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Current understanding of structural and molecular changes in diabetic cardiomyopathy

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ABSTRACT

Diabetic Mellitus has been characterized as the most prevalent disease throughout the globe associated with the serious morbidity and mortality of vital organs. Cardiomyopathy is the major leading complication of diabetes and within this, myocardial dysfunction or failure is the leading cause of the emergency hospital admission. The review is aimed to comprehend the perspectives associated with diabetes-induced cardiovascular complications. The data was collected from several electronic databases such as Google Scholar, Science Direct, ACS publication, PubMed, Springer, etc. using the keywords such as diabetes and its associated complication, the prevalence of diabetes, the anatomical and physiological mechanism of diabetes-induced cardiomyopathy, the molecular mechanism of diabetes-induced cardiomyopathy, oxidative stress, and inflammatory stress, etc. The collected scientific data was screened by different experts based on the inclusion and exclusion criteria of the study. This review findings revealed that diabetes is associated with inefficient substrate utilization, inability to increase glucose metabolism and advanced glycation end products within the diabetic heart resulting in mitochondrial uncoupling, glucotoxicity, lipotoxicity, and initially subclinical cardiac dysfunction and finally in overt heart failure. Furthermore, several factors such as hypertension, overexpression of renin angiotensin system, hypertrophic obesity, etc. have been seen as majorly associated with cardiomyopathy. The molecular examination showed biochemical disability and generation of the varieties of free radicals and inflammatory cytokines and becomes are the substantial causes of cardiomyopathy. This review provides a better understanding of the involved pathophysiology and offers an open platform for discussing and targeting therapy in alleviating diabetes-induced early heart failure or cardiomyopathy.

1. Introduction

A significant public health issue that affects the entire world's population is diabetes mellitus. The steady and silent impact of diabetes mellitus (DM) in the development of functional cardiac disorder is well evident. Hyperglycemia and insulin resistance (IR) are two features of type 2 diabetes (T2DM), a metabolic condition that is chronic and increases the risk of heart failure (HF) [1]. Even in the absence of myocardial ischemic or microvascular atherosclerotic disease, long-term diabetes causes structural and functional changes in the myocardium that cause HF to develop and progress. These changes are a direct result of abnormal myocardial metabolism and IR [2]. In addition to increasing the risk of HF hospitalization, all-cause mortality, and CV mortality, the presence of diabetes with HF is a poor prognostic indicator. For instance, epidemiologic studies showed that individuals with HF and diabetes had a 50–90 % increased risk of CV mortality, regardless of the HF phenotype [3]. Many studies reported the risk of HF due to DM independent of hypertension (HTN), coronary heart disease (CHD), and valvular heart disease (VHD) [4,5]. The idea of diabetic cardiomyopathy (DCM) was first proposed by Rubler et al after post-mortem studies in diabetic

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patients with cardiac failure. They excluded alcohol, hypertension, coronary and structural heart disease as possible etiologies and considered only DM as the etiologic factor [2]. Moreover, a relative increase in left ventricular (LV) thickness, LV mass, and other related structural abnormalities has been also observed in the diabetic heart that develops LV dysfunction [6]. These changes are also accompanied due to microvascular modifications followed by myocardial fibrosis and remodeling in the extracellular matrix [7]. Thus, in-depth understanding of molecular changes involved in pathophysiological alterations must be looked at for managing the potential loss of left ventricular dysfunction in a patient with DM.

2. Global burden

The Framingham Heart Study reported an increased incidence of HF in diabetic patients in comparison to the age-matched population independent of other concomitant diseases like obesity, hypertension, dyslipidemia, and coronary heart disease [8]. International diabetic federation reported that 463 million people are currently suffering from DM and by 2045, the number of diabetic cases will rise to more than 700 million. However, almost 232 million cases of DM are currently undiagnosed. Moreover, 79 % of the total diabetic population is living in low- and middle-income countries, where the prevalence is alarming because of low socioeconomic status [9]. According to a recent temporal analysis of a sizable UK cohort, the prevalence of DM in HF has significantly increased (18 % in the early 2000s against 26 % in recent years) [10].

3. Diabetic cardiomyopathy

Among cardiovascular diseases, DCM is the utmost cause of mortality and debility among the diabetic population other than cardiovascular diseases (CVDs) such as myocardial angina, myocardial infarction (MI), stroke, arterial disorder, and congestive HF [11]. Hypertension, hypercholesterolemia, persistent hyperglycemia, and other risk factors like a sedentary lifestyle have been observed to be significantly involved in raising the risk of cardiovascular complications in diabetics [12]. Data from both clinical and experimental studies represents that DCM is a major complication that contributes to HF other than atherosclerosis, high blood pressure, and other related complications [13]. DCM consists of earlier short-term, physiological adaptation to metabolic changes, and thereafter degenerative changes for which the myocardium has only limited capacity to heal [12,14]. There are many factors (Fig. 1) such as prescription drugs, metabolic characteristics, and lipid status that may also influence the progression of DCM [15]. Therefore, the treatment during the early stages of DM can potentially delay or obstruct the progression of other consequences [16]. The different stages of DCM have been mentioned in Table 1.

4. Structural changes in diabetic cardiomyopathy

4.1. Microvascular dysfunction

Coronary microcirculation regulates the coronary blood flow and maintains the oxygen demand in cardiac tissue. Microvascular dysfunction especially in the coronary artery causes impaired

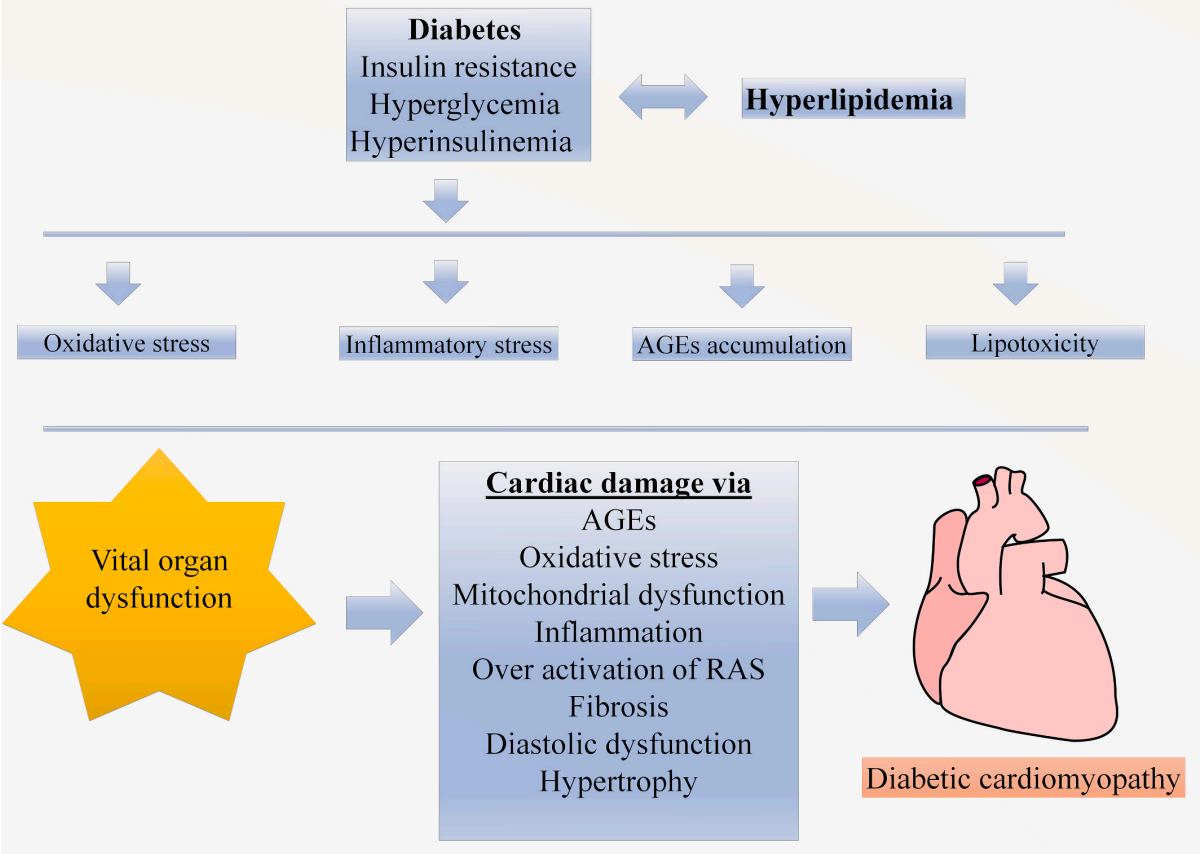

Fig. 1. Physiological and biochemical changes in diabetic cardiomyopathy.

Table 1
Stages of diabetic cardiomyopathy.

Stages	Molecular changes	Functional changes	Structural changes	Reference
Early stage	• Depletion of GLUT4 • Increased FFA • L-carnitine deficiency • Imbalance in Ca^{2+} homeostasis • Insulin resistance	No overt functional abnormalities or possible overt diastolic dysfunction or changes in ejection fraction	Normal LV size with no sign of hypertrophy	[17–19]
Middle stage	• Increased AT II • Reduced IGF-I • Increased TGFβ1 • Mild CAN	Abnormal diastolic dysfunction and normal or slightly decreased ejection fraction	Slightly increased LV mass, wall thickness, and evidence of hypertrophy	[20–22]
Last stage	• Microvascular changes • Hypertension • CAD • Severe CAN	Abnormal diastolic dysfunction and ejection fraction	Significantly increased LV size, wall thickness, and well evidence of hypertrophy	[21–23]

GLUT-4: Glucose transporter-4, FFA: Free Fatty Acid, ATII: Angiotensin-II, IGF—I: Insulin-Like Growth Factor-1, TGF-β: Tissue Growth Factor, CAN: Cardiovascular Autonomic Neuropathy, CAD-Coronary Artery Disease, LV-Left Ventricle.

myocardial reserve volume and involves functional alteration of the myocardium [24]. Persistent hyperglycemia causes increased advanced glycation end products (AGEs) production concurrent to decreased production of NO in endothelial cells of coronary artery and this contributes to the development of DCM and subsequent CVD-related untoward events [25].

4.2. Interstitial fibrosis

DCM is characterized by interstitial and perivascular fibrosis. Cardiac biopsy showed that significant increase in collagen deposition in between intramural vessels and in an around myofibers in heart of diabetic patients [26]. A major elevation in collagen type III was reported after endomyocardial biopsies of the T2DM cases without any major CAD and hypertension [27]. This leads to myocardial fibrosis and cardio dynamic changes in the diabetic heart. The pathophysiology of the myocardial fibrosis of a diabetic heart includes a raised TGFβ1 receptor II, plasma MMP1, TIMP metallopeptidase inhibitor 1 (TIMP1), amino-terminal pro-peptide of type I and type III procollagen [28].

4.3. Cell death

Necrosis and apoptotic cell death are observed in biopsies of diabetic myocardium having concurrent HF [29]. Activated myocardial apoptosis due to leptin deficiency plays a major role in causing cell death through Rac1 mediated raised Reduced nicotinamide adenine dinucleotide phosphate (NADPH) and mitochondrial-derived ROS in diabetic myocardium [30]. Activation of the RAAS is linked with elevated oxidative stress, programmed cell death, and necrosis in myocardial and endothelial cells of cardiomyocytes in diabetic patients and also in end-stage HF. This represents another potential mechanism for cell death [31].

5. Physiological alterations in diabetic cardiomyopathy

5.1. Autonomic neuropathy

Chronic DM causes CAN that ultimately affects heart rate control, vascular hemodynamics, and cardiac morphology as well. The over-stimulation of the sympathetic nervous system and suppression of parasympathetic nervous system activity is also well evident in DCM and other cardiac disorders [32].

5.2. Left ventricular hypertrophy

LV hypertrophy is characterized by an increased myocardial mass of the left ventricle, a major risk factor associated with HF that downs myocardial performance [33]. In the Framingham study, a significant increase in LV wall thickness was observed only in women with DM [34]. In a multiethnic subject with T2DM, the chances of increased LV mass are much greater after adjusting different covariates even hypertension [35]. In fact, in this same population, increased LV mass was observed only in diabetic cases, but not in cases with altered fasting blood glucose (BG) or impaired tolerance to glucose [36]. This indicates that the changes in cardiac geometry develop only after long-term steady-state hyperglycemia with or without obesity.

5.3. Systolic dysfunction

Systolic dysfunction develops in a later stage and usually starts after diastolic dysfunction. Compromised systolic dysfunction is often not detected using standard 2-dimensional echocardiography techniques. But, tissue Doppler strain analysis and peak systolic velocity calculation, and subtle systolic function have been described in around 24 % of randomly selected cases having DM, excluding subjects' cases having CAD or LVH [37].

5.4. Diastolic dysfunction

DCM in humans is identified by diastolic dysfunction. The tissue Doppler analysis reveals that 40–75 % of cases have diastolic dysfunction in both types of diabetic cases, independent of coronary artery disease. Cardiographic markers for diastolic dysfunction like E/E' and E/A ratios were abnormal in T2DM cases [38]. Moreover, diastolic dysfunctions have an interrelation with raised cardiac triglyceride levels concurrent with impaired Ca^{2+} ion reuptake [39].

5.5. Impaired contractile reserve

The contractile reserve is the most independent index and is calculated as the variation between myocardial contractility at rest and at stress either by exercise or by inotropic agents such as dobutamine [40]. Recent studies about DCM show multiple mechanisms that cause diastolic and systolic impairment with concurrent reduced contractile reserve. These mechanisms include accumulation of AGEs [41], adipokines [42], impairment of myocardial insulin signaling [43], altered calcium homeostasis [44], and lipotoxicity [45] that play a major role in developing reduced contractile reserve in DCM. Fig. 1 depicted the biochemical and structural changes in diabetic cardiomyopathy.

6. Molecular alterations underlying diabetic cardiomyopathy

Fig. 2 represents potential molecular abnormalities in the development of diabetic cardiomyopathy. We will present summaries of the molecular pathways that have been postulated to contribute to the development of diabetic cardiomyopathy in the following subsections, with an emphasis on both established and novel or developing mechanisms (summarised in Table 2). Many of these topics demand a thorough, impartial assessment. Due to space restrictions, we want to give

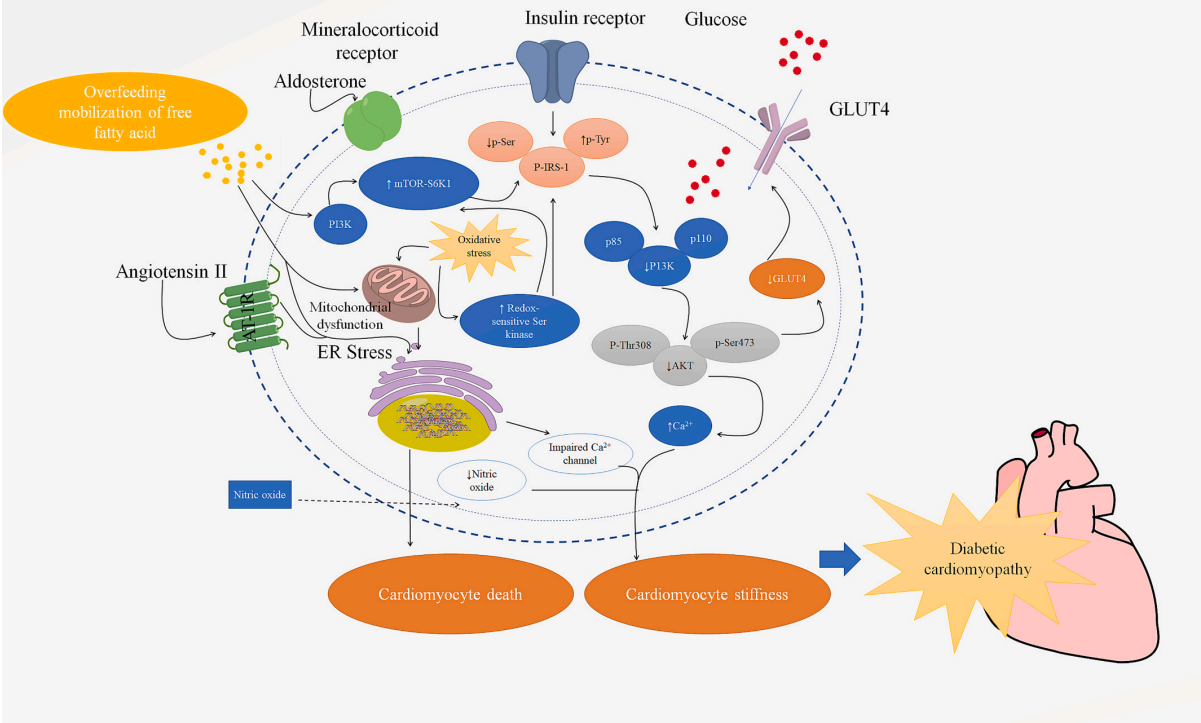

Fig. 2. Potential molecular abnormalities in the development of diabetic cardiomyopathy.

the reader an overview of the intricate pathophysiology of diabetic cardiomyopathy as a starting point for future in-depth investigation. In addition, though they are discussed separately, it is significant to realize that many of these mechanisms are closely related. The legend accompanying Fig. 2 includes examples of these interactions.

6.1. Myocardial lipotoxicity

T2DM is often associated with obesity which leads to myocardial lipotoxicity followed by cell death [46]. Regan and coworkers identified lipofuscin deposits, a brown lipid containing pigment granules in transmural LV biopsies obtained from patients with T2DM concurrent to raised myocardial triglycerides (TGs) and cholesterol [47]. Similarly, the staining of cardiac sections of a failing heart independent of ischemia with oil red-o staining showed a raised lipid deposition provoked by persistent hyperglycemia [45]. Hyperglycemia, obesity, insulin resistance, and impaired glucose tolerance (IGT) are related to raising intramyocardial lipids, independent of circulating triglycerides level [48]. However, raised myocardial triglycerides and their deposition is linked to diastolic but not systolic dysfunction [39]. Lipid-induced cell death might be an important contributor to developing DCM via activating ceramide biosynthesis [49]. In addition to this, alteration in the phospholipid makeup of the endoplasmic reticulum (ER) membrane has also been reported to cause swelling and trauma to ER [50,51].

6.2. Oxidative and nitrosative stress

Oxidative stress acts as a major contributor to the progression of DCM [52]. The mechanism behind the generation of ROS in the myocardium is still controversial probably due to lipid overload and vice versa.

Cellular sources of ROS and/or RNS generation within the heart include cardiac myocytes, endothelial cells, and neutrophils. A major part of cellular ROS is produced in mitochondria and enzymatic systems that further generate the ROS in the cytosol mediated by NADPH oxidase [53]. These ROS and/or RNS initiate cellular damage through several mechanisms like oxidation, interference with NO, and modulation of detrimental intracellular signaling pathways such as increased expression of myocardial myosin heavy chain gene expression. This leads to cardiac dysfunction by direct damage to proteins and deoxyribonucleic acid (DNA), as well as by inducing apoptosis that led to cellular death [54]. Moreover, loss of the antioxidant defense system could also stimulate several other responses including activation of matrix metalloproteinase (MMP) to alter the architecture of the extracellular matrix and initiate cardiomyocyte hypertrophy that triggers ventricular remodeling [55]. Furthermore, Nrf2 (leucine zipper protein) activates the expression of hemoxygenase, an antioxidant protein in response to oxidative stress. However, persistent hyperglycemia and insulin resistance suppress Nrf2 expression and reduce their activity via Erk 1/2-mediated pathway. This further promotes oxidative stress and indirectly develops lipid accumulation, inflammation, fibrosis, and associated cardiac dysfunction in DCM [56].

6.3. Calcium signaling and ryanodine receptor

The calcium signaling system is the major pathway involved in activating the contractile system of cardiac myocytes through the ryanodine receptor (RyR), sarcoplasmic reticulum, and eNOS [57]. Moreover, RyRs play a major role in the cyclic rise and fall in intracellular Ca^{2+} ion of Ca^{2+} ions from the sarcoplasmic reticulum (SR) required for normal cardiac functions. DCM directly affects the ryanodine receptor complex and causes both reduction in ryanodine sensitivity to Ca^{2+} as well as a reduction in receptor volume that causes impaired myocardial contractility in DCM [33,58]. Apart from this, extremely important myocyte-specific enhancer factor 2C (MEF2C) downregulation is associated with the compromised activity of both sarcoplasmic endoplasmic

Table 2
Potential molecular abnormalities in the development of diabetic cardiomyopathy.

Molecular abnormalities	Consequence in the pathogenesis of diabetic Cardiomyopathy	References
Hyperglycaemia	Increased AGEs and ROS synthesis, Deactivation of NOS, myocardial collagen accumulation with fibrosis.	[13,22,121]
Myocardial lipotoxicity	Altered glycolysis, pyruvate oxidation, lactate causes apoptosis, perturbation of cardiac tissue bioenergetics with contraction/relaxation coupling.	[46,122]
PKC	Stimulation of DAG/PKC signal transduction pathway causes decreased tissue blood flow, raised vascular permeability, changes in neovascularization and increased extracellular matrix deposition.	[123,124]
RAAS	Cardiomyocyte hypertrophy and apoptosis	[63,125]
Aldosterone activation	Myofibroblast growth with interstitial and focal perivascular accumulation of collagen.	[64,126,127]
HIF-1/VEGF	Up-regulation of HIF-1α through hypoxia/ROS stimulates angiopoietin, PGF, PDGF-β and VEGF. In diabetes, VEGF and its receptors, VEGF-R1 and VEGF-R2, reduced significantly, leads impairment of angiogenesis.	[128,129]
Endothelial dysfunction	Altered endothelial NO synthesis with raised vasoconstrictor PGs, glycated proteins, endothelium adhesion molecules and platelet and vascular growth factors enhance vasomotor tone and vascular permeability and limit growth and remodeling.	[130–133]
Ca^{2+} ion signaling and Raynodine receptor	Reduction in ryanodine receptor and its sensitivity to Ca^{2+} ion. Reduced MEF2C activity followed by SECRCA2a and NCX-1 downregulation.	[57,59]
Inflammatory cytokines	Activation neutrophils, mast cells, dendritic cells, macrophages, eosinophils, nuclear transcription factor, NFκB regulated proinflammatory cytokines like TNFα, interleukins MCP1, ICAM1, and VCAM1. NLRP-3 regulated inflammation and cellular death via NFκB and TXNIP	[61,62,134]
Autophagy	Reduced PI3K/Akt signaling initiates myocardial insulin resistance and autophagy, AMPK activation inhibits MTOR and activates autophagy, SIRT1/3 downregulation stresses the tissues, and FOXOs activation directly activates the autophagy protein.	[77,135,136]
Altered substrate utilization and mitochondrial bioenergetics	transcriptional repression of GLUT4 by down regulation MEF2C. Activation of transcriptional enzymes via PPARα involved in β oxidation. PDH overexpression suppresses the glucose oxidation and PPAR-α target gene mCPT1 activated lipotoxicity.	[68]
miRNA	miRNA-143, miRNA-181, miRNA-103, miRNA-107 and miRNA-802 regulates systemic glucose metabolism and insulin sensitivity. Dysregulation of the	[80,86,137–139]
Epigenetics	miRNA biogenesis via cardiomyocyte-specific deletion of dicer progresses to cardiomyopathy and HF. miRNA-133 induces fibrosis via modulating CTGF expression. Inheritable modification in gene expression, Imbalance between HATs AND HDACs	[25,99,100]

reticulum Ca^{2+} ATPase2a (SECRCA2a) and well as GLUT4 leading to decreased myocardial functions [59]. Reduced insulin-activated endothelial NO synthase (eNOS) activity and NO production in coronary arteries suppress sarcoplasmic reticulum (SR) Ca^{2+} ion uptake and increase the overload of intracellular Ca^{2+} ions. This results in increased cardiac stiffness and impaired myocardial relaxation in DCM [60].

6.4. Inflammatory cytokines and the innate immune system

Activation of different cells of the innate immune system like neutrophils, mast cells, dendritic cells, macrophages, eosinophils, nuclear transcription factor, NFκB regulated proinflammatory cytokines like tumor necrosis factor α (TNFα), interleukins (IL) 6 and IL8, monocyte chemotactic protein 1 (MCP1), intercellular adhesion molecule 1 (ICAM1), and vascular cell adhesion molecule 1 (VCAM1) contribute to myocardial oxidative stress, remodeling, fibrosis followed by LV dysfunction [61]. Recently, NACHT, LRR, and PYD domains-containing protein 3 (NLRP-3) were reported to be a novel regulator of inflammation and cellular death via NFκB and thioredoxin interacting/inhibiting protein (TXNIP) in DCM. Moreover, activated NFκB also observed to be associated with increased NADP oxidase mediated generation of ROS, peroxynitrite, and superoxide that further increases oxidative stress and decreases ATP synthesis and NO bioavailability and thereby altering cardiac functions in DCM [62].

6.5. Renin angiotensin aldosterone system

In chronic diabetic cases, RAAS gets activated and plays a major role in the pathogenesis of DCM. Evidence suggested the upregulation of proinflammatory angiotensin II receptor 1 (AT2R1) and downregulation of anti-inflammatory AT2R in early DM [63]. Increased plasma aldosterone level and tissue mineralocorticoid receptors (MR) overexpression are linked with insulin resistance, raised BG level, and altered lipid profile (Jia et al., 2017). Studies indicated that inhibition of the aldosterone/MR signaling pathway decreases both morbidity and mortality in diabetic cases with concurrent HF. Enhanced AT2R1 and MR stimulation increases coronary artery endothelial leukocyte/monocyte adhesion, cytokine production, and macrophage infiltration and this results in cardiac remodeling, fibrosis, and diastolic dysfunction in DCM [64].

6.6. Altered substrate utilization and mitochondrial bioenergetics

In the state of persistent hyperglycemia, diabetic myocardium depends almost on the use of FFA for getting ATP and its normal functioning [18]. Many mechanistic approaches are accountable for to shift in substrate utilization. High-fat diet administration showed decreased myocardial GLUT4 levels with alteration in GLUT4 translocation. It causes decreased glycolytic breakdown and glucose oxidation and thus FFA oxidation rates become subsequently increased through the Randle cycle [65,66]. This further activates peroxisome proliferator-activated receptor α (PPARα) signaling pathways followed by transcriptional

enzyme activation involved in β oxidation. Concurrently, pyruvate dehydrogenase (PDH) was also found to be expressed that further suppresses glucose oxidation [67]. Moreover, evidence showed that myocardial lipotoxicity in DCM cases remains associated with activation of the PPAR-α target gene mCPT1, which controls the mitochondrial FA uptake [68]. This is further supported by other studies that suggest the downregulation of mRNA for GLUT4 and MEF2C in the case of HF of diabetic cases in contrast to failing hearts in patients without diabetes [69]. Similar to myocardial ischemia, altered mitochondrial beta-oxidation of fatty acids has been observed in DCM that even lead to cardiac remodeling and decreased cardiac efficiency [70]. The understanding of mitochondrial bioenergetics, remodeling of the mitochondrial proteome, and reduced respiratory capacity is well studied by using ^{31}P NMR spectroscopy, in both types of DM, independent of CAD [71].

6.7. Advanced glycation end products

Chronic hyperglycemia induces glycation of fibrinogen and albumin resulting in the generation of AGEs that further upregulates the expression of AGEs receptors [72]. Through a series of event, it builds oxidative stress and activates the generation of ROS and inflammatory cytokines, and then promote endothelial and myocardial damage [73]. Increased activation of Janus kinase (JAK), mitogen-activated protein kinase (MAPK) pathway, altered isovolumetric relaxation time and diastolic LV diameter is well evident and reported to be interrelated with myocardial stiffness [74]. AGE production and its cross-linking of collagen molecules in myocardial tissues not only further increases the production of ROS but also it led to the loss of cardiac elasticity due to its fibrosis with subsequent reduction of myocardial compliance [75,76].

6.8. Autophagy

Autophagy is a physiological phenomenon in which long-lived proteins, ribosomes, lipids, and even complete cellular organelles are swallowed up by double-membrane structures, that subsequently targets lysosomes for cellular degradation [77]. Controlled and constitutive autophagy plays a key role in maintaining normal cellular structure and function of cardiac tissue [78]. But variation in this pathway leads to cardiac dysfunction and HF, especially during raised, cellular stress [79]. There is strong evidence that insulin signaling is an important controller of myocardial autophagy [80]. A high fructose diet was reported to be associated with the deposition of autophagosomes as demonstrated by increased levels of the autophagic markers microtubule-associated protein 1A/1B-light chain 3 and nucleoporin p62 [81]. The concurrent raised p62 level further increases the chances of turnover for autophagosomes. Phosphatidylinositol 3-kinase (PI3K) Akt signaling that negatively controls autophagy by inhibiting the mammalian target of rapamycin (MTOR) gets suppressed. Reduced PI3K/Akt signaling starts the possibility of myocardial insulin resistance and thus initiates autophagy [82]. There is a raising consensus that initiation of autophagy can either antagonize disease pathogenesis or contribute to the progression of disease depending on the amplitude of the induction [83]. Therefore, it can be speculated that acute autophagy induction (e.g. ischemic heart) might be beneficial otherwise persistent autophagy induction such as in a diabetic heart could be deleterious [84]. Therefore, autophagy activation in type 1 and type 2 diabetic hearts may either increase or decrease, mediated through PI3K/Akt vs AMPK pathways depending on disease severity.

6.9. MicroRNAs

DCM is related to all-around changes in patterns of gene expression associated with microRNAs (miRNAs). These gene expression regulators are endogenous, noncoding, single-strand RNAs with an average length of 22 nucleotides that remains encoded with small, inverted repeats inside the genome. miRNAs regulate gene expression through the repression of translation and by promoting the degradation of target mRNAs. Alteration in these miRNA levels exhibits important roles in the pathogenesis of several diseases including DM and associated complications [80]. Recently updated data showed a part of involvement for miRNA-143, miRNA-181, miRNA-103, miRNA-107 and miRNA-802 in the regulation of systemic metabolism of glucose and sensitivity towards insulin. This implicates miRNAs in the pathogenesis of insulin resistance and T2DM [85,86]. A change in myocardial miRNA content is a recognized mechanism that is linked to alteration in cardiac contractility indices. Dysregulation of the miRNA biogenesis in the heart by cardiomyocyte-specific deletion of dicer leads to rapidly progressive dilated cardiomyopathy and HF globally [87]. Recent studies have also connected with the dysregulation of specific miRNAs in DCM [88]. Around 40 % of miRNA-1 of the total myocardial miRNA pool, has been shown to downregulate Pim-1 (proto-oncogene) due to hyperglycemia and its restoration seems to be effective in the prevention of cardiomyocyte apoptosis, ventricular dilatation, and LV failure [89]. Myocardial expression of miRNA-133 has been augmented in DM that further modulates connective tissue content by regulating connective tissue growth factor (CTGF) expression, suggesting its involvement in fibrosis of diabetic hearts [90,91]. The involvement of specific miRNAs in the regulation of systemic metabolism may contribute to identifying the molecular defects associated to DCM [92,93].

6.10. Epigenetics

Epigenetics is an inheritable modification in gene expression patterns, different from alteration in DNA change. Genetic alteration by histone acetylation regulates gene expression. The histone acetylation-mediated genetic alterations are largely regulated through the functional interplay between histone acetyltransferases (HATs), and histone deacetylases (HDACs), which catalyze histone acetylation and deacetylation [94]. Dysregulation of histone acetylation promotes the development of diseases, and HDAC inhibition serves as a therapeutic option to potentially treat a multitude of diseases like cancer and CVDs [95–98]. There are four classes of HDACs identified, depending on sequence identity and domain organization. Out of this, Class II HDACs (HDAC5, HDAC9) can suppress cardiac hypertrophy, while class I HDACs promotes cardiac hypertrophy [99]. Another well-established epigenetic regulator is the methylation of nuclear DNA. DNA methylation takes place mainly on CpG islands (CGIs) in the 5′ regulatory regions of many genes. Altogether, epigenetic modifications, which have the potential to influence the expression of the entire genome, may represent an under-investigated mechanism, which may potentially add to the pathogenesis of DCM factors, such as oxidative stress [100].

6.11. Potential chemical compounds:

Considering the duration of clinical studies and cost involved, currently many medications have been proposed to move them forward in the drug discovery to manage DCM. Levosimendan, a potent inodilator, has been reported as a classical inotropes that maintain cardiac mitochondrial energy and thus reducing congestion in acute HF with hypertension. Moreover, with its unique pharmacology it is recommended in wide range of cardiac functional abnormalities related to HF, particularly in undergoing cardiac surgery [101]. A phosphodiesterase type 5 inhibitor (PDE5 inhibitor) reported to reduce reduction in HF-associated hospitalization rate among patients of HF with preserved ejection fraction (HFpEF) and combined pre-capillary and post-capillary pulmonary hypertension [102]. Sildenafil, vardenafil and tadalafil are used clinically an undergoing through intensive investigation for DCM management [103]. Trimetazidine, an anti-ischemic agent that selectively inhibits the long-chain enzyme 3-ketoacyl coenzyme A thiolase, particularly in stressed myocardium and shifts energy utilization from free fatty acid oxidation to glucose oxidation [104,105]. Moreover, reported to improve left ventricular ejection fraction (LVEF), exercise

capacity, and cardiovascular events among patients with DCM [106,107]. Istaroxime possesses unique luso-inotropic property thus increases SERCA2a pump activity and inhibit Na^+/K^+ ATPase. This improves both myocardial relaxation and contraction including cardiac indexes without severe adverse cardiac events in DCM cases [108–110]. A second line anti-anginal agent for patients with chronic stable angina, ranolazine, mainly acts by inhibiting the late inward sodium current, and improves Ca^{2+} handling and ameliorates impaired myocardial relaxation and diastolic dysfunction in DCM [111–113]. Ranolazine has been reported to decrease left ventricular end-diastolic pressure (LVEDP) and also improved systolic function and reduced cardiovascular events [114,115]. Coenzyme Q10 reported to increase ATP production and cellular energy and thus have cardiovascular protective effects [116]. Improved left ventricular ejection fraction (LVEF) has been reported in a meta-analysis by coenzyme Q10 A supplementation [117,118]. Elamipretide, another mitochondrial antioxidant, stabilizes cardiolipin. Thus, acts as a mitochondrial ROS scavenger and ameliorates left ventricular diastolic dysfunction (LVDF) [119]. A mitochondria-targeted methylglyoxal scavenger, Elamipretide, also stabilizes cardiolipin and scavenges the mitochondrial ROS. Alagebrium, an AGE crosslink breaker, has been also studied extensively. An RCT conducted among both diabetic and non-diabetic patients with diastolic HF showed that it reduces the left ventricular mass, improved diastolic dysfunction, and improved quality of life [120]. However, more preclinical and clinical studies are needed to address safety and efficacy of these drugs.

7. Conclusion

The diabetes-related cardiac disease develops due to various metabolic, structural, and functional alterations. Recent advancements in the understanding of molecular and functional changes within the heart unfold various management opportunities. However, we explored these multifaceted aspects of triggers that are even progressive, for early detection and preventing further related complications that impose a greater healthcare challenge. Therefore, a greater understanding of interrelated pathologies as well as intracellular signaling pathways of diabetic hearts will benefit in tackling and mitigating diabetic cardiomyopathy via novel therapeutic strategies.

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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.

Data availability

No data was used for the research described in the article.

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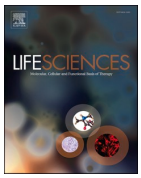

Corrigendum

Corrigendum to "Current understanding of structural and molecular changes in diabetic cardiomyopathy" [Life Sciences 332 (2023) 122087]

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The authors regret that one of the author's name has been wrongly written as Ziad Saeed Almalki, his correct name is Ziyad Saeed Almalki.

The author's name listed in this corrigendum are correct and complete.

The authors would like to apologise for any inconvenience caused.

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