Current advances in the study of diabetic cardiomyopathy: From clinicopathological features to molecular therapeutics (Review)

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Abstract. The incidence of diabetes mellitus has become a major public health concern due to lifestyle alterations. Moreover, the complications associated with diabetes mellitus deeply influence the quality of life of patients. Diabetic cardiomyopathy (DC) is a type of diabetes mellitus complication characterized by functional and structural damage in the myocardium but not accompanied by coronary arterial disease. Currently, diagnosing and preventing DC is still a challenge for physicians due to its atypical symptoms. For this reason, it is necessary to summarize the current knowledge on DC, especially in regards to the underlying molecular mechanisms toward the goal of developing useful diagnostic approaches and effective drugs based on these mechanisms. There exist several review articles which have focused on these points, but there still remains a lot to learn from published studies. In this review, the features, diagnosis and molecular mechanisms of DC are reviewed. Furthermore, potential therapeutic and prophylactic drugs are discussed.

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1. Introduction

Cardiovascular disease has become a major global health issue which is attributed to multiple factors, including diet, smoking, lifestyle and environmental change (1). The sharp increase in the diabetic population has been proposed to be closely associated with the rising prevalence of cardiovascular disease. According to statistics, the number of diabetic patients worldwide has currently increased to 1.8 billion, and has doubled since the year 2000. It is predicted that the global diabetes population will increase from 285 million to 439 million between 2010 and 2030 (2). Compared to non-diabetic individuals of the same age, the risk of heart failure in male and female diabetic patients is increased 2-fold and 5-fold, respectively (3).

Diabetic cardiomyopathy (DC) was firstly proposed by Rubler *et al* (4) in 1972. At that time, four cases of heart failure in patients with diabetic glomerulosclerosis were autopsied but no other causes of heart failure other than diabetes were found. Thus, the concept of DC was proposed. DC is currently defined as an obvious change in myocardial structure and function in diabetic patients, excluding ischemic diseases, hypertension, or other diseases that can induce myocardial damages (5,6).

In a recent review, the correlation between hyperinsulinemia or insulin resistance, cardiac dysfunction and hyperglycemia was discussed (7). The authors also summarized the recent advances in the research on DC, its pathogenesis and the underlying molecular mechanisms, and the promising prophylactic and curative approaches (7). Here, we aimed to summarize the current advances in DC with strong emphasis on the molecular mechanisms.

2. Epidemiology and features of DC

The incidence of DC is not yet clear due to a lack of large data of outcomes from different populations with diabetes mellitus (DM). A higher prevalence rate (40 to 60%) of diastolic dysfunction in type 2 DM (T2DM) patients has been reported in the literature (8). Autopsies have revealed that DC has a number of pathological features, including cardiomyocyte hypertrophy, interstitial fibrosis, periodic-acid-Schiff (PAS)-positive infiltration, thickening of the basal membrane of coronary arterioles, and myocardium microvascular lesions (9-11). The

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structural changes in DC are characterized by a near-normal left ventricular end-diastolic volume, increased left ventricular weight and thickness, cardiac hypertrophy and fibrosis, and fat deposition (12,13). The functional alterations include an impaired diastolic function without obvious decreased systolic function, and a decreased ventricular wall elasticity (14).

3. Diagnosis of DC

Currently, the diagnosis of early DC has not yet made substantial progress, and the mainstream methods for DC diagnosis include imaging methods and serum biomarkers. The pathological changes in early DC include cardiac hypertrophy, fibrosis and lipid deposition. Abnormal cardiac function is characterized by early diastolic dysfunction and late systolic dysfunction. The diagnostic criteria for DC refer to the method of Tarquini *et al* (15), which are mainly as follows: Presence of DM, exclusion of coronary artery disease, valvular or congenital heart disease, exclusion of hypertensive heart disease, exclusion of viral myocarditis by endomyocardial biopsy and left ventricular ejection fraction (LVEF) <50%, left ventricular end-diastolic volume index (LVEDVI) >97 ml/m². For distinguishing these pathological features, the following methods can be employed.

Echocardiography and Doppler imaging. In the early stages of DC, echocardiography can be the prior method for assessing cardiac structural and functional abnormalities in diabetic patients due to its inexpensive and non-invasive advantages (16,17). Tissue Doppler imaging (TDI) measures left ventricular isovolumetric diastolic time, early mitral annular diastolic motion velocity (Ve), late diastolic motion velocity (Va) and the Ve/Va ratio (18). By comparing these data, cardiac diastolic function images can be divided into 2 types: Restricted mitral flow pattern and unrestricted mitral flow pattern. Unrestricted mitral flow patterns include normal, impaired and false normalization (16-18). This technique has high sensitivity and specificity, and is currently considered to be a reliable method for evaluating left ventricular diastolic function in patients with coronary heart disease (19,20). Intravenous contrast echocardiography is based on the elevated sonic reflectivity of contrast agents; therefore, the contrast injection can aid in the accurate monitoring of the endocardial borders, and the measuring of ventricular size and ventricular motion. The complement of intra-cardiac echocardiography (ICE) into 2D-echocardiography provides an improved evaluation of left ventricular function (21). A previous study demonstrated that alterations in the contractility, systolic function and microcirculation can be well observed via ICE in T1DM murine models (22).

Speckle tracking echocardiography (STE) is a novel imaging technique for achieving mechanical deformation of the myocardia (23). It uses the images acquired from echocardiography to quantify the inter-pixel distance during the cardiac cycle. Therefore, morphological alterations of myocardial deformation can be detected (23,24). It has been demonstrated that the diabetic microangiopathy in T2DM patients is closely associated with the myocardial deformation through 3D-STE (25). In this regard, ~24% of diabetic patients are diagnosed with systolic functional impairment

by 2D-STE, which cannot be detected through conventional methods (26).

Magnetic resonance imaging (MRI). MRI is a highly sensitive tool that not only detects abnormal wall motion and cardiac hypertrophy, but also provides information concerning arrhythmias and cardiomyopathy. Rijzewijk *et al* (27) believe that contrast-enhanced MRI can be used to predict the progression of ventricular arrhythmias, myocardial steatosis and heart failure in patients with a history of ischemic heart disease. Cardiac MRI can detect myocardial metabolic abnormalities through different radioactive elements and positron emission tomography (PET) (28).

Cardiac catheterization and coronary angiography. Cardiac catheterization is currently the best technique for assessing intracardiac hemodynamics and is considered to be the gold standard for the diagnosis of diastolic cardiac dysfunction, but it is not widely used due to its invasiveness (29,30). Left and right ventricular catheterization can be employed to assess left ventricular end-diastolic pressure and mean pulmonary arterial wedge pressure, respectively (29,30). The left ventricular end-diastolic pressure >16 mmHg or a pulmonary capillary wedge pressure >12 mmHg can be used as criteria for the diagnosis of diastolic dysfunction (31). Coronary angiography is mainly used to determine coronary artery stenosis, which tends to occur in late DC (32-34).

Serum biomarkers

Matrix metalloproteinases (MMPs) and matrix metalloproteinase inhibitory factors. Previous studies have found that extracellular matrix proteins are associated with persistent ventricular remodeling (35,36). MMPs are endogenous proteolytic enzymes that degrade type I and type III collagen during the development of heart failure, thereby promoting myocardial fibrosis; they can also affect the expression of microRNAs (miRNAs) and cause myocardial contractile dysfunction (37-39). During the process of myocardial fibrosis, serum MMPs (especially MMP-9) are increased, while tissue inhibitory factors of MMPs are decreased (40). Ban *et al* (41) measured serum MMP-7 in patients with DC via enzyme-linked immunosorbent assay (ELISA), and found that MMP-7 was significantly higher in patients with diastolic dysfunction than in patients with normal diastolic functions.

Homocysteine (Hcy). Hcy is a type of sulfur-containing amino acid that is an intermediate metabolite of methionine. It has been reported that plasma Hcy levels are positively correlated with the risk of cardiovascular events (42). For every 5 μ mol/l increase in plasma Hcy, the risk of ischemic heart disease is increased by 32%, and for each 5 μ mol/l decrease, the risk is reduced by 16% (43). Previous studies have shown that high Hcy (HHcy) and hyperglycemia can both lead to DC by inducing oxidative stress and reducing the level of peroxisome proliferator-activated receptor γ (PPAR- γ) (44-46), but whether there is a synergistic mechanism between them is not yet clear. Mishra *et al* (44) found that in HHcy and hyperglycemic murine models, the ventricular end-diastolic diameter was increased, and PPAR- γ , tissue metalloproteinase-4, and

thioredoxin inhibitor levels were decreased, whereas those of MMP-9 were increased, suggesting that endogenous Hcy reduces the expression of PPAR- γ and induces the decoupling of endothelial-myocytes (EMs), resulting in diastolic dysfunction and further progression of DC.

Other biomarkers. The serum procollagen type III aminopeptide (PIIINP) level reflects the metabolism of type III collagen. A previous study proposed that PIIINP is an important indicator of early left ventricular dysfunction in obese patients with insulin resistance (47). Epshteyn *et al* (48) found that 96% of diabetic patients with left ventricular dysfunction had increased levels of brain natriuretic peptides (>90 pg/ml). Cardiac troponin is a type of protein released from ischemic or inflammatory disease-damaged cardiomyocytes. Russell *et al* (49) reported that the levels of troponin T were elevated in the blood of neonates with congenital cardiomyopathy or cardiac insufficiency in mothers with diabetes. However, in adult DC patients, its clinical significance remains uncertain.

Early diagnosis and intervention of DC can slow disease progression, and provide an improved prognosis. Therefore, a combination of multiple techniques for the diagnosis of DC is recommended. For example, a combination of NT-proBNP quantification and echocardiography has more reliable diagnostic value for DC diagnosis than either technique alone (50). In addition, further identification of novel biomarkers is needed, such as microRNAs and long non-coding RNAs (lncRNAs).

4. The pathogenesis of DC

Hyperglycemia. Hyperglycemia plays a key role in the pathogenesis of DC. Hyperglycemia has been shown to directly or indirectly damage cardiomyocytes, fibroblasts and endothelial cells via the accumulation of reactive oxygen species (ROS) (51). Hyperglycemia can increase the production of ROS through the electron chain, which can induce apoptosis of cardiomyocytes (52). ROS activate polyADP-ribose polymerase (PARP), consequently causing an increase in glycosylation and inhibition of glyceraldehyde phosphate dehydrogenase (GAPDH), which transforms the glycolysis process into a cascade of cardiomyocyte injury (53). This process involves increased production of glycation end products, activation of hexosamine pathways, and increased production of protein kinases (PKCs). High levels of ROS, PARP, glycation end products, and aldose reductase production induced by hyperglycemia can lead to cell apoptosis (54,55).

Lipotoxicity. In the diabetic state, increased hepatic fat synthesis and fat lysis in adipocytes promote the formation of circulating fatty acids and triglycerides (56,57). The transportation of fatty acids into cardiomyocytes requires the intermediation of insulin, hyperinsulinemia and hyperlipidemia can increase the fatty acid transportation, and thus induce lipotoxicity in cardiomyocytes (58). The following three mechanisms are included in lipotoxicity: i) Increased production of ROS [increased levels of oxidized fatty acids can increase the mitochondrial membrane potential and thus increase production of ROS (55,59)]; ii) increased production

of ceramide [ceramide is a sphingomyelin that induces apoptosis of cardiomyocytes by inhibiting the mitochondrial respiratory chain (59)]; and iii) effects on myocardial contractile function. Elevated fatty acid levels in cardiomyocytes can cause the opening of potassium channels, resulting in shortening of the action potential duration and opening of L-type calcium channels, ultimately affecting the calcium storage of calcium pump of sarcoplasmic reticulum and impairing myocardial contractile function (60,61). Excessive fatty acid uptake and metabolism not only cause the accumulation of intermediate metabolites of fatty acids, increase the oxygen demand and uncoupling of mitochondria, but also increase the production of ROS, reduce the synthesis of ATP, cause mitochondrial dysfunction, and increase apoptosis (62). Therefore, hyperlipidemia plays a core role in the pathogenesis of DC.

Hyperinsulinemia. Insulin resistance and subsequent hyperinsulinemia are typical pathophysiological characteristics of diabetes mellitus. In the normal heart, 2/3 of the energy provided for myocardial contraction is derived from fatty acid oxidation, and the remaining 1/3 is derived from glucose and lactic acid metabolism (63). Glucose utilization is significantly limited in patients with hyperinsulinemia or insulin resistance, therefore myocardial energy metabolism is more dependent on fatty acid oxidation (64). Moreover, hyperinsulinemia induces cardiomyocyte hypertrophy through a variety of mechanisms. Multiple epigenetic and genetic changes caused by hyperinsulinemia lead to the dysregulation of extracellular and intracellular protein expression, especially extracellular matrix proteins, leading to cardiomyocyte hypertrophy and myocardial fibrosis (65).

Disruption of calcium homeostasis. A balanced regulation of calcium metabolism in cardiomyocytes guarantees normal cardiac contractility (66). Oxidative stress, aggregation of long-chain acetylcarnitine, and changes in lipid membrane components can affect myocardial calcium homeostasis (66-68). Recent reports have shown that calcium pump ATPase, sodium-potassium ATPase and sodium-calcium exchange, and changes in ryanodine receptor function are involved in the pathogenesis of DC (69,70).

Renin-angiotensin-aldosterone system abnormalities. The mechanism of the renin-angiotensin-aldosterone system (RAAS) in the development of diabetes to heart failure has long been known (71,72). Research has confirmed that upregulation of the RAAS system in diabetic patients is closely related to cardiac hypertrophy and fibrosis (71-75). Angiotensin directly acts on cardiomyocytes and cardiac fibroblasts via angiotensin receptor-1, causing cardiac hypertrophy and fibrosis (76).

5. The molecular mechanism of DC

The main characteristic of DC is the disorder of energy metabolism, which is caused by glucose toxicity, lipotoxicity and the dysregulation of mitochondrial function (12). P53 and cytochrome C oxidase 2 (SCO2) are important regulators of the mitochondrial respiratory chain, which play an essential role in the pathogenesis of DC (12,77-80). In a diabetic

condition, the production of ROS activates the P53/SCO2 signaling system in cardiomyocytes, thereby increasing the oxygen consumption of mitochondria, and causing excessive production of ROS and lipid deposition, which induce cardiac function insufficiency (81).

In order to maintain the efficient function of the myocardium, the β -adrenergic receptors of cardiomyocytes of diabetic patients are activated, promoting the synthesis of nicotinamide adenine dinucleotide phosphate oxidase and ROS; this pathway mediates myocardial reformation (82-84). The significant factors involved in the development of myocardial reformation and heart failure are p38 mitogen-activated protein kinase and heat shock protein-27, which are both phosphorylated during the process (85).

In a diabetic condition, a series of signaling pathways are activated and involved in cardiomyocyte hypertrophy and interstitial fibrosis. For example, in the case of acute hyperglycemia, mannoses bind to coagulins and the coagulin-complements, which is an important mechanism leading to vascular dysfunction and cardiomyopathy (86,87). The level of serum transforming growth factor- β 1 (TGF- β 1) is also significantly reduced (88). Thrombospondin-1 activates the potential TGF- β 1 complex in DC, stimulating cardiomyocytes to secrete collagen fibers III (89). The nuclear factor κ B (NF- κ B) pathway has also been found to promote the pathogenesis and progression of DC in diabetic animal models. This signaling pathway is involved in oxidative stress, inflammation, endothelial dysfunction, cardiac hypertrophy and fibrosis (90). Cardiomyocytes contain numerous messenger systems to regulate their normal physiological functions, and these messenger systems produce synergistic or antagonistic effects. Diabetes almost simultaneously causes lesions in these messenger systems, making the condition more complex. The signaling pathways involved in the pathogenesis of DC are described below.

Nrf2-ARE signaling pathway. An antioxidant response element (ARE) is a promoter sequence located at the 5' end of the protective gene such as superoxide dismutase (SOD) or glutathione S-transferase (GST), and is a specific DNA-promoter-binding sequence that can be activated by a variety of oxidative and electrophilic compounds, thereby activating phase II detoxification enzymes and antioxidant enzyme gene expression, and protecting normal tissues (91). NF-E2 related factor 2 (Nrf2) is a transcriptional factor that regulates the transcriptional activity of its gene by binding to the 5' end ARE sequence of its own gene (92). It is believed that Nrf2 plays a key role in cellular oxidative injury protection and the regulation of cell sensitivity to stress. Nrf2 upregulates the expression of antioxidant genes; thus, activation of Nrf2 is beneficial for cells to resist oxidative stress (93). Yoh *et al* (94) found that hyperglycemia and oxidative stress can accelerate renal injury, and Nrf2 is an important factor in preventing the occurrence of diabetic complications. He *et al* (95) found that hyperglycemia damages cardiomyocytes through the ROS system and induces DC. Nrf2-depleted rats can quickly develop DC and exhibit increased levels of glucose-induced apoptosis at lower concentrations, therefore, Nrf2 has been suggested to be a key regulator of ARE's anti-oxidative stress and can prevent the progression of DC.

Hemeoxygenase 1 (HO-1), or heat shock protein 32 (HSP32), is a stress protein induced by a variety of factors, and oxidative stress can activate its expression. HO-1 induction is considered to be a common marker of oxidative stress (96). Shi *et al* (97) showed that activation and intra-nuclear expression of Nrf2 protein can promote the expression of anti-oxidative protein HO-1, which can significantly reduce renal oxidative stress injury in type 1 diabetic mice. The overexpression of HO-1 can protect the myocardia from ischemia/reperfusion injury, and bilirubin produced by HO-1 can protect cardiac function under an ischemic condition (98-102). Therefore, HO-1 is an important antioxidant protease of the Nrf2-ARE pathway. The Nrf2-ARE pathway is a key approach for the body to resist oxidative stress injury. Oxidative stress is an important mechanism of the pathogenesis of DC. Resisting oxidative stress and scavenging ROS are potent strategies for the treatment of DC and have been demonstrated to be an effective anti-oxidative stress enzyme system *in vivo*, and also an important cardioprotective factor for the prevention and treatment of DC. Activation of Nrf2 is a key step in cellular antioxidative stress. It is important to elucidate whether HO-1 exerts cardioprotective effects against DC by activating the Nrf2-ARE pathway (98).

TGF- β 1/Smad signaling pathway. TGF- β 1 and its downstream Smad proteins are involved in the pathological process of myocardial interstitial fibrosis and cardiac hypertrophy (103). In normal hearts, the levels of TGF- β 1, type I and type III collagen are extremely low, while diabetic hearts are stimulated by multiple factors such as hyperglycemia, local renin-angiotensin system (RAS), and oxidative stress inflammation. Therefore, the expression of TGF- β 1 is upregulated and eventually leads to the differentiation of cardiac fibroblasts into myofibroblasts, which also induces the over-synthesis of collagen, fibronectin and proteoglycans (104). The process of myocardial fibrosis is accompanied by upregulation of TGF- β 1 and its downstream Smad2 and Smad3 proteins (105-111). In vascular smooth muscle cells, TGF- β 1 promotes the phosphorylation of Smad2 and Smad3 to form a Smad4 trimer (112). This complex translocates into the nucleus and binds to Smad-associated DNA sequences to promote the transcription of fibrogenic factors such as fibronectin and type I collagen; TGF- β 1-mediated gene expression in human fibroblasts depends on the presence of Smad3 (105-112). In Smad3 gene-deficient mice, myocardial fibrosis can be reduced by 60%, indicating that Smad3 is essential for the development of myocardial fibrosis (113). At present, myocardial fibrosis still lacks effective treatment methods. In-depth study of the role of TGF- β 1/Smad signal transduction pathways in diabetic myocardial fibrosis is expected to provide new and effective therapies for the treatment of DC.

NF- κ B signaling pathway. The NF- κ B signaling pathway mainly mediates inflammatory responses. It has been shown that NF- κ B can activate the expression of inflammatory factors such as interleukin (IL)-1, tumor necrosis factor (TNF) and interferon (IFN), which in turn can promote activation of NF- κ B bypass (114). The activation of the NF- κ B signaling pathway is closely related to the occurrence of cardiovascular disease in diabetes, and is an important intermediate link in

various signaling pathways in the pathogenesis of diabetic vascular complications (115). Excessive glucose in diabetic patients causes non-enzymatic glycation, producing advanced glycation end products (AGEs) that bind to receptors of AGEs and release large amounts of ROS to activate NF- κ B translocation into the nucleus, which in turn initiates transcription of inflammatory factors such as TNF- α , ultimately leading to damage of cardiovascular endothelial cells and proliferation of smooth muscle cells, subsequently promoting cardiovascular disease in diabetes (116-127).

At present, it is believed that the pathogenesis of DC is related to inflammation. Feng *et al* (128) studied myocardial ischemia-reperfusion injury in rats and found that knocking out the MyD88 gene reduced the myocardial infarction size and improved cardiac function compared to wild-type mice. Furthermore, less inflammatory cell infiltration and lower expression of monocyte chemoattractant protein-1 (MCP-1) and intercellular adhesion molecule-1 (ICAM-1) were found in MyD88-deficient mice, suggesting that the knockdown of MyD88 attenuates the NF- κ B activation during ischemia-reperfusion.

PKC signaling pathway. Protein kinase C (PKC) is a family of serine/threonine kinases that are widely present in cells. Most of the neurotransmitters, hormones and growth factors can activate PKC through activating phospholipase C, which produces a lipid-derived secondary messenger (such as diacylglycerol) that phosphorylates the serine/threonine residue of the target protein (129). Previous studies have found that excessive activation of PKC can lead to cardiac hypertrophy and fibrosis, suggesting that PKC inhibitors may prevent and delay cardiac hypertrophy and myocardial fibrosis (130,131). Hyperglycemia increases the *de novo* synthesis of diacylglycerols in cardiomyocytes, vascular smooth muscle cells and endothelial cells, which in turn activates PKC. In addition, Ca^{2+} , angiotensin, endothelin, vascular endothelial growth factor (VEGF) and osmotic factors can activate PKC. The possible mechanism is that the above factors bind to the cell membrane receptors, and diacylglycerol is activated by membrane phospholipids to activate PKC (130,131). Similarly, the PKC inhibitory therapy should be an essential part of DC treatment. PKC inhibitors have been initially used in the clinical treatment of diabetic vascular complications, but their long-term efficacy and side effects still need to be further observed (132-135).

PPARs. Several PPAR isoforms, including PPAR- α , PPAR- β/δ , and PPAR- γ , have been shown to be expressed in cardiomyocytes and act as key regulators for glucose and lipid metabolism, and energetic homeostasis. Interestingly, they are also involved in other cellular events such as inflammation and oxidative stress (136). PPAR- α is relatively highly expressed in the heart, and its activation influences cellular free fatty acid (FFA) uptake and mitochondrial FFA oxidation (137). PPAR- α regulates the assembly and transport of lipoproteins, and regulates the defenses of both oxidant and anti-oxidant. Previous research has shown that overexpression of PPAR- α results in decreased sarcoplasmic reticulum Ca^{2+} uptake, contractile dysfunction, left ventricular hypertrophy and increased B-type

natriuretic peptide (138). Conversely, depletion of PPAR- α prevents fasting-induced FFA metabolic gene expression and enhances glucose metabolism (139). With the progression of DC, long-term exposure to increased FFAs was found to result in reduced PPAR- α expression, which was shown to further injure the cardiac function by inhibiting FFA oxidation and increasing intracellular lipid accumulation in rodent cardiomyocytes (140,141). However, clinical studies have suggested that PPAR- α is not significantly overexpressed in the cardiomyocytes of patients with type 2 diabetes mellitus (142,143). The activation of PPAR- α and the following FFA oxidation in cardiomyocytes under DC situation may act as a compensatory mechanism for substrate supply. Furthermore, a reduction in PPAR- α in advanced disease may have maladaptive consequences in terms of cardiac metabolism, including glucotoxicity and functional cardiac abnormalities. The role of PPAR- α in the progression of cardiac function decrease in DC has not been fully understood and warrants further investigation. Similarly, PPAR- β/δ isoforms are also abundantly expressed in cardiomyocytes and can regulate FFA metabolism (144). Enhanced PPAR- β/δ signaling promotes FFA metabolism and vice versa. Additionally, PPAR- γ provides anti-hypertrophic and anti-inflammatory effects in cardiocytes (145). PPAR- γ agonists promote insulin sensitivity and enhance cardiomyocyte glucose intake (136). Therefore, PPAR- γ may help maintain glucose and FFA metabolism, and can protect cardiac function.

MAPK and JNK activation. MAPK overactivation has been reported to contribute to the pathogenesis of DC and cardiac dysfunction. Erk1/2, p38 MAPK, and JNKs are 3 essential MAPK members that regulate cardiomyocyte growth, hypertrophy and remodeling (146-150). Increased phosphorylation of Erk1/2 and p38 MAPK was observed in streptozotocin-induced DC models (151). Previous research has demonstrated that obesity- or insulin resistance-induced heart failure is associated with the overactivation of S6 kinase 1 and Erk1/2 signaling (152,153). JNK can be activated under the conditions of oxidative stress and inflammation (154). In turn, enhanced JNK signaling in the diabetic heart contributes to oxidative stress, endoplasmic reticulum stress and interstitial fibrosis (4,154). In contrast, inhibition of JNK phosphorylation by a curcumin analog was found to prevent high glucose-induced inflammation and apoptosis in diabetic hearts (154,155). In addition to these observations, JNK may play an important role in cardiomyocyte apoptosis (155). As such, JNK activation has been showed to cause increased cardiomyocyte apoptosis as early as at day 3 and 7 in a type 1 diabetic rodent model (155). Collectively, activation of both MAPK and JNK signaling seems to significantly contribute to the development of DC.

AMP-activated protein kinase (AMPK) activation. AMPK is a serine/threonine kinase that can detect cellular energy status and regulate energy homeostasis (156). Activation of AMPK is involved in multiple cellular processes such as autophagy (157). Activation of AMPK has been shown to inhibit mTOR, which is a protein kinase that regulates autophagy (158). A previous study showed that high glucose inhibited autophagic activity and the AMPK pathway in

Figure 1. Overview of the mechanisms leading to heart failure in diabetic cardiomyopathy. DM, diabetes mellitus; ROS, reactive oxygen species; RAAS, renin-angiotensin-aldosterone system; TGF- β , transforming growth factor- β ; AGE, advanced glycation end products; NF- κ B, nuclear factor κ B.

a DC cell model, thereby stimulating the interaction of beclin 1 (BECN1) and the anti-apoptotic protein BCL2 (159). Activation of AMPK results in phosphorylation of MAPK8, which in turn drives BCL2 phosphorylation and dissociates from the BECN1-BCL2 complex (15). Thus, AMPK restores cardiomyocyte autophagy through BCL2, preventing cardiomyocyte apoptosis. Dissociation of BCL2 from BECN1 via activation of MAPK8-BCL2 signaling may restore autophagy by driving AMPK activation and is important for the prevention of DC processes (160).

MicroRNAs. DC is associated with the dysregulated expression of miRNAs, short single-stranded noncoding RNAs of ~20 nucleotides in length (161). Importantly, miRNAs bind to the 3'-untranslated region (3'UTR) of the mRNAs of target genes. Therefore miRNAs can participate in the regulation of multiple events in the pathogenesis and progression of DC, such as mitochondrial function, Ca^{2+} handling, ROS production, apoptosis, autophagy and fibrosis (162,163). miR-15a, miR-21, miR-24, miR-29, miR-30d, miR-103, miR-126, miR-146a, miR-150, miR-191, miR-223, miR-320, miR-375 and miR-486 have all been reported to be overexpressed in type 2 diabetic patients (163-168). miR-103, miR-107, miR-143 and miR-181 play essential roles in the regulation of cellular insulin sensitivity and glucose metabolism (163,169). High expression levels of miR-454, miR-500, miR-142-3p/5p and miR-1246 have been found in the circulating blood of patients with cardiac diastolic dysfunction (170). Other microRNAs, such as miR-113a, miR-133a and miR-150, have been reported to be related to cardiomyocyte hypertrophy and interstitial fibrosis (171).

6. Treatment of diabetic cardiomyopathy

At present, the therapeutic strategies for DC are still based on drug treatment. The principles include primarily acting

against the pathogenesis of DC, and delaying the development of heart failure (172). Controlling blood sugar is fundamental for effectively reducing the cardiovascular morbidity of diabetes. Diet control and regular exercise are necessary for disease treatment. Clinical studies have found that the use of hypoglycemic agents to control blood glucose in patients with early stages of myocardial dysfunction can effectively delay the progression of cardiomyopathy in diabetic patients (173). Studies have confirmed that the use of metformin in diabetic patients can effectively reduce the mortality (174).

Most diabetic patients have hyperlipidemia in the early stage of the disease. Clinical studies have shown that statins and fibrates can effectively reduce the blood lipid levels and the mortality of cardiovascular disease in diabetic patients (175,176). A large amount of ROS produced by oxidative stress can directly damage myocardial cells and vascular endothelial cells, causing myocardial dysfunction (177). A variety of antioxidant drugs such as vitamin E and angiotensin-converting enzyme inhibitors (ACEIs) can reduce the levels of ROS in the blood and therefore protect the myocardium (178). For DC patients with symptoms of heart failure, beta blockers have been shown to have a significant effect on improving ventricular function (179). Sharma and McNeill (180) tested the inhibitory effect of metoprolol on DC in animal models and found that metoprolol reduced fatty acid oxidation and improved ventricular function. Increased levels of angiotensin 2 in myocardial tissue, leading to increased aldosterone secretion, enhanced the content of ROS and led to myocardial cell damage and apoptosis (181).

In recent years, physical therapy has also been gradually applied to the treatment of diabetic complications. Studies have shown that hyperbaric oxygen therapy can reduce the fasting blood glucose by at least 20% in patients with type 2 diabetes, and reduce insulin resistance in obese diabetic patients (182).

On the other hand, hyperbaric oxygen was found to reduce myocardial cell damage in DC rats (183). These studies indicate that hyperbaric oxygen therapy has considerable promise in the treatment of cardiovascular disease and DC.

In addition, stem cell therapy is the future of disease treatment, and it has been proven to be effective in treating a variety of cardiovascular diseases. Although stem cell therapy has not been applied to clinical DC treatment to date, *in vivo* and *in vitro* research suggests that bone marrow mesenchymal stem cells can effectively promote the growth and differentiation of cardiomyocytes in DC rats and significantly improve cardiac function (184,185). Neel and Singla (186) found that induced pluripotent stem cells can effectively inhibit cardiomyocyte apoptosis and fibrosis in DC rats, and significantly improve the cardiac function of model animals. The protective effects of stem cells on the cardiovascular system in the DC model indicate that it has broad prospects in the treatment of DC.

Although the current treatments have largely improved the short-term prognosis of patients with diabetic cardiomyopathy, there are still no convincing or effective prevention strategies to avoid repeated and prolonged rehospitalization. The main challenges remain in the complexity of the pathogenesis of DC and the inefficiency of diagnostic approaches. Future studies need to focus on the improvement in diagnosis by coupling different diagnostic approaches. Advances in next generation sequencing and imaging technologies may help overcome these challenges.

7. Conclusions

DC is a major complication of diabetes that requires further elucidation. DC is closely correlated with cardiac mortality and morbidity. Echocardiography is currently the most commonly used diagnostic method for DC diagnosis. Novel modalities including MRI, PET and multiple serum/plasma biomarkers are emerging. However, the present methods have their limits, and therefore a combination of multiple methods should be recommended for the diagnosis of DC. The pathophysiology and pathogenesis of DC have not been fully elucidated. The presently proposed hypothesis (Fig. 1) includes hyperglycemia-associated metabolic and oxidative stress, lipotoxicity and hyperinsulinemia, and the treatment of DC is still based on drug therapy. The principles are mainly aimed at the pathogenesis of DC, and delay of the development of heart failure. Controlling blood sugar is fundamental for effectively reducing the cardiovascular morbidity of diabetes. Diet control and regular exercise are necessary for disease treatment. New therapeutic approaches covering cell-based or gene-based therapies are currently being investigated. Further research is required for understanding the mechanisms involved in the development of DC to enhance the discovery of clinically effective targets for preventing this condition and its progression to heart failure. We apologize to those authors for whom we did not cite their valuable works due to the large number of papers to be cited.

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Competing interests

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