

Cardiac Dysfunction in Diabetes

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Abstract

In the worldwide, the burden of diabetes mellitus (DM) and its associated complications are currently markedly increasing. These patients are at significantly higher risk of developing heart failure (HF) independent from other risk factors such as hypertension, coronary artery disease (CAD) and dyslipidaemia. The pathophysiology and pathogenesis of cardiac dysfunction in diabetic patients are still unclear. On the other hand, it has been currently demonstrated that impaired cardiac functions is associated with several mechanisms such as insulin resistance, hyperinsulinemia, longstanding hyperglycaemia-associated metabolic and oxidative stress, microvascular dysfunction, lipotoxicity, and cardiac autonomic neuropathy. The development of cardiac dysfunction due to DM is defined as “diabetic cardiomyopathy” (DCM). The clinical manifestations of DCM may present from asymptomatic ventricular dysfunction overt HF. The most frequently used diagnostic methods are standard echocardiography and cardiac magnetic resonance imaging. A tight glycaemic control appears to play the central role for prevention and treatment of DCM. The management of DCM also includes lifestyle modifications, metabolic modulators, lipid-lowering therapy, treatment of coexistent hypertension or CAD, and medications for HF if presents. In this article, we aimed to provide a short review on the definition, classification, pathophysiology, diagnosis and management of DCM.

Keywords: Diabetic Cardiomyopathy; Heart Failure; Echocardiography

Introduction

Diabetes mellitus (DM) is one of the major risk factors for development of the cardiovascular diseases and the global burden of DM is increasing very fast. Currently the number of affected people is over 300 million and it is estimated that there will be about 500 million people with DM by within 20 years [1]. In the worldwide, cardiovascular diseases are the most common cause of morbidity and mortality in patients with DM [2]. Especially coronary artery disease (CAD) is major etiological factor of mortality in diabetic patients. Although CAD is very common, heart failure (HF) is another major cause of mortality and morbidity in patients with DM [3]. Diabetic patients are under increased risk for HF development after adjusting concomitant risk factors such as hypertension, dyslipidemia and CAD [4,5]. According to the Framingham Heart Study, the development risk of HF in diabetic patients is increased two-fold in men and five-fold in women compared with age-sex matched non-diabetic population [6]. Also, Euro Heart Failure Survey and United Kingdom Prospective Diabetic Study suggested that the presence of DM is an independent predictor of the risk of developing HF [7,8]. Additionally, up to 75% of patients with idiopathic dilated cardiomyopathy were found to be diabetic. Leyden first reported that diabetic cardiomyopathy (DCM) is a typical complication of DM in 1881. Mayer asserted that DM is a metabolic disorder that can induce heart disease in 1888. Currently, DCM was defined as a myocardial dysfunction by Rubler in 1972 after post-mortem studies in patients with DM in the absence of CAD,

valvular heart diseases, hypertension, and use of alcohol [9]. DCM is characterized by increased interstitial fibrosis in cardiomyocytes and left ventricular (LV) hypertrophy, which are both cause myocardial dysfunction [10]. It is associated with both type 1 and type 2 DM and presents as by diastolic and systolic dysfunction [11]. Although it is not seen rare, diagnosis of DCM is difficult in the daily clinical practice. Echocardiography and cardiac magnetic resonance imaging (MRI) are usually used in the diagnostic work-up. HF due to DCM leads to poor morbidity and mortality. Also, DCM complicates the management of DM by affecting the pharmacokinetics of anti-diabetic medications. Therefore, early diagnosis of DCM is very important for the disease management. However, DCM is still underdiagnosed and poorly understood by most physicians, even cardiologists and diabetologists. In this context, we focus definition, classification, pathophysiology, diagnosis and management of DCM in this review.

Pathophysiology

The pathophysiological mechanisms of DCM could not been completely explained yet. There are many complex factors which involve in the process of development of DCM. Common pathophysiological mechanisms including microvascular dysfunction, alterations in the renin-angiotensin-aldosterone system (RAAS), subcellular component abnormalities, metabolic disturbances, and maladaptive immune responses play crucial roles in the development of DCM as a result of insulin resistance, hyperglycemia and hyperlipidemia (Figure 1) [12,13]. As a result of this pathological processes, diastolic dysfunction and cardiac hypertrophy develop in the early-stage, and systolic functions impair in the late stages.

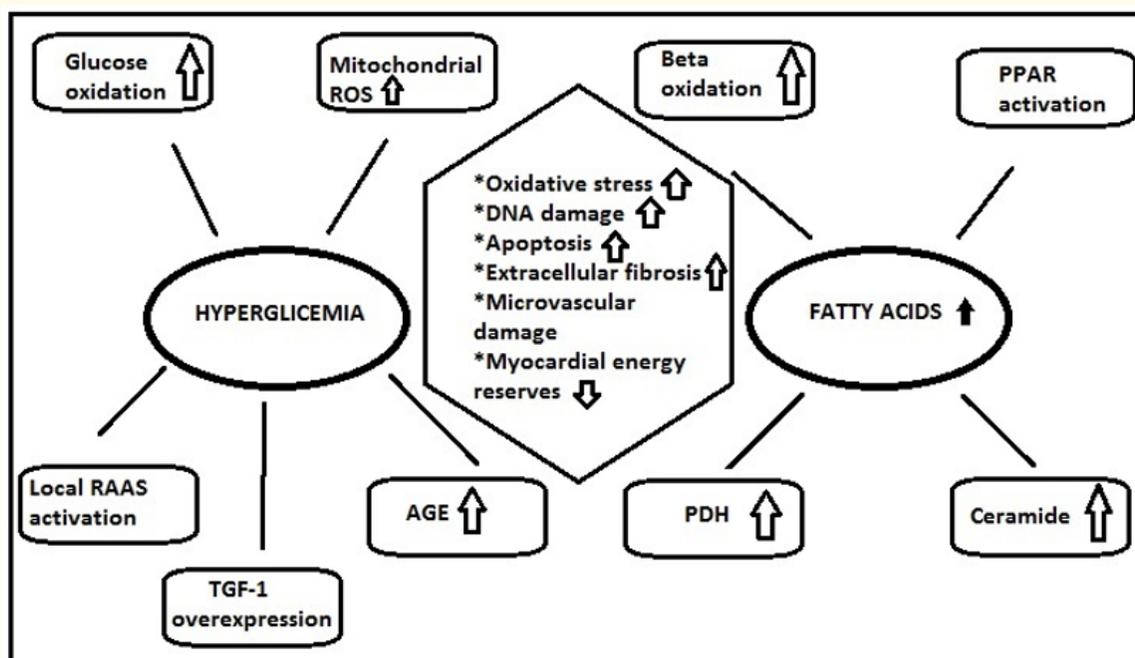


Figure 1: Pathophysiological mechanisms of diabetic cardiomyopathy.

AGE: Advanced Glycation End-Products; PPAR: Poly-Adenosine Diphosphate Ribose Polymerase, PDH: Pyruvate Dehydrogenase; RAAS: Renin-Angiotensin-Aldosterone System; ROS: Reactive Oxygen Species; TGF-1: Transforming Growth Factor-1.

Hyperglycemia and hyperinsulinemia

Hyperglycemia is considered to be a central trigger in the pathophysiology of DCM, because it causes many molecular and metabolic changes in cardiomyocytes [14]. Increased glucose metabolism due to hyperglycemia leads to an increase in oxidative stress by exacerbating glucose oxidation and mitochondrial generation of reactive oxygen species (ROS) [15]. Increased oxidative stress and ROS cause cellular DNA damage and accelerate cardiomyocyte apoptosis. Also, oxidative stress leads to myocardial dysfunction and fibrosis by inducing of production of super oxides in the mitochondrial respiratory chain. In addition, oxidative stress-induced DNA damage and increased ROS activate poly ADP ribose polymerase (PARP) as a reparative enzyme [16]. PARP mediates the ribosylation and inhibition of glyceraldehyde phosphate dehydrogenase, redirecting glucose metabolism from its usual glycolytic pathway to an alternative biochemical pathway that results in the development of many mediators and causes hyperglycemia-induced cellular injury. These include increased in advanced glycation end product (AGE) levels, hexosamine and activation of protein kinase C. The increased AGEs due to persistent hyperglycemia may cause to increase arterial and myocardial stiffness, endothelial dysfunction and atherosclerosis by the alter structural proteins [17]. Intracellular and extracellular proteins, such as collagen and elastin are particularly vulnerable to accumulation of AGE crosslink. AGEs can easily make covalent crosslink with extra- and intracellular proteins and in this way, they change the structure and function of these proteins.

The crosslinks including collagen and elastin results increased myocardial stiffness and impaired cardiac relaxation. AGEs also induce intracellular oxidative stress which can cause to cellular damage. Additionally, activation of local RAAS due to hyperglycemia contributes to cardiomyocyte fibrosis and necrosis [18,19]. Hyperinsulinemia which maintains glucose homeostasis, promotes cellular hypertrophy by binding to the insulin-like growth factor receptor. Also, hyperinsulinemia activate multiple transcription factors that regulate extracellular and intracellular protein expression. This activation of such transcription factors stimulate overexpression of transforming growth factor-1 by cardiac fibroblasts, resulting fibrous tissue deposition and extracellular matrix synthesis in cardiomyocytes [20].

Cardiac lipotoxicity

Abnormal lipid metabolism often play an important role in the process of cardiac structural alterations in diabetic patients. Cardiomyocytes use both glucose metabolism and free fatty acids (FFA) in equivalent ratios for the energy requirement. Because of decreased glucose transporter proteins, glucose use markedly reduces, FFA uptake of cardiomyocytes increase and also energy production of the heart shifts to beta-oxidation of FFA [21]. The development of mitochondrial uncoupling due to increased FFA oxidation causes to contractile dysfunction and decreased myocardial energy reserves. FFAs reduce the activation of pyruvate dehydrogenase enzyme and this may results accelerated cardiomyocytes apoptosis by accumulation of glycolytic intermediate substances [22]. Also, using FFAs for adenosine triphosphate metabolism requires more oxygen that results in more toxic productions which cause myocyte dysfunction and impaired myocardial mechanisms. Additionally, in diabetes, some lipid metabolites such as diacylglycerols and ceramides impair insulin metabolic signalling further promoting cardiac dysfunction. Abnormal accumulation of lipids and lipid metabolites contributes to cardiac insulin resistance, reduced bioavailable nitric oxide (NO), inflammation, fibrosis and diastolic dysfunction [23].

Microvascular dysfunction

Many anatomical and functional alterations is often seen in coronary vascular bed in diabetic patients. Major pathophysiological changes due to hyperglycemia and hyperinsulinemia are in impairment of the NO production, increased production of vasoconstrictor prostaglandins, glycated proteins, endothelium adhesion molecules, and platelet and vascular growth factors, which increase vasomotor tone and vascular permeability, growth and remodelling [24]. The microangiopathic changes including basal membrane and arteriolar thickening, capillary microaneurysm, and reduced capillary density, which results periarterial fibrosis and focal subendothelial proliferation in diabetics [25]. All of these changes result in myocardial and ventricular hypertrophy, impairment coronary collateral circulation,

and accelerated distal atherosclerosis in coronary arteries, as a result of endothelial dysfunction. These results play crucial role in the pathogenesis of DCM.

Impaired copper metabolism

In diabetic patients particularly who have microvascular complications and hypertension, serum copper levels are markedly increased. The main copper-binding proteins are ceruloplasmin and albumin in plasma. Hyperglycemia and hyperinsulinemia reduce the copper-binding properties of these proteins and as a result of this, copper levels increase in the extracellular matrix [26]. Additionally, glycosylated proteins have an increased affinity toward copper. Markedly increased levels of copper in the extracellular matrix is considered to stimulate the oxidation-reduction system, which leads to increase oxidative stress [13]. Therefore, production of toxic free radicals increase and this causes to myocardial structure changes and dysfunction by increased myocyte apoptosis and fibrosis.

Cardiac autonomic neuropathy

Cardiac autonomic neuropathy (CAN) is one of the most dangerous complications of diabetes. Impairment of sympathetic innervations and adrenergic receptor expression and altered myocardial catecholamine levels are main pathophysiological changes of diabetic cardiac autonomic neuropathy process. These changes present clinically as resting tachycardia, orthostasis, exercise intolerance, and silent myocardial ischemia in patients. CAN is seen in 17 - 22% of patients with DM and strongly associated with morbidity and mortality. CAN basically impair the balance of autonomic nervous system that results in loss of heart rate variability and abnormalities in microvascular physiology [27]. Sympathetic denervation causes myocardial dysfunction by decreasing myocardial perfusion which leads to ischemia and necrosis. Also, alterations in myocardial autonomic neurotransmitter levels and beta receptor regulation contribute to cardiomyocyte apoptosis and fibrosis that leads to systolic and diastolic dysfunction [27].

Diagnosis

Early diagnosis of the cardiac involvement in patients with DM is very important, because development of heart failure worsens the prognosis. Although overt DCM takes many years to develop, cardiac abnormalities can be determined with echocardiography or cardiac MRI at the early stages before any heart failure clinic onset [28]. There are a useful four-stage classification of DCM, including clinical features, echocardiographic changes, and serum markers for diagnosis and classification in clinical practice (Table 1) [29]. The detection of myocardial dysfunction and the exclusion of coexistent factors such as hypertension and age, that causes similar myocardial abnormalities are crucial two components in the clinical diagnosis of DCM. Evidences of diastolic dysfunction and LV hypertrophy in the echocardiography and cardiac MRI, are essential to consider the diagnosis of DCM, but they are not specific for DCM. The diastolic functions are evaluated with strain rate imaging, Doppler studies of transmitral velocities, mitral flow patterns and mitral annulus velocities by tissue Doppler imaging in the echocardiographic examination. Echocardiographic findings at rest may be completely normal especially in the early-stage of DCM. Therefore, when typical echocardiographic changes of DCM are not seen at rest, in cases of high clinical suspicion echocardiographic assessment should be performed during exercise stress test. In echocardiographic assessment, also LV relaxation impairs, early diastolic filling decrease, atrial filling deceleration time and isovolumetric relaxation time increases, which are indicators of diastolic dysfunction [30]. Systolic dysfunction may develop very late even in subsequent years after early basic pathologic changes such as diastolic dysfunction and cardiac hypertrophy. It has been demonstrated that, a shortened ejection period and prolonged prerejection performance are associated with reduced resting LV ejection fraction (LVEF) and impaired systolic function in diabetic patients regardless of HF clinic [31]. Additionally, it is known that diabetic patients have a poor LVEF response to exercise, which shows a decreased cardiac reserve [31]. However, there have been reports of early LV systolic dysfunction with normal LVEF in diabetic patients. Assessment of systolic functions with advanced techniques such as strain, strain rate and myocardial tissue Doppler velocity may detect preclinical systolic abnormalities in these patients. Cardiac MRI is gold standard for cardiac dimensions, volume measurements and contractile functions, regardless of patient body habitus or echocardiographic window. Cardiac MRI also give important information's about LV filling features

and novel functional and morphological parameters assessments such as demonstration of fatty or fibrosis infiltrates [14]. These useful diagnostic tools are not available by echocardiography. Therefore, DCM has been diagnosed easier and broader with more frequent use of cardiac MRI. In this context, cardiac MRI provide a very valuable data particularly in the detection of early-stage of DCM compared with echocardiography. Also, resting electrocardiogram (ECG) may be useful in the diagnosis of DCM. It has been demonstrated that a poor R-wave progression which is defined as an R wave < 3mm in V1 - 3 derivations in resting basal ECG of diabetic patients appears to use as a diagnostic marker of DCM after excluding all the other pathologies which may cause similar ECG findings [32].

	NYHA classification	Metabolic status	Echo and coronary angiography	DM-related complications	Serum markers
Stage 1 DCM Diastolic dysfunction Hypertrophy	NYHA I	Metabolic syndrome; Impaired glucose tolerance	Increased LV mass, diastolic dysfunction, decreased tissue velocities, normal EF	-	NTproBNP MMP-3 Osteopontin Glucose Lipid profile HbA1c
Stage 2 DCM Systolic dysfunction Dilatation	NYHA II	Chronic hyperglycemia	Increased LV mass and wall thickness, diastolic and systolic dysfunction (EF<50%), mild dilatation	-	NTproBNP MMP-3 Osteopontin Glucose Lipid profile HbA1c
Stage 3 DCM Systolic dysfunction Dilatation Arterial hypertension	NYHA II-III	Insulin resistance, DM with microangiopathic complications	Diastolic and mild systolic dysfunction, dilatation	Microangiopathic complications, Arterial hypertension	NTproBNP MMP-3 Osteopontin Glucose Lipid profile HbA1c Troponins
Stage 4 DCM Systolic dysfunction Dilatation Coronary artery disease	NYHA II-IV	DM with micro and macroangiopathic complications	Moderate-severe systolic dysfunction, dilatation, coronary artery disease	Macroangiopathic complications, Coronary artery disease	NTproBNP Glucose Lipid profile HbA1c Troponins

Table 1: Classification of diabetic cardiomyopathy.

DM: Diabetes Mellitus; DCM: Diabetic Cardiomyopathy; EF: Ejection Fraction; LV: Left Ventricle; MMP-3: Metalloproteinase 3; NTproBNP: N-Terminal Pro B-Type Natriuretic Peptide; NYHA: New York Heart Association.

Management

Recently, a better understanding of the pathophysiology and pathogenesis in patients with DCM has provided improved several therapeutic options. These include lifestyle modifications, improved glycaemic control, the treatment of coexistent hypertension or CAD if present, lipid-lowering therapies, and the management of HF [33]. Weight loss, limitation of fat and total energy intake, and regular physical activity can improve metabolic abnormalities, tissue and systemic insulin resistance. In previous studies, it has been demonstrated that physical activity was associated with a significant reduction in cardiovascular disease and all-cause mortality in diabetic patients [34,35]. Healthy eating patterns that are suitable for diabetic patients may also provide similar beneficial effects as well as regular physical activity [33]. Poor glycaemic control has been found associated with an increased risk cardiovascular mortality with an increase of 11% for every 1% rise HbA1c levels [36]. In addition, the degree of diastolic dysfunction was correlated with HbA1c and insulin levels. A better glycaemic control has been shown that improve myocardial contractility parameters, which has been explained by more efficient myocardial energy substrate and improved microvascular perfusion. But, the beneficial effects of tight glycaemic control on macrovascular outcomes are still unclear. It has been suggested that tight glycaemic control markedly reduces the development risk of DCM in diabetic patients. This data supports that hyperglycemia has an important role in the pathogenesis of DCM. As a result of this, strict glycaemic control seems to play a crucial role for prevention and treatment of DCM. The RAAS has an important role in the pathogenesis of complications in diabetic patients. Angiotensin-converting enzyme (ACE) inhibitors have widespread beneficial effects on microvascular and macrovascular complications in diabetes and may affect myocardial fibrosis through effects on Angiotensin II. Meta-analyses of the major ACE inhibitor studies has been demonstrated that diabetic patients achieve similar reductions in cardiovascular mortality as nondiabetic patients with LV dysfunction. It has been shown that an angiotensin receptor blocker, candesartan improved diastolic dysfunction, reduce collagen synthesis, and increase collagen degradation in asymptomatic diabetic patients [37]. Also, a study showed that aldosterone antagonist has a beneficial effect in diastolic heart failure by their beneficial effects on myocardial hypertrophy and fibrosis [38]. These results emphasize the clinical importance of inhibiting the RAAS in diabetic patients who particularly develop diastolic dysfunction. Therefore, RAAS blockers should be kept in mind for all diabetic patients to improve cardiovascular outcomes. Beta blockers (β -blockers) are very well defined in the management of HF. β -blockers improve ventricular function and patient well-being, reduce hospitalizations due to worsening HF, and increases survival [39]. A meta-analysis of the 6 main HF studies which include the CIBIS II (Cardiac insufficiency Bisoprolol study II), BEST (β -Blocker Evaluation of Survival Trial), ANZ (Australia and New Zealand) Carvedilol, Carvedilol US Trials, COPENICUS (Carvedilol Prospective Randomized Cumulative Survival), and MERIT-HF (Metoprolol Controlled Release Randomized Intervention Trial in Heart Failure) has been demonstrated the important results in subgroup analysis of diabetic patients [40]. The pooled relative risk of the mortality in patients with DM and congestive HF on β -blocker treatment compared with placebo was 0.84 (95% CI, 0.73 - 0.96; $p < 0.011$). In another study, carvedilol was demonstrated to have better effects on glycaemic control and insulin resistance compared with metoprolol [41]. Overall, β -blockers should be given to all diabetic patients with any evidence of HF or LV systolic dysfunction, unless specifically contraindicated or not tolerated. The use of statins reduces cardiovascular mortality and ischemic events in patients with diabetes and vascular risk factors and is beneficial even for primary prevention in patients without known cardiovascular diseases. However, there is no study which evaluates the effect of statins on prevention or treatment of DCM. Therefore, the efficacy of statins in DCM remains to be determined. Metabolic modulators such as trimetazidine, ranolazine, and resveratrol reduce cardiomyocyte apoptosis and fibrosis through improved intracellular and extracellular metabolic abnormalities. As a result of this, a better metabolic control may improve myocardial dysfunction.

Conclusion

DCM is defined as myocardial structural and functional abnormalities in the absence of hypertension, coronary artery and valvular heart disease [9]. DCM is an important but less well-recognized complication of chronic diabetes, which is associated with worse cardiovascular outcomes. The pathophysiology and pathogenesis of DCM are still unclear, although suggested mechanisms include insulin resistance, chronic hyperglycemia-associated metabolic and oxidative stress, microvascular dysfunction, lipotoxicity, and cardiac auto-

nomic neuropathy [12,13]. The manifestations of DCM may vary from subclinical ventricular dysfunction to overt HF. The most frequently used diagnostic methods are standard echocardiography and cardiac MRI. Although strict glycemic control seems to play the central role for prevention and treatment of DCM, the management of DCM includes changes in lifestyle, treatment of dyslipidaemia, metabolic modulators, coexistent hypertension, dyslipidaemia or CAD therapy, and medication for heart failure if it develops [33]. Novel therapeutic approaches including targeting mitochondrial oxidative stress and stem cell or gene based therapy are currently studied. Further research is needed to understand the exact pathophysiological mechanisms involved in the development of DCM.

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