Cellular and molecular mechanisms, genetic predisposition and treatment of diabetes-induced cardiomyopathy

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A B S T R A C T

Diabetes mellitus is a common disease affecting millions of people worldwide. This disease is not limited to metabolic disorders but also affects several vital organs in the body and can lead to major complications. People with diabetes mellitus are subjected to cardiovascular complications, such as cardiac myopathy, which can further result in major complications such as diabetes-induced cardiac failure. The mechanism underlying diabetes-induced cardiac failure requires further research; however, several contributing factors have been identified to function in tandem, such as reactive oxygen species production, inflammation, formation of advanced glycation end-products, altered substrate utilisation by mitochondria, activation of the renin–angiotensin–aldosterone system and lipotoxicity. Genetic factors such as microRNAs, long noncoding RNAs and circular RNAs, as well as epigenetic processes such as DNA methylation and histone modifications, also contribute to complications. These factors are potential targets for developing effective new therapies. This review article aims to facilitate in depth understanding of these contributing factors and provide insights into the correlation between diabetes mellitus and cardiovascular complications. Some alternative targets with therapeutic potential are discussed to indicate favourable targets for the management of diabetic cardiomyopathy.

1. Introduction

Diabetes mellitus (DM) is a common condition affecting millions of people worldwide. The disease is associated with many complications in major organs, including prominent effects on the cardiovascular system. Even normotensive patients with good control of DM and no symptoms show some degree of cardiac dysfunction (Ritchie and Abel, 2020). Cardiomyopathy is a complication associated with both type 1 and type 2 DM. Cardiomyopathy can further result in cardiac failure despite a lack of other risk factors for heart failure, such as hypertension, coronary artery disease, atherosclerosis or valve disease (Yue et al., 2017). The structure and function of cardiac muscles are altered in cardiomyopathy (Dill-mann, n.d.). The first correlation between DM and heart failure was reported in 1972, on the basis of post-mortem observations in four patients with DM. The only explanations for their cardiac failure were diffuse areas of fibrosis observed throughout the myocardium, and myocardial hypertrophy revealed in histopathological studies, because the patients did not show any classical risk factors of heart failure; thus, the term "cardiomyopathy" was coined by Rubler () (Lee and Kim, 2017) (Naka-mura et al., 2022).

Individuals with DM have a higher risk of heart failure than people of the same age without DM. According to the Framingham Heart Study, the chances of developing heart failure are two times greater in men, and five times greater in women, with DM than in those without DM(Lee and Kim, 2017) (Karwi et al., 2022). Heart failure decreases quality of life and hinders the management and control of DM. Therefore, the effects of cardiomyopathy must be well understood and diagnosed early to enable proper treatment and improve patient health (Prentice, 2021).

2. Effects of hyperglycaemia, hyperinsulinemia and insulin resistance on the heart

Hyperglycaemia can occur because of either the inability of elevated insulin levels to overcome insulin resistance, as observed in type 2 DM, or the inadequate release of insulin by beta cells of the pancreas (autoimmune destruction), as in type 1 DM(Ritchie et al., 2017). Hyperinsulinemia, defined by abnormal levels of insulin in the blood as a consequence of insulin resistance, is a common pathological abnormality in type 2 DM and prediabetes (Lee and Kim, 2017). Long-term hyperglycaemia, hyperinsulinemia and insulin resistance lead to various forms of metabolic and molecular alterations in cardiomyocytes, thereby resulting in metabolic abnormalities and cardiac insulin resistance (Jia et al., 2018).

In the initial phase of cardiomyopathy, metabolic disturbances are observed, which result in the activation of complex molecular pathways in DM, thereby altering cardiac structure and function. The common

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cardiac abnormalities observed are increased reactive oxygen species (ROS), build-up of advanced glycation end-products (AGEs), altered calcium handling by mitochondria, mitochondria dysfunction, stimulation of the renin angiotensin aldosterone system (RAAS), endoplasmic reticulum stress, microvascular dysfunction and cardiomyocyte death (Lorenzo-Almorós et al., 2017) (Ritchie et al., 2017) (Jia et al., 2018). These events give rise to oxidative stress, remodelling of the extracellular matrix, metabolic disturbances and fibrosis in cardiomyocytes, and eventually lead to structural and functional changes, such as diastolic dysfunction, left ventricular hypertrophy or systolic dysfunction (Salvatore et al., 2021) (Ritchie et al., 2017). Cardiomyocyte hypertrophy is common in patients with hyperinsulinemia and is modulated by the activation of various transcription factors responsible for the regulation of expression of cellular and extracellular proteins through genetic and epigenetic changes. Transcription factor activation also results in the deposition of extracellular matrix proteins. The deposition and cardiomyocyte hypertrophy ultimately increase focal myocardial fibrosis (Lorenzo-Almorós et al., 2022) (Sun et al., 2019) (Fig. 1).

3. Pathophysiology of diabetic cardiomyopathy (Figs. 2 and 3)

The main mechanism underlying diabetes-induced cardiomyopathy remains unclear. Cardiomyopathy is a complication whose cause has been attributed to many factors. Each year, additional factors contributing to diabetic cardiomyopathy are identified. Some factors include insulin resistance, microvascular impairment, subcellular component abnormalities, metabolic disturbances, cardiac autonomic dysfunction, alterations in the RAAS, maladaptive immune responses, oxidative stress, inflammation and impaired Ca^{2+} handling, as well as alterations in substrate metabolism/utilisation, insulin signalling, gene regulation, mitochondrial dysfunction, endoplasmic reticulum stress, neurohumoral activation and cardiac cell death (Ritchie and Abel, 2020) (Lee and Kim, 2017) (Marfella et al., 2021). Several of these contributing factors are discussed in detail below.

3.1. Roles of increased reactive oxygen species

Extensive glucose metabolism is observed in hyperglycaemia, which induces oxidative stress through the generation of ROS from the mitochondria. The superoxide overproduction in the mitochondrial respiratory chain decreases the contractility of the myocardium and ultimately induces myocardial fibrosis. Oxidative stress due to ROS induces apoptosis in cardiomyocytes and DNA damage in cells (Al Hroob et al., 2019). The DNA damage activates DNA repair enzymes such as poly ADP ribose polymerase, which switches the usual glucose metabolism pathway to a substitute pathway, thus forming several mediators and resulting in cellular injury induced by hyperglycaemia, as indicated by increases in the activation of protein kinase C, polyol and hexosamine flux, and AGE levels (Lee and Kim, 2017) (Dhalla et al., 2020).

3.2. Roles of AGEs

AGEs are produced through a reaction involving non-enzymatic glycosylation of lipids, amino acids and lipoproteins exposed to sugars, thus altering their functions. AGEs contribute to covalent cross-linking between extracellular matrix proteins and connective tissues, and decrease collagen degradation; consequently fibrosis increases and myocardial damage occurs due to cardiac stiffness and altered diastolic relaxation (Varma et al., 2018) (Jia et al., 2017) (Grubić Rotkvić et al., 2021).

AGEs also activate inflammatory signalling, induce ROS overproduction, decrease nitric oxide production through AGE receptors—which are present on a variety of cells, including endothelial cells, smooth muscle cells and macrophages—and consequently lead to various microvascular complications (Kanamori et al., 2020).

3.3. Roles of altered calcium handling

Ca^{2+} has a crucial role in controlling excitation-contraction coupling, as well as controlling systolic and diastolic function in the heart. Under normal physiological conditions, when membrane/sarcolemma depolarisation occurs, a Ca^{2+} current is generated in L-type Ca^{2+} channels. Consequently, diffusion of Ca^{2+} ions and activation of the ryanodine receptor result in further generation of Ca^{2+} sparks and intensify the original Ca^{2+} signal through Ca^{2+}-induced Ca^{2+} release. Then, the efflux of Ca^{2+} into the cytoplasm from the sarcoplasmic reticulum (SR) is triggered (Tian et al., 2021) (Lou et al., n.d.). The Ca^{2+} then binds troponin-C, which initiates the interaction between actin and myosin and
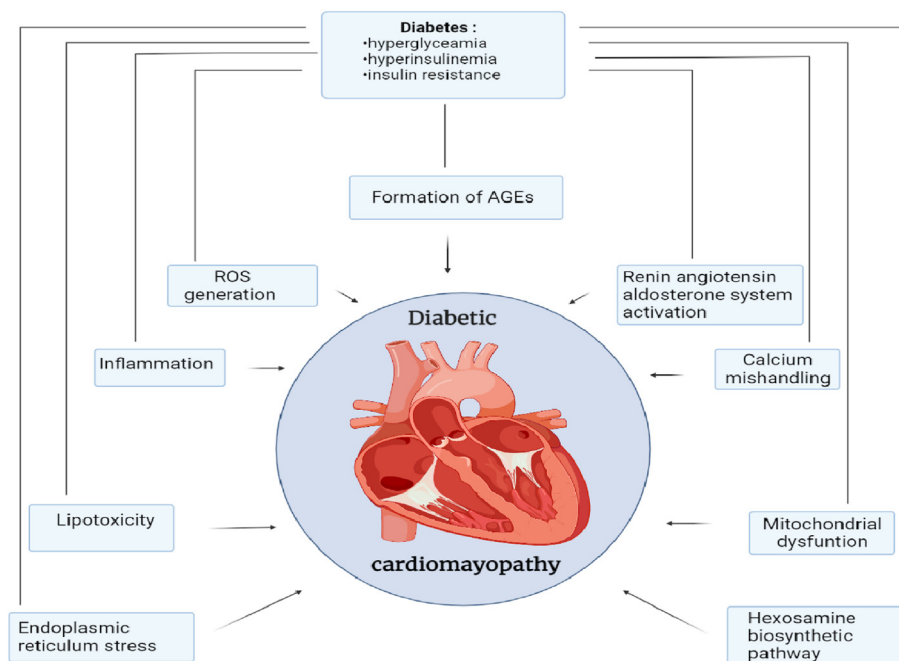

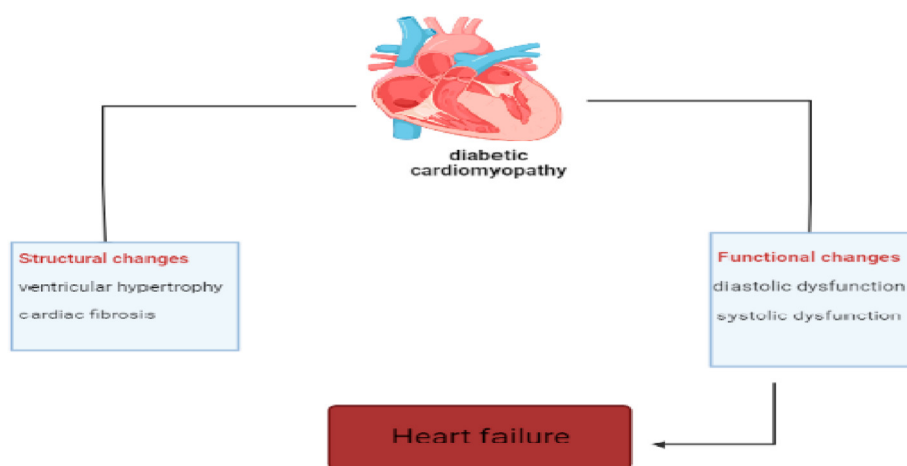**Fig. 1.** Factors involved in diabetic cardiomyopathy.

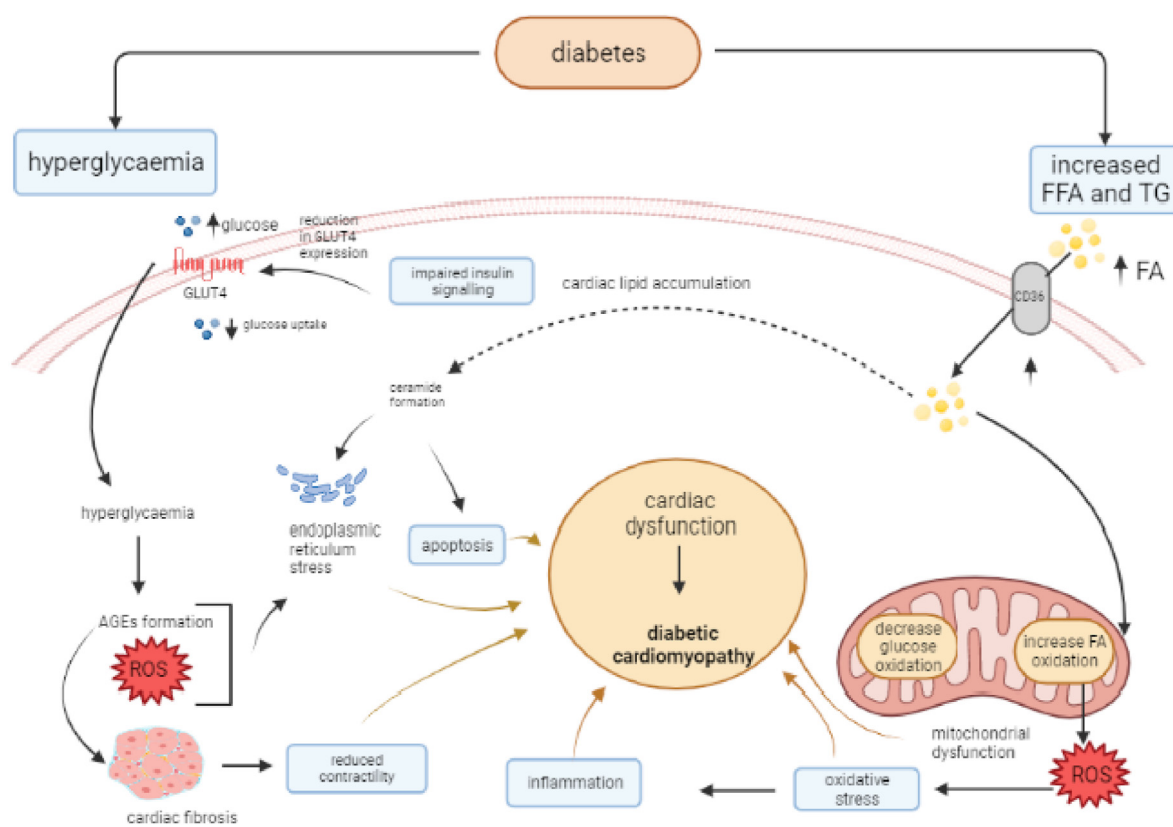Fig. 2. Consequences of diabetic cardiomyopathy.

Fig. 3. The mechanism of diabetic cardiomyopathy.

starts myofibrillar contraction (Dannenberg et al., 2021) (Cheng et al., 2019). In cardiac relaxation, Ca^{2+} is again redirected to the SR, while the sarcolemma Na+/Ca^{2+} exchanger and the plasma membrane Ca^{2+} pump out the remaining Ca^{2+} in the cardiomyocytes (Jia et al., 2018). The amount of Ca^{2+} entering the cytoplasm and the rate at which Ca^{2+} is withdrawn from the cytoplasm are two important factors determining the intensity, rate and span of contraction of myocytes. Any abnormalities in the handling of calcium can lead to alterations in cardiac function (Lou et al., n.d.).

In diabetic cardiomyopathy, a prolonged diastolic relaxation time is observed, owing to an increase in action potential due to impaired Ca^{2+} handling by the transporters. Animal studies have revealed the following differences in type 1 and type 2 diabetes rat models: extension of

intracellular Ca^{2+} decay, increased intracellular resting Ca^{2+}, delayed Ca^{2+} transients, decreased pumping efficiency of Ca^{2+} by the SR, weakened SR function of the reuptake of Ca^{2+} because of the crosslinking of AGEs to the SR Ca^{2+} ATPase pump, leakage of Ca^{2+} from SR and a decrease in SR Ca^{2+} load (Guzik et al., 2020) (Jia et al., 2018) (Li et al., 2019). The diminished SR capacity is mainly due to a decline in the expression of SR calcium ATPase (SERCA) messenger RNA and protein, accompanied by an excessive increase in the concentration of phospholamban, a protein responsible for decreasing SERCA's affinity towards calcium (Yan et al., 2020). These changes have been attributed to the initiation of cardiac diastolic dysfunction and contractility in cardiomyocytes, as observed in early stages of diabetic cardiomyopathy (Jia et al., 2018).

3.4. Roles of RAAS stimulation

In hyperglycaemia and insulin resistance, both systemic and cardiac tissue RAAS activation is observed, despite the excessive fluid and salt state (Jia et al., 2017). Stimulation of cardiac tissue RAAS increases the levels of angiotensin II and aldosterone and consequently affects cardiomyocytes in various ways. A 3.4-fold greater angiotensin II concentration has been reported in patients with diabetes than in people without diabetes (Lee and Kim, 2017) (Lastra-lastra et al., 2009). Increased production of angiotensin II and aldosterone enhances stimulation of the angiotensin II type 1 receptor and of mineralocorticoid receptor signalling in heart muscle tissue, thus activating an adaptive proinflammatory immune response causing inflammation and oxidative stress, increased cytokine expression, and leukocyte adhesion and infiltration of macrophages (Jia et al., 2017) (Grubić Rotkvić et al., 2021). Together, these responses further contribute to the activation of various profibrotic and growth signalling pathways, and ultimately result in the fibrosis of cardiomyocytes, diastolic dysfunction and sometimes even heart failure (Jia et al., 2017).

Moreover, abnormal activation of RAAS due to hyperglycaemia has been associated with an increase in arterial pressure and vascular resistance. In addition, inappropriate activation of mineralocorticoid receptor signalling and elevated angiotensin II have been suggested to activate the mammalian target of rapamycin-S6 kinase 1 signal transduction pathway and consequently further facilitate resistance to insulin (Lee and Kim, 2017) (Jia et al., 2017).

3.5. Role of inflammation

ROS elevation has been observed in DM and is considered to contribute to DM, an inflammatory disorder (Ritchie and Abel, 2020). Increased levels of ROS result in elevations in inflammatory cytokines and vice versa; this cycle of damaging induction of ROS and cytokines continues and creates highly pro-inflammatory conditions in the body (Tang et al., 2022) (Alonso et al., 2018). The presence of elevated chemokines, cytokines such as IL-6, IL-1β, IL-18, TGF-β1 and TNF-α, immune cells, macrophage and leukocyte infiltration, vascular cell adhesion molecule 1 (VCAM-1) and cell adhesion molecules 1 (CAM-1) has been confirmed in the myocardial interstitium of a patients with diabetes, thus suggesting the existence of chronic inflammation (Hu et al., 2017) (Kanamori et al., 2020) (Bugger and Abel, 2014). These inflammatory conditions activate fibroblasts in response to the secretion of inflammatory mediators and result in fibrosis, thus causing stiffening of the cardiac wall and diminished contractility (Ramesh et al., 2022) (Bajpai and Tilley, 2018).

3.6. Roles of mitochondrial dysfunction

Mitochondria provide energy (ATP) to the heart and have an important role in myocardium contraction. Furthermore, mitochondria have essential roles in numerous pathophysiological and physiological functions, such as the regulation of apoptosis, maintenance of Ca^{2+} levels in cells, modulation of cellular signalling pathways, thermo-regulation and maintenance of mitochondrial potassium (K+)-ATP channels (Joshi et al., 2013).

Under normal conditions, 90% of ATP for the myocardium is produced through mitochondrial oxidative phosphorylation (Jia et al., 2018). In the diabetic myocardium, circulating free fatty acids (FFAs) are elevated because of increased lipolysis in adipose tissue and insulin resistance leading to a shift in utilisation from glucose to FFAs, which undergo oxidation for the generation of ATP (Sivasankar et al., 2018) (El Hadi et al., 2019) (Jia et al., 2018). This shift impairs normal oxidative phosphorylation and induces oxidative stress (Jia et al., 2018). Under diabetic conditions, the normal ROS neutralising capacity of the heart is diminished, thus resulting in rapid ROS build-up. ROS alone can perturb the normal dynamics of the mitochondria, thereby causing mitochondrial

fragmentation and affecting mitochondrial function (Ritchie and Abel, 2020). Furthermore, hyperglycaemia is an important factor causing defects in myocardial mitochondria, such as decreased mitochondrial number and swelling of the mitochondria (Joshi et al., 2013).

3.7. Roles of lipotoxicity

Lipotoxicity is an accumulation of excessive fat resulting in alterations in various metabolic pathways and ultimately causing destructive effects in peripheral organs and adipose tissue. Lipotoxicity is a major cause of insulin resistance and impaired function of beta cells in the pancreas (Dilek and Havva, 2017). The main reason for excessive FFAs in diabetes is the impaired action of insulin on the adipose tissue and liver (Ritchie and Abel, 2020). In the heart, lipotoxicity arises because of excessive uptake of the elevated FFAs, thus exceeding the normal capacity for storage in the form of lipid droplets and oxidation, and leading to various cardiac-associated complications including cardiomyopathy (Nakamura and Sadoshima, 2020). This abnormal accumulation of FFAs in the heart is mainly due to the reciprocal alignment of cluster of differentiation 36 (CD36), which is responsible for uptake of fatty acids, and glucose transporter type 4 (GLUT 4), which aids in glucose uptake in the heart. This phenomenon also explains the preferential substrate shift from glucose to fatty acids for the generation of ATP in the mitochondria (Ritchie and Abel, 2020) (Quinaglia et al., 2019). Lipotoxicity further impairs the normal physiological process of autophagy and the insulin signalling pathway in the heart, and consequently results in changes in structure and morphology, and diminished myocardial function. These abnormalities enable oxygen within the myocardium and decrease the efficacy at which muscle fibres respond to electrical stimuli (Lee and Kim, 2017) (Granéli, 2018).

Some FFAs undergo non-oxidative processes and form intermediates, such as ceramides and diacylglycerol (DAG), that further exhibit lipotoxic effects (Ritchie et al., 2017). These lipid metabolites promote diabetic cardiomyopathy by affecting insulin signalling pathways. DAG impairs glucose metabolism by acting on protein kinase C, thus attenuating insulin metabolic signalling and the production of nitric oxide (Jia et al., 2017). Ceramides, which are composed of fatty acids and sphingosine, directly activate atypical PKCs, which then undergo phosphorylation; consequently, metabolic Akt insulin signalling is blocked, and GLUT4 translocation is attenuated (Jia et al., 2018) (Jia et al., 2017). In addition, these toxic substrates affect normal cellular processes and result in cellular damage, apoptosis and mitochondrial dysfunction, which gradually progresses to myocardial fibrosis and contractile dysfunction (Lee and Kim, 2017).

3.8. Roles of the hexosamine biosynthetic pathway

Under normal conditions, most glucose metabolism in the heart occurs through mitochondrial oxidation, glycolysis, glycogen synthesis and the pentose phosphate pathway. HBP is relatively a minor pathway through which glucose is metabolised in the heart; less than 5% of glucose is metabolised through this pathway (Ritchie and Abel, 2020). However, in hyperglycaemia, glucose metabolism through this pathway increases, thus elevating UDP-N-acetylglucosamine, an end product of this pathway, which plays an essential role in post-translational modification of the proteins present in the heart through O-GlcNAcylation (Zamora and Villena, 2019). Increased HBP is often considered a defensive mechanism in response to ischaemia or reperfusion, which prevents the cytosolic entry of calcium and decreases calcium overload and oxidative stress (Ducheix et al., 2018). In diabetes, long-term activation of HBP has detrimental effects on the heart. The most prominent effects include diminished mitochondrial function and energy production, impairment of insulin metabolic signalling, cardiomyocyte apoptosis, alterations in myocardial excitation-contraction coupling, and cardiac relaxation leading to cardiac dysfunction and sometimes even heart failure (Jia et al., 2018).

3.9. Roles of endoplasmic reticulum stress

The endoplasmic reticulum is the central organelle responsible for calcium homeostasis, lipid synthesis, protein folding and maturation. It also is the site of translocation of most secreted and integral membrane proteins in eukaryotic cells (Xu et al., 2012).

The function of the cardiac endoplasmic reticulum is impaired by lipotoxicity, oxidative stress, inflammation and the accumulation of misfolded proteins, thus resulting in endoplasmic reticulum stress and the unfolded protein response. Consequently, cellular protein production and removal of damaged or misfolded proteins is hindered, thus eventually leading to cell apoptosis (Jia et al., 2018). An increase in cardiomyocyte apoptosis contributes to the development of diabetic cardiomyopathy; apoptosis in the myocardium has been found to be 85 times greater in diabetic than non-diabetic hearts (Jia et al., 2018).

In addition, endoplasmic reticulum stress promotes the instability in the membrane of the SR, thus causing an imbalance in Ca^{2+} release from the SR into the cytosol, along with a decline in the action of calcium pumps in the SR. These events hinder the diastolic relaxation of cardiomyocytes and lead to a prolonged diastolic relaxation time, which marks the initial phase of diastolic dysfunction (Jia et al., 2015).

4. Involvement of genetics in diabetic cardiomyopathy

Abnormalities in cardiac gene regulation, particularly miRNA and epigenetic mechanisms, have been found to regulate the diabetic heart phenotype in a preclinical model (Mittal et al., 2021). Several small non-coding RNA genes have been implicated in the aetiology of a variety of disorders, potentially including diabetic cardiomyopathy (Evangelista et al., 2019). Several critical roles of these non-coding RNA in diabetic cardiomyopathy are discussed below.

4.1. Roles of miRNAs

These RNAs are extremely highly conserved and belong to a family of small non-coding RNA genes. They are single-stranded, and between 20 and 22 nucleotides in length. The primary function of these RNAs is to suppress gene expression by binding target mRNAs and causing transcript degradation or blocking translation (Zhang et al., 2019). These microRNAs are found in abundance in different types of cardiac cells, such as cardiomyocytes, endothelial cells and fibroblasts (Das et al., 2018). Evidence has suggested that miRNAs contribute to the regulation of cardiac hypertrophy, oxidative stress, myocardial fibrosis, apoptosis, cardiac electrical remodelling, mitochondrial dysfunction, epigenetic changes and other pathophysiological changes. These modifications are key factors in the pathogenesis of diabetic cardiomyopathy (Zhang et al., 2019). In addition, many miRNA alterations have been discovered in diabetic versus non-diabetic mouse heart tissues. Upregulation of 14 miRNAs (miR-518d, miR-500, miR-487a, miR-431, miR-371, miR-362, miR-341, miR-324-5p, miR-299-5p, miR-203, miR-187, miR-146b and miR-9-5p) and downregulation of 28 miRNAs (miR-497, miR-483, miR-467, miR-432-5p, miR-422b, miR-370, 369-5p, miR-346, miR-345, miR-335, miR-326, miR-320, miR-297, miR-207, miR-197, miR-146a, miR-133b, miR-133a, miR-122a, miR-93, miR-30d, miR-30a-5p, miR-26a, miR-24, miR-23b, miR-20a, miR-16 and miR-1) have been reported (Huynh et al., 2014). Many of these alterations cause the development of diabetic cardiomyopathy, or their consequences remain to be determined (Ritchie and Abel, 2020).

Several miRNAs have been associated with cardiac hypertrophy and fibrosis. Anti-hypertrophic miRNAs, such as miR-1, miR-133a, miR-373, miR-378, miR-23b, miR-181a and miR-30c, as well as pro-hypertrophic miRNAs, such as miR-208a, miR-195, miR-221 and miR-451, have been implicated in cardiac hypertrophic signalling. Beyond these, miR-150, miR-199a, miR-214, miR-29a, miR-125b and miR-212 have been found to be involved in hypertrophic growth (Guo and Nair, 2017). Myocyte enhancer factor signalling is affected by miR-133a and miR-373.

This pathway is key in the transcriptional regulation of myocardial hypertrophy, as well as the activation of the p300 gene, which leads to cardiac fibrosis (Guo and Nair, 2017). Downregulation of miR15a/b has been discovered in patients with diabetes, and fibrotic signalling of transforming growth factor receptor 1 and connective tissue growth factor (CTGF) have also been found to be involved in myocardial fibrosis (Zhang et al., 2019).

Apoptosis, pyroptosis and autophagy are involved in the progression of diabetic cardiomyopathy, and miRNAs have been demonstrated to have roles in these processes. In diabetes, elevated expression of miR-1,25 miR-30b,26 miR-206,27 miR-144,11 miR-195,23 miR-08a,28 miR-320,29 miR-378,30 miR-483, 3p31 and miR-34a32 has been reported to promote apoptosis in the diabetic heart, along with miR-30c,33 miR-221,34 miR-30a, miR-133a and miR-21235, which have been associated with the regulation of autophagy in the diabetic myocardium (Zhou et al., 2019). Further involvement of microRNAs in diabetic cardiomyopathy is supported by the finding that some microRNAs, such as miR-1, miR-373, miR-378 and miR-133a, are downregulated in diabetes, thus resulting in the development of oxidative stress (Evangelista et al., 2019).

miRNAs have also been associated with alterations in cardiac structure, the inflammatory response, mitochondrial dysfunction, myocardial electrical remodelling, and angiogenic regulation. In a model of diabetes, overexpression of miR-29 has been associated with structural damage to the heart and decreased expression of myeloid cell leukaemia 1, a protein promoting cell survival (Zhang et al., 2019). The production of ATP is affected by increased expression of miR-141, which decreases mitochondrial phosphate transport. The increase in the inflammatory response in the vascular smooth muscle cells in diabetes has been associated with perturbation of the negative regulatory loop involving miR-200 and Zeb1. Furthermore, through negative regulation of its downstream gene IGF2, miR-193, 5p has been found to actively participate in the progression of diabetic cardiomyopathy. The electrical remodelling of diabetic hearts is linked to miR-301a, which is responsible for the regulation of the voltage gated potassium channel Kv4 (Zhang et al., 2019).

Therefore, these findings suggest that up-regulation and down-regulation of specific types of miRNAs influence different molecular mechanisms and signal transduction pathways in the myocardium that are involved in the development of diabetic cardiomyopathy (Evangelista et al., 2019).

4.2. Roles of lncRNAs

Long non-coding RNAs (lncRNAs), are transcripts more than 200 nucleotides long that have roles in a variety of cellular and biological activities. They interact with one or more proteins and initiate multiple molecular mechanisms. They either are linked in their transcription site, where they interact with proteins and consequently regulate gene expression, or function as molecular decoys, which bind specific transcription factors and prevent them from interacting with DNA (Zhang et al., 2019) (Colantoni and Helmer-citterich, 2015). The main biological processes involving lncRNAs include genomic imprinting, nuclear organisation and compartmentalisation, regulation of transcription, nuclear-cytoplasmic trafficking and RNA splicing. Numerous lncRNAs have been implicated in the pathophysiology of many diseases in recent studies (Zhang et al., 2019).

By altering its expression due to hyperglycaemia, the widely expressed lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) has been associated with micro and macrovascular damage. This lncRNA targets serum amyloid antigen 3, a proinflammatory ligand, and induces the expression of TNF-α and IL-6 and the formation of ROS, thereby leading to endothelial dysfunction (De Rosa et al., 2018). Another lncRNA involved in the development of cardiomyopathy is the lncRNA AK081284, whose expression is elevated under high glucose conditions. Overexpression of AK081284 promotes cardiac fibrosis by

inducing the production of transforming growth factor β1 (TGFβ1) and collagen in cardiac fibroblasts (Zhang et al., 2018). The expression of myocardial infraction-associated transcript (MIAT) is elevated in the myocardium in patients with diabetes, where it acts as a competing endogenous RNA that sponges miR-22, 3p, increases the expression of DAPK2 and increases cardiomyocyte apoptosis (Zhou et al., 2017).

4.3. Roles of circRNAs

Competing endogenous RNAs sponge certain miRNAs through complementary base pairing and consequently inhibit the mRNA's translation. These RNAs also regulate the splicing or transcription, and interact with RNA-binding proteins, and hence can alter gene expression (Zhang et al., 2019) (Das et al., 2018).

A major factor contributing to diabetic cardiomyopathy is cardiac fibrosis. The upregulation of circRNA_000203 has been observed in the myocardium in patients with diabetes, and has been linked to increased expression of Col3a1, αSMA and Col1a2 in cardiac fibroblasts. In addition, circRNA_000203 prevents the downstream target moiety of Col1a2 and CTGF by sponging miR-26b 5p and leads to the expression of genes associated with fibrosis in the fibroblasts of the myocardium (Tang et al., 2017) (Wan et al., 2021). circRNA_010567 modulates miR-141 along with its target gene TGF β1, thus mediating the resection of fibrosis-associated protein. The circRNA_010567/miR-141/TGF β1 pathway is an important regulatory pathway that is involved in myocardial fibrosis and leads to the development of diabetic cardiomyopathy (Zhou and Yu, 2017).

5. Roles of epigenetics in diabetic cardiomyopathy

Epigenetics refers to changes in the functions of genes that are inherited without causing any changes in the sequence of nucleotides. It involves modifications in chromatin and DNA that persist across cell division cycles without any changes in the DNA sequence (Singh et al., 2011). Common epigenetic processes include DNA methylation, histone acetylation and RNA-based mechanisms (De Rosa et al., 2018).

5.1. DNA methylation

DNA methylation facilitates gene silencing. The main target molecule of DNA methylation is cytosine residues in CpG dinucleotides (Singh et al., 2011). DNA methylation involves methyl group addition at the 5′ position of cytosine nucleotides, catalysed by the DNA methyltransferases DNMT1, DNMT3a and DNMT3b (Hathaway et al., 2017). The methylation of cytosine molecules in DNA alters the structure of chromatin and decreases the affinity of transcription factors and other proteins involved in translation towards target sequence binding, thereby decreasing transcription (Singh et al., 2011) (Hathaway et al., 2017).

Very little information is available on the roles of epigenetic mechanisms in diabetic cardiomyopathy. However, recent studies have indicated the probable involvement of epigenetics in the progression of diabetic cardiomyopathy (Zheng et al., 2017). DNA methylation partially regulates insulin gene expression, because the demethylation of insulin promoter CpGs is essential for the maturation of β-islet cells. Elevated methylation of the transcriptional co-activator peroxisome proliferator-activated receptor (PPAR)γ co-activator-1 α, an important regulator of mitochondrial signalling pathways, has been observed in the pancreatic islets of patients with type 2 DM, and found to correlate with gene silencing and perturbed oxidative phosphorylation in the mitochondria (Tate et al., 2017). TNF-α increases DNA methyltransferase levels and consequently leads to decreased SERCA activity through hypermethylation of the SERCA2a promoter region, thus affecting calcium handling (Zheng et al., 2017). Undermethylation of the AT1b angiotensin receptor proximal promoter upregulates genes involved in the renin-angiotensin-aldosterone system pathway, thereby suggesting a major role of DNA methylation in cardiac hypertrophy (Bogdarina et al.,

2007). Recent studies have proposed that the oxidative damage induced by ROS in diabetes causes cardiac cell death via p53-dependent activation. This pathway includes the de novo methylation of p53-inducible p21WAF1/CIP1, a gene whose protein product binds and inhibits a variety of cyclin-cyclin dependent kinase complexes, and contributes to the development of diabetic cardiomyopathy (Tate et al., 2017).

5.2. Histone modification

Covalent post-translational histone modifications include acetylation, methylation, phosphorylation, SUMOylation and ubiquitylation. These modifications may alter the structure of chromatin, or recruit histone modifiers and affect the gene expression and function of various tissues (Tate et al., 2017). Histone acetylation is an important epigenetic mechanism for the regulation of gene expression. Two important enzymes that maintain the equilibrium of acetylation of histone molecule are the histone acetyltransferases, which catalyse acetylation and consequently activate gene transcription, and histone deacetylases, which silence genes by removing acetyl groups (Ke et al., 2021).

The activity of histone deacetylase 3 (HDAC3) is markedly enhanced in the hearts of diabetic mice, and the inhibition of these enzymes suppresses the oxidative stress and inflammation induced by diabetes, thus improving cardiac remodelling and ameliorating dysfunction in mice (Xiao et al., 2021). The modification of histones also affects fibroblast differentiation by activating TGF-β-induced pro-fibrotic mechanisms along with ECM-associated protein expression, thereby promoting fibrosis (Tate et al., 2017). Studies have identified HDACs as a factor contributing to cardiac hypertrophy, although substantial evidence remains lacking; notably, the class I HDACs have been recognised to be pro hypertrophic (Ke et al., 2021). In diabetic conditions, chronic hyperglycaemia results in the formation of ROS, epigenetic activation of NF-κB-p65 and histone H3K4 methylation in the vascular endothelial cells of the aorta. These changes together ultimately stimulate the progression of diabetic cardiomyopathy (Deng et al., 2021). HDACs also have roles in the inflammatory processes in diabetes. In vivo studies have revealed increased recruitment of NF-κB and histone acetyltransferases, as well as histone acetylation, at the promoters of genes responsible for inflammation, thus increasing the release of the inflammatory cytokines in diabetic conditions, and indicating an association of HDACs with inflammation and cardiomyopathy (Ke et al., 2021).

6. Emerging approaches in the treatment of diabetic cardiomyopathy

Conventional therapy for diabetes-induced cardiomyopathy includes angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, which effectively decrease the chances of formation of fibrosis in the myocardium and left ventricular stiffness; beta-blockers, which can prevent and often reverse the structural and functional alterations that occur during the progression of cardiomyopathy; and aldosterone antagonists, which prevent vascular damage and minimise myocardial fibrosis (Murtaza et al., 2019) (Arad et al., 2020). For the management of glycaemic control, several anti-hyperglycaemic agents are used, such as sulfonylureas, which enhance the secretion of insulin from the pancreatic beta cells; alpha-glucosidase inhibitors, which slow the assimilation of carbohydrates and diminish postprandial increases in blood glucose levels; and thiazolidinediones, which increase insulin sensitivity in skeletal muscle and adipose tissue (Parim et al., 2018) (Longo et al., 2022).

Apart from these traditional approaches, several new treatment strategies are emphasised for the management of diabetic cardiomyopathy (Table 1). A major factor leading to cardiomyopathy is oxidative stress arising from the production of ROS, which can be a potential target for intervention. The use of better antioxidants, such as MitoQ, and coenzyme Q10 supplementation, may be a promising approach (Marwick et al., 2018). Another promising approach is the development of drugs

Table 1
Newer anti-hyperglycaemic agents and their characteristics (Borghetti et al., 2018), (Mehta et al., 2020), (Li and Zhou, 2020), (Verma et al., 2019).

Drug class	Drug name	Unique identifier	Study	Effect on heart
Glucagon-like peptide-1 agonists	Lexisenatide Exenatide Semaglutide Efpeglenatide Liraglutide	CT01147250 NCT01144338 NCT03914326 NCT03496298 NCT01179048	ELIXA (lexisenatide vs placebo) EXSCEL (exenatide vs placebo) SUSTAIN6 (semaglutide vs placebo) AMPLITUDE-O (efpeglenatide vs placebo) LEADER (liraglutide vs placebo)	Reduction of MACE[a] Improvements in EF[b] and wall motion No signs of effects on heart failure
Dipeptidyl peptidase-4 inhibitors	Sitagliptin Saxagliptin Linagliptin	NCT00790205 NCT01107886 NCT01243424	TECOS (sitagliptin vs placebo) SAVOR-TIMI 53 (saxagliptin vs placebo) CAROLINA (linagliptin vs glimepiride)	Improvement in cardiac function No significant effect on the incidence of heart failure except for saxagliptin, which increases the incidence of heart failure
Sodium-glucose co-transporter-2 inhibitors	Canagliflozin Empagliflozin Dapagliflozin	NCT01032629 NCT02998970 NCT01730534	CARMELINA (canagliflozin vs placebo) EMPA-REG OUTCOME (empagliflozin vs placebo) DECLARE-TIMI 58 (dapagliflozin vs placebo)	Preservation and enhancement of cardiomyocyte integrity Improvement in diastolic function Regulation of mitochondrial function Beneficial effects on heart failure incidence

[a] MACE = major adverse cardiac events.
[b] EF = ejection fraction.

targeting AGEs. Some drugs, such as benfotiamin, aminoguanidine, ala-gebrium (ALT-711), ALT-946 and tenilsetam, have been developed to restrict the glycation pathway. Some of these drugs are used in preclinical settings, whereas others have been approved for use in humans (Nenna et al., 2015). Gene therapy is a recent development that may potentially provide a reliable therapeutic approach by modulating the cardiac-specific genes and their expression. The main mechanism in-volves either up- or down-regulation of the primary genes involved in the development of cardiomyopathy. Inhibition of the E3 ubiquitin ligase mitsugumin 3 and cardiomyocyte-specific deletion of FoxO1 have shown positive responses in a preclinical model and potential for use in future approaches (Borghetti et al., 2018). miRNAs are involved in the patho-logical process of diabetic cardiomyopathy, and thus may serve as novel targets for therapeutic interventions. miRNA replacement therapy is one such approach in development, in which a synthetic miRNA is used to mimic an endogenous miRNA to perform the same biological function. However, many challenges in delivery and stability remain to be over-come in this approach (Ghosh and Katare, 2018). Development of ncRNA (miRNA and lncRNA) inhibitors or mimics involved in cardiac fibrosis may serve as ideal targets (Tao et al., 2018).

To maintain mitochondrial function, activation of sirtuins by increasing the $NAD^+/NADH$ ratio in diabetic cardiomyopathy has also been proposed as a therapeutic option. Metabolic flexibility may be restored with agents such as trimetazidine and ranolazine, which prevent the oxidation of fatty acids. This approach can help restore substrate utilisation by maintaining the balance between fatty acid utilisation and glucose metabolism (Gollmer et al., 2019).

7. Herbal medicines as emerging therapies for diabetic cardiomyopathy

Plants have been used since ancient times for the treatment and management of several diseases, including diabetes. Many studies have been conducted on various plants that have been shown to be beneficial in the management and prevention of diabetic cardiomyopathy. Magnolia herbal medicine from China has been studied extensively for its anti-diabetic properties, and its extract has been found to significantly decrease ventricular wall thickness and attenuate cardiac hypertrophy. Furthermore, it has the potential to decrease inflammation, lipid accu-mulation in the heart and oxidative damage, thereby decreasing cardiac structural changes (Zhao et al., 2016). Resveratrol, a plant constituent found in grapes, blueberries, raspberries, mulberries and peanuts, has shown promise in the management of diabetic complications, through

preventing cardiomyocyte apoptosis by inhibiting ROS production from NADPH and improving the antioxidant capacity in the diabetic heart (Huang et al., 2020). Taxifolin is a flavonoid obtained from *Pseudotsuga taxifolia* (Columbian fir), which has antioxidant potential. A study on the effects of taxifolia on diabetic cardiomyopathy has revealed its ability to inhibit apoptosis and restore the membrane potential of mitochondria. It also decreases angiotensin II in the myocardium and attenuates oxidative stress, and therefore is a potential candidate for the treatment of car-diomyopathy (Sun et al., 2014). Astragalus polysaccharides obtained from *Astragalus membranaceus* have shown potential to prevent and manage diabetic cardiomyopathy by improving cardiac function. This treatment also inhibits the deposition of collagen in the myocardium, thereby decreasing myocardial wall thickening; it can also restore normal glucose metabolism by facilitating the GLUT-4 gene expression in the myocardium (Tian et al., 2017). Shengmai prepared from ginseng, a widely used Chinese herb, significantly ameliorates fibrosis and hyper-trophy in diabetic hearts, and enhances cardiac function. It can also facilitate the restoration of mitochondrial structure and function by ameliorating mitochondrial metabolic abnormalities due to lipotoxicity (Tian et al., 2018). Curcumin phytoconstituents of *Curcuma longa*, commonly known as turmeric, have been used extensively because of their antioxidant properties. This treatment has antifibrotic ability and enhances left ventricular function. Moreover, it has been used in the management of oxidative stress and found to efficiently decrease inflammation and cardiomyocyte apoptosis. Its overall effects directly enhance and improve cardiac function in diabetes (Tian et al., 2017).

8. Conclusions

Diabetes is a common phenomenon worldwide, and cardiovascular complications have a major role in mortality and morbidity. Diabetic cardiomyopathy, the most prominent cardiovascular complication, re-quires special attention. Although the precise mechanism has not been established for diabetic cardiomyopathy, available research has provided insights into the roles of many factors involved. These factors may serve as target molecules for the development of mechanism-specific therapy for diabetic cardiomyopathy.

Many prospects can be evaluated and researched for better under-standing of the complication. Target-specific treatments can decrease heart failure in diabetes. Many therapeutic targets have been identified and shown promise for the treatment of diabetic cardiomyopathy. Gene therapy and therapies targeting genetic aspects of the disease may be beneficial and potentially more potent than current therapies. Herbal

remedies also have a broad treatment scope, because many plants and their extracts have demonstrated therapeutic potential in counteracting the pathological factors involved in the complication. However, much more in-depth knowledge and research remain needed for the development of favourable treatments, and many obstacles and difficulties must be overcome to develop promising therapies in the future.

CRediT authorship contribution statement

Urvashi Sharma: Conceptualization, Writing – original draft. **Manodeep Chakraborty:** Conceptualization. **Devid Chutia:** Writing – original draft. **Nihar Ranjan Bhuyan:** Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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