stage characterized by an increase in cardiac fibrosis, further impairment in diastolic function and the appearance of systolic dysfunction.[18] Maisch et al. have even suggested four stages of DC as listed below:[19,20]

- Stage 1: Diastolic dysfunction with preserved EF;
- Stage 2: Combination of systolic and diastolic dysfunction;
- Stage III: Systolic and/or diastolic HF in patients with diabetes and microvascular disease and/or microbial infection and/or inflammation and/or HTN but without CAD; and
- Stage IV: HF that may also be attributed to overt infarction or ischaemia.

Two distinct phenotypes of DC were proposed by Seferović and Paulus rather than successive stages of the same disease.[21] These phenotypes include an HFpEF or restrictive cardiomyopathy phenotype and an HF with reduced ejection fraction (HFrEF) or dilated cardiomyopathy. Numerous pharmacological regimens for the HFrEF phenotype have been proven to be highly efficacious in controlled trials; evidence is relatively scarce for the treatment of the HFpEF phenotype.[22] It is proposed that in the early stage of DC, concentric LV remodelling or hypertrophy with eventual diastolic dysfunction is the primary abnormal manifestation, which may gradually progress to systolic dysfunction and later to clinical HF. Yet a few studies propose that DC–HFpEF is a separate entity from DC–HFrEF.[20]

Epidemiology, risk factors and clinical features

In the general population, the prevalence of DC has been noted to be ~1.1% as per the available data from the current medical literature, which may rise to as much as 17% in patients with DM.[23,24] Morbidity and mortality may reach 31% over 10 years.[23] Major impediments to optimal diagnosis of DC include non-homogeneity of various study cohorts and a lack of consensus on diagnostic criteria for DC.

Metabolic abnormalities consequent to DM (more in T2DM) that have been predictive of DC include hyperglycaemia, insulin resistance and hyperinsulinaemia.[25] An analysis of 20,985 patients with T2DM in the national Swedish registry revealed a hazard ratio of 3.98 for the development of HF in patients with HbA1c ≥10.5% compared with patients with HbA1c <6.5% (adjusted for age, sex, duration of T2DM and other CVD risk factors).[11] In another study, patients with HbA1c >7.5% had a higher prevalence of diastolic dysfunction than those with HbA1c <7.5%.[12] A reduction in HbA1c levels reduced the risk of developing HF. The risk of HF increases with age and duration of T2DM.[26] Female patients have also been noted to have a predilection for developing DC.[27] The most common risk factors for congestive heart failure (CHF) are dyslipidaemia and HTN, which are more frequent in the diabetic population compared with the general population.[28] DC represents another distinct cause of HF, which is independent of the presence of vascular disease.[21,29]

The majority of patients with DC have asymptomatic LV dysfunction initially.[30,31] Patients predominantly present with complaints of exertional dyspnoea, fatigue and peripheral oedema with associated clinical signs of CHF.[3]

Pathophysiology of diabetic cardiomyopathy

Multiple complex metabolic pathways have been proposed in the pathogenesis of DC (*Table 1*), including cardiac insulin resistance, structural alterations in the myocyte, changes in metabolic substrate utilization, impairment of oxidative phosphorylation and increased production of reactive oxygen species (ROS).

Alterations in cardiac structure

Increased stiffness of the cardiomyocyte with a decrease in diastolic compliance, resulting in impaired cardiac relaxation, has been observed in DC, especially the HFpEF phenotype.[32] This may be attributed to

Table 1: Pathophysiological mechanisms of diabetic cardiomyopathy

Serial number	Underlying pathophysiological mechanism
1	Alterations in cardiac structure
2	Cardiac insulin resistance
3	Increased dietary fructose
4	Altered substrate utilization
5	Mitochondrial dysfunction
6	Inflammation
7	Renin–angiotensin–aldosterone system activation
8	Autonomic neuropathy
9	Increased cardiac endoplasmic reticulum stress and apoptosis
10	Microvascular dysfunction
11	Derangement of protein homeostasis and signalling pathways

various microcellular abnormalities. Insulin causes the translocation of glucose transporter type 4 (GLUT4) to the cell membrane and subsequent glucose uptake. Impairment of insulin metabolic signalling decreases GLUT4 recruitment to the plasma membrane and reduces glucose uptake. This causes a reduction in sarcoplasmic reticulum (SR) calcium (SERCA) pump activity and a resultant increase in intracellular calcium (Ca^{2+}) inside the cardiomyocyte.[25] Low intracellular Ca^{2+} concentration in diastole is a prerequisite for normal cardiac function and enables adequate ventricular relaxation and filling.[33]

Impaired insulin signalling curtails insulin-stimulated coronary endothelial nitric oxide synthase activity with a secondary reduction in nitric oxide (NO) levels, which is a hallmark of DC. Decreased NO levels result in the phosphorylation of titin with a secondary increase in myocyte stiffness.[25] Stimulation of the insulin-like growth factor-1 receptor, which is produced by cardiomyocytes, can cause cardiomyocyte hypertrophy mediated by extracellular signal-regulated kinase-2 (Erk 1/2) and phosphatidylinositol-3-kinase (PI3K) signalling pathways.[34] Hyperglycaemia and hyperinsulinaemia activate the transforming growth factor beta 1 (TGF-β1) pathway and dysregulation of the degradation of the extracellular matrix.[35]

Hyperglycaemia brings about an increase in advanced glycation end products (AGEs), which in turn induces myocardial structural alterations, such as connective tissue cross-linking and fibrosis. AGEs may bind to the cell surface receptor for AGEs, thereby promoting Janus kinase and mitogen-activated protein kinase (MAPK) pathway-mediated abnormal structural alterations in the myocardium.[35] AGEs cause an increase in the generation of ROS, activation of the TGF-β1/suppressor of mothers against decapentaplegic pathway, production of connective tissue and fibrosis.[36,37]

Cyclic adenosine 5'-monophosphate-responsive element modulator (CREM) is a transcription factor that has a role in the regulation of cyclic adenosine monophosphate signalling and cardiac gene expression. Transcription factors from the CREM family may contribute to cardiac fibrosis, secondary to hyperglycaemia and raised free fatty acids (FFAs).[38]

Cardiac insulin resistance

Insulin has a major role in the mediation of cardiac myocyte homeostasis by controlling protein synthesis and influencing the type of metabolic substrate used by the myocyte.[39] As mentioned previously, insulin

resistance impedes the translocation of GLUT4 to the cell membrane with a secondary reduction in glucose uptake and downstream NO levels. Cardiac insulin receptor knockout also increases cardiac ROS production and induces mitochondrial dysfunction. Insulin receptor substrate (IRS) is a docking protein that acts as a major substrate for insulin and mediates many of insulin's actions, including binding and activation of PI3K and the subsequent increase in glucose transport.[40] Double IRS-1/2 knockout reduces cardiac myocyte adenosine triphosphate (ATP) content, decreases cardiac metabolism and function and promotes cardiac fibrosis and consequent failure.[41]

Mitsugumin 53 (MG53) is an E3 ubiquitin ligase that has been postulated to have an important role in insulin signalling.[42] Studies in mouse models revealed a correlation between elevated cardiac MG53 protein levels and increased proteasomal degradation of the insulin receptor and IRS-1. Overexpression of MG53 by the cardiomyocyte was also noted to inhibit insulin signalling pathways and bring about increased cardiac fibrosis.[43] Hence, downregulation of cardiac MG53 may be a potential therapeutic target in the prevention and treatment of DC.

Causative factors such as obesity and dysregulation of the renin–angiotensin–aldosterone system (RAAS) may impair cardiac insulin metabolic signalling pathways mediated by the mammalian target of rapamycin (mTOR)/S6 kinase 1 (S6K1).[25,44] Inflammatory mediators, such as tumour necrosis factor-alpha (TNF-α), may induce cardiac insulin resistance through activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and c-Jun N-terminal kinase.[25] Forkhead box-containing protein O subfamily (FoxO1) is a transcription factor that may contribute to insulin resistance in mice subjected to a high-fat diet. Cardiac FoxO1 deletion was noted to be preventive of HF in these animal studies.[45,46] FoxO1 may yet be another novel therapeutic target in the management of DC.

Increased dietary fructose

Fructose absorption and metabolism in humans are mediated through GLUT2 and 5 present in the liver.[25] Excessive dietary fructose metabolism may affect oxidative stress, cardiac myocyte autophagy, insulin resistance and interstitial fibrosis via protein modifications such as O-linked N-acetylglucosamine (O-GlcNAc) and generation of AGEs.[47] Ventricular myocytes exposed to elevated fructose levels exhibit increased mitochondrial complex I and II hydrogen peroxide production, suggestive of inefficient mitochondrial electron transport chain function.[48] In a milieu of increased fructose metabolism secondary to fructokinase-C overexpression, exposure to relatively low-level fructose suppressed mitochondrial oxidative phosphorylation in neonatal mouse cardiac myocytes.[49] Thus, in a setting of increased fructose metabolism, low levels of fructose may inhibit cardiomyocyte mitochondrial function. Fructose 1-phosphate is converted into dihydroxyacetone phosphate and isomerized to acetyl-coenzyme A (CoA) and glyceraldehyde-3-phosphate. Acetyl-CoA may either be oxidized in the tricarboxylic acid cycle or channelled into FFA synthesis. Phosphorylation of fructose also brings about a reduction in ATP production.[50,51]

Altered substrate utilization

In the background of insulin resistance and hypertriglyceridaemia, the myocardium switches to FFAs rather than glucose as the metabolic substrate for energy production.[39] The switch from glucose to FFAs co-occurs with diminished oxidative phosphorylation and leakage of mitochondrial protons, resulting in a secondary increase in ROS production. Accelerated mitochondrial ROS production brings about NO destruction with decreased NO bioavailability.[52] Greater FFA release

from adipose tissue in addition to the enhanced capacity of myocyte FFA transporters contributes further to the development of DC.[25,39]

Activation of peroxisome proliferator-activated receptor-α (PPAR-α) affects the uptake and mitochondrial oxidation of FFAs.[25] Studies on PPAR-α-null mice have demonstrated that PPAR-α controls the expression of numerous genes involved in mitochondrial β-oxidation, peroxisomal β-oxidation, fatty acid uptake and/or binding and lipoprotein assembly and transport.[53,54] Deletion of cardiac PPAR-α induces a switch from FFA to glucose utilization.[55] Elevated FFAs bring about a decrease in PPAR-α expression in DC.[56] Reduced PPAR-α in advanced DC has adverse consequences on cardiac metabolism, including glucotoxicity and functional cardiac abnormalities. PPAR-β/δ has a role in regulating the expression of transcriptional genes and FFA metabolism; an increase in PPAR-β/δ signalling promotes FFA utilization, whereas the deletion decreases FFA oxidation.[57] In addition, PPAR-γ has cardiac anti-hypertrophic and anti-inflammatory effects.[25] Thiazolidinediones are insulin sensitizers that mediate their actions by regulating gene expression through binding to PPAR-γ receptors.[58] They cause dose-dependent fluid retention in ~20% of patients. This action is mediated through the PPAR-γ receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubules, which promote sodium reabsorption.[59] Most instances of fluid retention respond to diuretic therapy with thiazides or spironolactone (mild oedema) or loop diuretics (severe fluid retention). Increased intravascular volume may exacerbate HF. The risk of HF and death is higher with rosiglitazone than with pioglitazone.[60]

Accelerated expression of cluster of differentiation 36 (CD36), a predominantly membrane-located transport protein, which upregulates FFA uptake across sarcolemma and other endosomal membranes, has been observed in DC.[61] CD36 has a significant role in AMP-activated protein kinase (AMPK)-mediated stimulation of FFA uptake in cardiomyocytes. Following activation, AMPK brings about early activation of glucose uptake and glycolysis, thereby improving cardiac function in patients with diabetes.[62] Reduced AMPK activation in DC results in increased FFA uptake, triacylglycerol accumulation and decreased glucose utilization.[63] Diacylglycerols, ceramides and other lipid metabolites with downstream protein kinase C (PKC) activation impair insulin signalling, which further aggravates DC.[64] Ceramide may cause direct activation of atypical PKCs, resulting in the inhibition of insulin metabolic signalling. Comparative gene identification 58 (CGI-58) is a co-activator of adipose triglyceride lipase and a lipid droplet-associated protein.[65] A knockout of the CGI-58 gene results in an exacerbation of insulin resistance.

Systemic insulin resistance causes a reduction in ketogenesis. Ketones (e.g. β-hydroxybutyrate) have a potentially useful role as an alternative substrate in DC due to reduced cardiac glucose utilization.[66] Empagliflozin, which is a sodium–glucose cotransporter 2 (SGLT2) antagonist, has been noted to increase ketone levels, thereby providing a more efficient energy source in DC.[67]

Mitochondrial dysfunction

Various abnormalities in the mitochondria have an underlying role in the pathogenesis of DC and HF.[68] Mitochondrial oxidative phosphorylation provides 95% of intracellular ATP production in cardiomyocytes, but in T2DM, mitochondria switch from glucose to FFA oxidation for ATP production, which is accompanied by increased ROS generation and impaired oxidative phosphorylation.[25] Changes in mitochondrial Ca^{2+} metabolism bring about mitochondrial respiratory dysfunction, causing cell death.[69]

Impaired Ca^{2+} handling has a role in increasing the duration of the action potential and prolongation of diastolic relaxation time; this plays a role in the development of diastolic dysfunction noted in the HFpEF phenotype of DC.[68] Mitochondrial ROS are generated within the electron transport chain during oxygen metabolism. Insulin resistance and hyperglycaemia result in the mitochondrial inner membrane getting hyperpolarized, with secondary inhibition of electron transport and greater ROS production. Increased cardiomyocyte nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase activity, reported in insulin resistance, is a source of elevated cardiomyocyte ROS.[70] An increase in the activity of xanthine oxidase and microsomal P-450 enzyme with NO synthase uncoupling has an aetiopathogenic role in DC.[71]

Inflammation

A major pathogenic mechanism underlying DC is a maladaptive pro-inflammatory response involving the innate or non-specific immune system (neutrophils, dendritic cells, mast cells and macrophages), activation and expression of pro-inflammatory cytokines (TNF-α, interleukins [ILs] 6 and 8, monocyte chemotactic protein 1, intercellular adhesion molecule 1 and vascular cell adhesion molecule 1), bringing about oxidative stress, fibrosis and diastolic dysfunction.[25] The nuclear transcription factor (NF-κB) promotes cytokine expression. The toll-like receptor-4 promotes an increase in NF-κB levels and associated pro-inflammatory responses.[72]

Hyperglycaemia, insulin resistance and high FFA levels activate the human nucleotide-binding oligomerization domain (NOD)-like receptor(NLR) family pyrin domain-containing 3 inflammasome, a novel molecular marker in DC, leading to the activation of procaspase-1. The activated form caspase-1, via IL-1β and IL-18 precursors, promotes multiple pro-inflammatory pathways involving NF-κB, chemokines and ROS.[73] An increase in coronary trans-endothelial migration of monocytes and macrophages is followed by polarization into the pro-inflammatory M1 subtype under the influence of increased ROS and decreased NO levels.[25]

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a leucine zipper protein that aids in the expression of antioxidant proteins in response to oxidative stress. Hyperglycaemia and insulin resistance suppress Nrf2 expression and activity via an Erk 1/2-mediated pathway.[74]

Renin–angiotensin–aldosterone system activation

Increased RAAS activation in a background of insulin resistance and hyperglycaemia has an important pathogenic role in DC.[75] Serum angiotensin II (AT II) levels are elevated in insulin resistance and T2DM.[76] Upregulation of pro-inflammatory AT II receptor 1 (AT-1R) with downregulation of anti-inflammatory AT-2R is noted in early T2DM.[77] Hyperglycaemia-induced activation of the RAAS in type 1 DM is hypothesized to play a role in the pathogenesis of DC.[75] Insulin resistance, hyperglycaemia and dyslipidaemia have been observed to be associated with elevated plasma aldosterone levels and overexpression of tissue mineralocorticoid receptors (MRs).[78] Inhibition of the aldosterone/MR signalling pathway has been demonstrated to reduce morbidity and mortality in patients with diabetes and mild-to-moderate HF.[79] Activation of the RAAS upregulates the mTOR/S6K1 signalling pathway, which impairs insulin signalling and induces insulin resistance.[80] Enhanced AT-1R and MR activation results in an increase in the pro-inflammatory M1 phenotype, thereby exacerbating the adverse structural alterations causing diastolic dysfunction.[44]

Autonomic neuropathy

Cardiac autonomic neuropathy (CAN) has been demonstrated to be independently associated with LV dysfunction in patients with T2DM and no pre-existing CVD.[81] A decrease in parasympathetic activity with a relatively higher sympathetic nervous system activity, an early feature of CAN, causes an elevation of myocardial catecholamine levels and activation of adrenergic receptors, more specifically beta-1 adrenergic (β1) receptors.[82] This enhances the increased activation of the systemic and tissue RAAS activity and hyperglycaemia, which promote interstitial fibrosis and diastolic dysfunction.[83]

Increased cardiac endoplasmic reticulum stress and apoptosis

The toxic combination of cardiac ROS, inflammation, lipotoxicity and accumulated misfolded proteins impedes cardiac endoplasmic reticular function and causes endoplasmic reticulum (ER) stress.[25] ER stress and the unfolded protein response result in an inhibition of cellular protein synthesis and reduced breakdown of misfolded or abnormal proteins. These ultimately bring about increased cell apoptosis, which is a significant risk factor for the development of DC.[84] ER stress induces a Ca^{2+}-dependent pathway-mediated autophagy involving the inositol-requiring enzyme 1 (IRE1) and protein kinase RNA-like endoplasmic reticulum kinase pathways.[85] Inhibition of the mammalian target of rapamycin complex 1 (mTORC1) also promotes autophagy.[85]

Microvascular dysfunction

DC may be associated with coronary microvascular dysfunction, which impairs coronary blood flow, myocardial perfusion and ventricular function, thereby increasing the incidence of CVD.[86] MR antagonists have a role in managing coronary microvascular dysfunction and preventing CVD in patients with type 2 DM.[87] Both structural (obstruction of the lumen, vascular wall infiltration, rarefaction and remodelling, perivascular fibrosis) and functional (impaired dilatation or increased constriction of arterioles and pre-arterioles, endothelial and smooth muscle cell dysfunction and ischaemia–reperfusion injury) abnormalities in the coronary microcirculation may be noted.[88] In view of disturbances in NO-mediated vasodilation in DC, vascular function in the initial stages is often maintained by endothelium-derived hyperpolarizing factors (EDHFs). Eventually, both NO- and EDHF-induced vasodilation are impaired, leading to significant microcirculatory dysfunction.[89] Elevated plasma endothelin-1 (ET-1) levels have also been noted to be associated with the pathogenesis of cardiac fibrosis and diastolic dysfunction in DC.[90]

Derangement of protein homeostasis and signalling pathways

Misfolded and oxidized proteins are generated following intracellular myocardial metabolic activity.[91] The ubiquitin–proteasome system is responsible for the degradation of these abnormal proteins; impairment of this system causes impaired cardiac contractility and adverse cardiac remodelling.[92] Other abnormalities of signalling pathways that have been described previously in this review include increased PKC, MAPK, NF-κB, SGLT2, O-GlcNAc and CREM signalling and reduction in AMPK, PPAR-γ and Nrf2. These aberrant responses induce cardiac insulin resistance, downstream metabolic disorders and structural abnormalities characteristic of DC. Some of these molecules may act as biomarkers of DC but may be used as potential therapeutic targets.[93]

An increased expression of miRNAs (short single-stranded non-coding RNA molecules), which control the expression of transcriptional and post-transcriptional target genes, is seen in DC. The miRNAs have a

role in the regulation of mitochondrial function, ROS production, Ca^{2+} metabolism, apoptosis and fibrosis.[94] Exosomes are extracellular vesicles, which act as intercellular mediators of communication. Cardiomyocytes release exosomes rich in miR-320, which are transported to coronary endothelium, causing a reduction in NO production and a heat shock protein 20-mediated inhibition of angiogenesis.[32,95]

Biomarkers

Various cardiac biomarkers have been used for detecting HF; many of these have failed to diagnose DC in a timely manner. The association of brain natriuretic peptide (BNP) with HF is blunted, owing to an inverse correlation between BNP and insulin resistance. On the other hand, *N*-terminal pro-BNP (NT pro-BNP) and atrial natriuretic peptide are superior predictors of HF.[96] Yet they may be more accurate in symptomatic patients or those with restrictive filling or pseudo-normalized mitral flow patterns. There was no correlation of these natriuretic peptides with diastolic dysfunction among asymptomatic patients and those with relaxation abnormalities. Natriuretic peptides have a limited diagnostic role in preclinical DC. Other experimental predictors that have been explored include soluble forms of suppression of tumourigenicity 2 (sST2), galectin-3, TGF-β1, growth differentiation factor-15 and long non-coding RNAs.[97–100]

Management strategies

In view of the available information regarding the underlying pathophysiology of DC, management strategies can be formulated accordingly. Yet, despite the increase in knowledge of the underlying mechanisms of DC, there are no approved therapeutic modalities for this condition.

Lifestyle measures such as dietary modification and regular physical activity have a major role in the management of DC.[101–103] Glycaemic control needs to be optimized adequately; a 1% reduction in HbA1c was associated with a 16% risk reduction in the development of HF in the UK Prospective Diabetes Study.[12] With regard to pharmacotherapy, recent trials of sodium–glucose cotransporter 2 inhibitors (SGLT2i), such as empagliflozin, canagliflozin and dapagliflozin, have demonstrated a significant reduction in the risk of major adverse cardiac events (MACEs) in patients with T2DM.[104–106] This benefit was independent of the glucose-lowering effects of SGLT2i. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been approved for reducing the risk of MACE in patients with T2DM and established CVD (dulaglutide, liraglutide and subcutaneous semaglutide).[107–109] The Harmony Outcomes trial (Effect of Albiglutide, When Added to Standard Blood Glucose Lowering Therapies,

on Major Cardiovascular Events in Subjects with Type 2 Diabetes Mellitus; ClinicalTrials.gov identifier: NCT02465515; albiglutide) showed a reduction of 29% in the risk of HF hospitalization with GLP-1 RAs.[110] MR antagonists, such as eplerenone, are associated with a reduction in LV mass and in NT pro-BNP levels, suggestive of a clinical benefit in HF prevention in patients with T2DM.[111]

Trimetazidine is an anti-anginal drug that is a selective inhibitor of long-chain 3-ketoacyl coenzyme A thiolase, an enzyme required for fatty acid oxidation.[112] It shifts energy utilization from FFA oxidation to glucose oxidation in the cardiomyocyte. It also has a role in stimulation of autophagy, inhibition of fibrosis and prevention of apoptosis.[113,114] Other drugs that may have a role in the management of DC include modifiers of calcium homeostasis (istaroxime and ranolazine), ROS scavengers, MitoQ (a derivative of coenzyme Q), coenzyme Q10, elamipretide (small peptide-targeting cardiolipin), GKT137831 (NADPH oxidase 1/4 dual inhibitor), AGE formation inhibitors (aminoguanidine, alagebrium and MitoGamide), aldose reductase inhibitors (AT-001), recombinant human neuregulin-1, apelin, guanylate cyclase activators (cinaciguat/vericiguat), mitochondrial aldehyde dehydrogenase 2 activators (Alda-1 and AD-9308), phosphoinositide 3-kinase γ (PI3Kγ) inhibitors, canakinumab (monoclonal antibody that targets IL-1β), HMG-CoA reductase inhibitors (statins), angiotensin 1–7, dipeptidyl peptidase III (DPP III) and inhibitors of fibrosis (glucose-stimulated insulinotropic polypeptide and cathelicidin-related antimicrobial peptide).[100] However, the efficacy of these agents needs to be explored further in large-scale prospective trials.

Conclusion

DC is an underrecognized cardiac complication of T2DM. Different mechanisms have been put forward to explain the pathogenesis of DC. A comprehensive knowledge of these underlying pathways and mediators will aid in the development of diagnostic and prognostic markers, as well as therapeutic targets. As DC has a prolonged latent course and a significant association with glycaemic control, early detection and management can go a long way in the prevention of symptomatic disease and reduction of CVD burden. Current screening strategies are not sensitive enough to detect subclinical disease. Further studies for a better understanding of the mechanisms involved in the pathogenesis of DC need to be prioritized so as to aid in the development of screening protocols, assessment of biomarkers and novel management strategies. Research should be channelled towards a better understanding of cellular and sub-cellular targets underlying the development of DC and the development of targeted pharmacotherapy for the same. ❑

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