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REVIEW ARTICLE

# Progression of Diabetic Cardiomyopathy among Type 2 Diabetic Patients: A Review Article

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## ABSTRACT

**Background:** Insulin resistance, compensatory hyperinsulinemia, and the development of hyperglycemia promote diabetic cardiomyopathy, a subtype of heart disease that develops apart from other cardiac risk factors like hypertension and coronary artery disease (CAD). The prevalence of heart failure symptoms was 19% in people with type 2 diabetes, and the chance of developing heart failure was two to eight times higher in those people. We intended to outline an overview of the Progression of Diabetic cardiomyopathy among Type 2 Diabetic Patients.

**Conclusions:** Diabetes is one of the rare but rapidly increasing causes of cardiomyopathy globally. The condition is a common consequence of diabetes that is responsible for a great deal of death and disability. We provide a synopsis of the several potential pathogenic mechanisms that are now being studied that could lead to diabetes-related cardiomyopathy, including fibrosis, cell signaling disturbance, and left ventricular (LV) hypertrophy. Heart failure develops from these alterations.

**Keywords:** Diabetic cardiomyopathy; Progression; Type 2 Diabetic Patients

## INTRODUCTION

Insulin resistance, compensatory hyperinsulinemia, and the development of hyperglycemia promote diabetic cardiomyopathy, a subtype of heart disease that develops apart from other cardiac risk factors like hypertension and coronary artery disease [1]. After four diabetic individuals showed signs of cardiac failure in 1972, diabetic cardiomyopathy was diagnosed as a distinct illness. This was backed up by a 1974 secondary analysis of the Framingham Heart Study, which found that, after adjusting for other risk factors like age, hypertension, obesity, dyslipidemia, and CAD, the risk of heart failure was 2.5 times higher in women with diabetes than in those without the disease, and 2.4 times higher in men [2]. Diastolic dysfunction and heart stiffness are both common complications in people with type 2 diabetes. People with type 2 diabetes, according to the Framingham Heart Study, are two to eight times more likely to develop heart failure, and 19% of those people experience heart failure symptoms [2]. The risk of heart failure is 2.5 times higher in people with type 2 diabetes, according to a retrospective cohort analysis of 8,231 people with the disease. The study found that 30.9% of people with diabetes had heart failure, compared to 12.4% of people without diabetes. Additionally, regardless of age, blood pressure, obesity, or the presence of coronary artery disease (CAD), a 1% rise in hemoglobin A1c was linked to an 8% increase in the likelihood of heart failure, according to an observational study including 25,958 males and 22,900 females with type 2 diabetes. This finding implies that type 2 diabetes stands alone as a risk factor for incident heart failure [3].

## THE FUNDAMENTAL PROCESSES UNDERLYING DIABETIC CARDIOMYOPATHY

Little is known about the pathophysiological mechanisms underlying DCM. Insulin resistance, microvascular impairment, metabolic disturbances, abnormalities in subcellular components, cardiac autonomic dysfunction, changes in the renin-angiotensin-aldosterone system (RAAS), and

maladaptive immune response are some of the hypothesized mechanisms for the multifactorial occurrence of DCM. According to an old view, hyperglycemia is a critical factor in the development of DCM. However, many complex processes and interactions between various metabolic and molecular events in the heart and plasma also contribute to its pathogenesis. High blood sugar, inflammation, and altered lipid profiles are the hallmarks of type 2 diabetes. The majority of diabetic complications, including diabetic nephropathy and diabetic coronary artery disease DCM, are caused by reactive oxygen species (ROS) or nitrogen species, which are produced by all of these disorders. [4].

***EFFECTS OF HYPERGLYCEMIA ON THE HEART:***

Chronic hyperglycemia causes cardiomyocytes to undergo several molecular and metabolic alterations. Hyperglycemia-induced increased glucose metabolism raises oxidative stress by forming ROS in the mitochondria. Myocardial fibrosis and diminished cardiac contractility result from oxidative stress caused by the mitochondrial respiratory chain's excessive superoxide generation [5].

ROS and oxidative stress speed up DNA damage to cells and the death of cardiomyocytes. Similarly, DNA damage caused by oxidative stress activates poly ADP ribose polymerase (PARP), an enzyme that repairs DNA. By rerouting glucose metabolism away from the typical glycolytic pathway, PARP creates an alternative metabolic pathway that damages cells by producing a variety of mediators. Increased levels of AGEs, hexosamine and polyol flow, and protein kinase C activation are among the damage associated with these conditions [5].

Many extracellular and intracellular proteins that are assumed to play a significant role in diabetes complications can be covalently crosslinked by AGEs. Elastin and collagen crosslinking results in myocardial stiffness and reduced cardiac relaxation. AGEs harm the heart in both humans and animals [6].

***CARDIAC AUTONOMIC NEUROPATHY (CAN) IN DIABETIC CARDIOMYOPATHY:***

An association between neurological activation states and the onset of DCM was found in earlier research [7]. Activation of the sympathetic nervous system increases the production and signaling of β1-adrenergic receptors, leading to an increase in cardiomyocyte apoptosis, impaired contractile performance, interstitial fibrosis, and hypertrophy of the cardiomyocytes [8].

Heart failure is associated with decreased acetylcholinesterase activity, altered muscarinic receptor density and composition, and decreased parasympathetic nervous system activation. Direct or indirect vagus nerve stimulation may directly benefit cardiovascular remodeling and clinical outcomes [9]. CAN, a chronic consequence of diabetes mellitus, causes heart rhythm and vascular hemodynamics irregularities. The prevalence of CAN can reach 60% in individuals with a long-term history of diabetes mellitus. CAN changes the myocardium's contractile activity and affects coronary circulation and blood flow. Because of aberrant sympathetic tone, patients with CAN have decreased vascular elasticity and increased peripheral vascular resistance. Other researchers have documented a decrease in the myocardial perfusion reserve. This could explain at least some of the ventricular dysfunction linked to diabetic CAN [4]. Diabetes patients with CAN frequently experience cardiac dysfunction. According to certain research, diastolic dysfunction is more common in patients with more severe CAN. Although exercise-induced myocardial dysfunction (MD) has been demonstrated in patients with resting normal ventricular function, individuals with diabetes CAN display abnormal cardiac contractility responses to stress [4].

***CONTRIBUTIONS OF INSULIN RESISTANCE AND HYPERINSULINEMIA:***

Insulin resistance and hyperinsulinemia are common clinical abnormalities in T2DM and prediabetic situations. Through several pathways, hyperinsulinemia causes cardiomyocyte hypertrophy. Diabetes mellitus-related Cardiomyocyte hypertrophy is transcriptionally regulated. Hyperinsulinemia induces several epigenetic and genetic changes that activate transcription factors that control the expression of extracellular and cellular proteins. When these transcription factors are activated, extracellular matrix proteins are deposited, and cardiomyocytes enlarge, which leads to focal myocardial fibrosis in diabetes mellitus [10].

***ACTIVATION OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM:***

According to data from studies on humans and animals, RAAS plays a significant part in diabetes-induced cardiac dysfunction. The intracardiac RAAS is activated by hyperglycemia and has varying effects on cardiomyocytes. Myocardial cells from diabetic patients had 3.4 times greater intracellular angiotensin II levels than those from non-diabetics [11].

Inside the cell membrane In animal models, AGT II stimulates cell proliferation. Cardiac fibroblast proliferation and cardiomyocyte hypertrophy are both triggered by AGT II's direct impact on cell signaling. Aldosterone, oxidative stress, and inflammation are a few other variables that may mitigate the damaging effects of AGT II on the heart that result in myocardial damage in diabetes mellitus. In addition, insulin resistance may be facilitated by the enhanced activation of mineralocorticoid receptor signaling and AGT II through the mammalian target of the rapamycin-S6 kinase 1 signal transduction pathway [12].

***EFFECTS OF ALTERED LIPID METABOLISM ON THE MYOCARDIUM:***

The heart may utilize glucose and fatty acids (FAs) for energy within normal physiological parameters. FA translocase and the cluster of differentiation 36 (CD36) mediate the uptake of FAs, while glucose transporter 4 (GLUT4) mediates insulin-stimulated glucose transport, which is the mechanism by which glucose is uptake [13]. On the other hand, GLUT4 internalizes and returns to its intracellular position in T2DM and insulin resistance situations, while CD36 preferentially localizes to the sarcolemma [14].

The inverse placement of GLUT4 and CD36 impacts the development of metabolically inflexible cardiac metabolic disorders. Consequently, diminished glucose uptake due to systemic and cardiac insulin resistance in diabetes mellitus promotes a substrate shift toward increased free fatty acid (FFA) oxidation, leading to a loss in cardiac efficiency [15]. Ectopic lipid buildup occurs in non-adipose tissues such as skeletal muscle, heart, and liver due to diabetes mellitus, which overstrains the cellular oxidation capacity. One possible cause of DCM is cardiac steatosis [16]. Patients with obesity and type 2 diabetes have lower-than-normal contributions from glucose oxidation to cardiac energetics; instead, FA metabolism supplies the energy requirements of the heart [16]. Patients with obesity and type 2 diabetes have elevated cardiac triglyceride buildup and FA uptake due to elevated plasma FFA levels. In this situation, excessive FA absorption and transport by cardiomyocytes will likely surpass the capability of mitochondrial oxidative enzymes, resulting in lipotoxic damage to the myocardium. A portion of the extra FA enters nonoxidative pathways, where it produces harmful FA intermediates like ceramide. Toxic substances cause apoptosis, cell damage, mitochondrial malfunction, contractile failure, and cardiac fibrosis after interfering with normal cellular signaling [17]. Lipoapoptosis refers to cellular death caused by lipotoxicity. It can be triggered by various processes, such as inflammation, membrane instability, palmitate toxicity, endoplasmic reticulum stress, diacylglycerol, and ceramide production. Myocardial fibrosis and structural damage are two consequences of lipoapoptosis that impact heart function [18].

***MALADAPTIVE IMMUNE RESPONSES:***

Adaptive and innate immune system alterations can amplify DCM [19]. Macrophage polarization to alternative (M2) or traditional (M1) phenotypes and proinflammatory T helper cells are often activated by insulin resistance or obesity [2]. In addition, chronic overfeeding causes white adipose tissue to undergo immunological responses and low-grade inflammation. The polarization of macrophage M2 in insulin-resistant and obese situations decreases inflammation, whereas the polarization of macrophage M1 increases it. The pro-inflammatory cytokines released by M1 macrophages impaired systemic and cardiac insulin signaling, and DCM was promoted [2].

Conversely, macrophage M2 receptor 1 and interleukin 10 work together to prevent cardiac fibrosis and cardiomyocyte hypertrophy. T helper lymphocytes, an additional type of immune cell, were detected in patients with diffuse chronic myeloid leukemia. The visceral adipose tissue of mice fed a high-fat diet has a greater CD8+CD4+ T-cell ratio compared to lean animals [20].

T helper cells secrete more chemokines, growth factors, and proinflammatory cytokines, which worsen cardiac fibrosis and poor diastolic relaxation. Regarding the heart, regulatory T-cells normally mitigate the inflammatory effects of T helper cells [21].

***SUBCELLULAR COMPONENT ABNORMALITIES :***

The development of DCM is linked to metabolic problems, including stress on the endoplasmic reticulum (ER), poor calcium handling, and mitochondrial dysfunction [22].

Excessive reactive oxygen species (ROS) generation disrupts endogenous protein folding and post-translational modifications, causing ER damage. The proteasomes speed up their degradation of misfolded proteins in response to an adaptive response activated when the endoplasmic reticulum (ER) is under stress. When insulin resistance and a high-carbohydrate diet coexist, nutrients overflow into cells, preventing the ATP-producing transfer of electrons to oxygen and potentially leading to mitochondrial oxidative damage due to increased

reactive oxygen species (ROS). Thus, mitochondrial ROS generation damages DNA, lipid membrane components, and proteins. ROS-mediated fibrosis builds up and produces diastolic dysfunction, which can result in heart failure [4].

***MICROCIRCULATION IMPAIRMENT IN THE MYOCARDIUM:***

Damage to the body's microcirculation is the pathological hallmark of vascular problems caused by diabetes. Diabetic retinopathy, neuropathy, and nephropathy are unique microvascular consequences; impaired microcirculation in the heart is another example [22,23].

Coronary microvasculature is frequently impaired in patients with type 2 diabetes, insulin resistance, and diabetic cardiomyopathy. Reduced quantities of bioavailable nitric oxide are the source of this impairment. Nitric oxide stimulates guanylyl cyclase and kinases in coronary vascular smooth muscle cells, which is necessary for coronary relaxation. Both increased nitric oxide breakdown and decreased nitric oxide synthesis occur in settings of reduced insulin sensitivity [23].

Insulin resistance and hyperinsulinemia can constrict blood vessels of various sizes. Hyperinsulinemia may cause vascular smooth muscle cells to differentiate into osteoblast-like cells, which could explain the observed rise in vascular stiffness. Increased vascular stiffness can be caused by increased osteocalcin expression, alkaline phosphatase activity, and the formation of mineralized nodules in vascular smooth muscle cells due to increased receptor activator of nuclear factor κB levels [24].

Consequently, impaired activity of vascular smooth muscle cells and endothelial cells is associated with an increased risk of developing coronary artery disease (CAD) in cases when DCM is present [4].

***PROGRESSION OF DIABETIC CARDIOMYOPATHY:***

Most of the left ventricular filling (about 90%) in a healthy, normal heart happens passively before the next contraction of the left atrium. In healthy individuals, the left atrial contraction accounts for approximately 10% of the ventricular filling phase (active filling phase) [25].

Diastolic filling irregularities, including those in obesity and type 2 diabetes, are marked by metabolic and anatomical problems that lead to decreased ventricular wall compliance and impaired passive filling phase of the left ventricle. This can be partially compensated as the disease progresses by the left atrium contributing more to active filling. Conventional echocardiography is a standard method used in the clinical setting for the noninvasive diagnosis of diastolic dysfunction [25].

There are three unique stages in the course of diabetic cardiomyopathy, each with its own pathophysiological characteristics and clinical outcomes as follows:

***Early stage:***

Metabolic abnormalities such as insulin resistance and hyperglycemia do not coincide with substantial changes in the structure and function of the myocardium during the early stages of diabetic cardiomyopathy. Echocardiography and magnetic resonance imaging (MRI) can, though, identify problems with myocardial relaxation. Animal studies have shown that the so-called Western diet, which is heavy in refined carbohydrates and lipids, can cause changes in insulin signaling, insulin resistance throughout the body, and poorer relaxation during diastole without causing systolic dysfunction [2].

Other abnormalities in echocardiographic diastolic measures, such as an aberrant myocardial performance index, an abnormally long duration of isovolumic relaxation, and impaired septal annular wall motion, were also indicative of these impairments [26].

***Advanced stage:***

In advanced diabetic cardiomyopathy, cardiac fibrosis is worsened by myriad cellular changes, including malfunctioning autophagy of cells that have died through apoptosis and necrosis, oxidative stress, and a maladaptive immunological response. As a result, both diastolic and systolic functions undergo substantial alterations [27].

***Late stage:***

As diabetic cardiomyopathy progresses, myocardial fibrosis, metabolic changes, and neurohumoral activation exacerbate coronary microcirculation, diastolic function, and systolic function [28].

The decomposition of this molecule is accelerated by increases in oxidative stress, which further reduces nitric oxide levels. There is a correlation between interstitial fibrosis and reduced cardiac relaxation, which is brought about by an increase in inflammation, a decrease in bioavailable nitric oxide, and an increase in reactive oxygen species [2].

Some of the structural abnormalities associated with diabetic cardiomyopathy include capillary microaneurysms, thickened and sclerotic small coronary vessels, hypertrophy, collagen formation in connective tissue, heart muscle fibrils loss over time, thickening of the basement membrane, hyaline

arteriolar sclerosis, and capillary microaneurysms [29].

***DIAGNOSTIC MARKERS:***

**ECG:** Prolonged QT intervals, increased QT dispersions, and T peak-Tend dispersions are some cardiac electrophysiological abnormalities seen in patients with DCM. These repolarization anomalies, which have been found to imply LVDD, describe the asynchronous cardiac action. [30].

**Serum markers:** Some new markers show potential for clinical diagnosis and treatment. Fibrotic markers have a crucial role. A lower TIMP-1/active MMP-9 ratio and increased levels of active MMP-9 and MMP-7 have been associated with diastolic dysfunction (DM-DD). Also, it was found that serum PIP level was inversely connected with A-Ar (estimated passive diastolic function) in early type 2 diabetes, suggesting that fibrosis could be the main reason for diastolic dysfunction. We have also looked into a couple of other indicators. A strong correlation exists between the diastolic function index (E/e') and a stress response cytokine known as GDF-15, which is elevated in asymptomatic DCM [31,32].

**Echocardiography:** Echocardiography is a diagnostic tool worth considering. It is affordable and helpful for assessing structural and functional cardiac issues. When evaluating left ventricular diastolic function, the transmitral Doppler is the most used [4].

Tissue Doppler imaging (TDI) monitors the velocities of myocardial tissues during the cardiac cycle to accurately assess diastolic and systolic myocardial functions on a regional and global scale. TDI is far more sensitive and accurate than transmitral Doppler when diagnosing DCM [4].

Doppler echocardiography has traditionally been used to measure left ventricular size and evaluate mitral inflow velocity curves to detect and define the degree of left ventricular diastolic dysfunction [33].

Parameters such as mitral annular e' velocity, E/e' ratio, LA maximum volume index, and the initial recommended strategy of using the mitral inflow E/A ratio are now part of the updated recommendations for evaluating LV diastolic function, according to the American Society of Echocardiography. As assessed by Doppler echocardiography, it is necessary to confirm LV diastolic dysfunction in patients exhibiting clinical signs of heart failure and an E/A ratio of 2 or above. Be on the lookout for further symptoms and indications of heart failure since an E/A ratio greater than 2 can be a standard variety in young individuals [33]. To diagnose left ventricular diastolic dysfunction and identify patients with an elevated left ventricular filling pressure, additional testing is required in cases where the mitral inflow E/A ratio is between 0.8 and 1.9 or is less than or equal to 0.8 together with the following conditions: left atrial volume index (LAVI) greater than 34 mL/m2, right atrial regurgitation peak velocity greater than 2.8 m/s as measured by CW Doppler echocardiography, and an average mitral E/e' ratio greater than 14 [33].

New features in 2D speckle tracking echocardiography can now be used to evaluate left ventricular diastolic dysfunction. One such feature is an LA contractile strain rate of less than -1.66/s, which shows reduced function of the LA pump and enhances the precision of diagnosing left ventricular diastolic dysfunction in diabetic cardiomyopathy patients [33].

**Cardiac CT:** Contrary to 2D echocardiography, which can evaluate LV diastolic functional parameters like the E/A ratio, E/e', etc., to diagnose and categorize the severity of LV diastolic dysfunction, cardiac CT mainly evaluates anatomic remodeling, like dilated LA or dilated LV, in patients with LV diastolic dysfunction. Research has demonstrated that high-degree left ventricular diastolic dysfunction mediates the relationship between elevated LA pressure and left ventricular hypertrophy [34].

According to research by Kaiume et al. [35], a maximum transverse diameter of the heart, a maximum anteroposterior diameter of the left atrium (LA) greater than 43.9 mm, and a maximum anteroposterior diameter of the thorax greater than 0.165 are all potential indications of left ventricular diastolic dysfunction.

**Cardiac MRI:** Cardiac MRI is an excellent diagnostic technique for Fabry disease and amyloidosis, two illnesses affecting the heart muscle. Due to its greater reproducibility compared to echocardiography, cardiac MRI has recently replaced echocardiography as the preferred approach for estimating left ventricular mass and volume [37]. Another tool that can identify left ventricular diastolic dysfunction using phase-contrast MRI is echocardiography, which can quantify pulmonary inflow and mitral inflow velocities. A newly discovered technology called cardiac MRI golden angle allows for acquiring 150 to 250 frames per cardiac cycle. It is well-known that tissue Doppler imaging and echocardiography can assess the degree of left ventricular diastolic function by measuring myocardial and mitral velocities. Additionally, phase

contrast cardiac MRI can assess myocardial velocities. Doppler echocardiography and tissue Doppler imaging have consistently shown excellent agreement with the mean e' and E/e' calculated from cardiac MRI in individuals with left ventricular diastolic dysfunction [38].

Patients with severe left ventricular diastolic dysfunction often have gradually enlarged left atriums, which is a significant sign of elevated left ventricular filling pressures. Cardiac magnetic resonance imaging (MRI) provides a more accurate assessment of left atrial ejection fraction (LAEF) and more precise results than echocardiography for measuring LA size. Booster pump stresses, lower LAEF, decreased LA reservoir, and higher LA volumes are all associated with LV diastolic dysfunction [39].

## CONCLUSIONS

One of the rare but rapidly increasing causes of cardiomyopathy globally is diabetes, and the condition is a common consequence of diabetes that is responsible for a great deal of death and disability. We provide a synopsis of the several potential pathogenic mechanisms that are now being studied that could lead to diabetes-related cardiomyopathy since our understanding of the pathological processes producing this condition is improving. Early on, several structural and functional alterations take place, including fibrosis, cell signaling disturbance, and left ventricular (LV) hypertrophy. Heart failure develops from these alterations.

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